Protocol Name: A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions

Short Title: ArthroCare Cartilage Trial (ACT)

Protocol Number: SM-2012-02

Protocol Version: Version 4.0

Protocol Date: October 27, 2016

Sponsor: Smith & Nephew, Inc.
1450 E. Brooks Road
Memphis, TN 38116
US

Nondisclosure Statement

smith&nephew

Table of Contents

1. STUDY PROTOCOL SIGNATURE PAGE

Confidentiality Statement:

This Clinical Investigational Plan (CIP) contains privileged or confidential information, which is the property of the Sponsor. Information may not be disclosed to a third party without written authorization from the Sponsor.

Regulatory Statement:

This study will be conducted according to the protocol, the US Code of Federal Regulations 21 CFR Part 50, 54, 56, and 812, the ethical principles of GCP as defined in ICH E6, and the ICH Guidelines. All aspects of this study will be conducted in accordance with all national, state, and local laws of the pertinent regulatory authorities.

Investigator's Statement:

I understand the protocol *"*A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Study to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions."

I agree to conduct this study in accordance with the design and specific provisions of the protocol in this CIP and to inform all who assist me in the conduct of this study of their responsibilities and obligations. I agree to await Institutional Review Board (IRB)/Research Ethics Board (REB) approval of the CIP and Informed Consent Form (ICF) before initiating the study, to obtain informed consent prior to subject enrollment in the study, to collect and record data as required by this CIP and corresponding Case Report Forms (CRF), to prepare Annual, Final, and Adverse Events (AE) Reports as required, and to maintain study documentation for the period of time required.

I agree to ensure the rights, safety, and well-being of the subjects involved in the study.

Investigator's Printed Name:	
Investigator's Signature:	Date of Signature:

2. TABLE 1: LIST OF ABBREVIATIONS

ACT	ArthroCare Cartilage Trial
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
ICRS	International Cartilage Repair Society
IFU	Instructions For Use
IKDC	International Knee Documentation Committee
IRB	Institutional Review Board
KOOS	Knee Injury and Osteoarthritis Outcome Score
MRI	Magnetic Resonance Image
RF	Radiofrequency
REB	Research Ethics Board
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
WORMS	Whole-organ MRI Score

3. TABLE 2: STUDY SYNOPSIS

Title	A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions
Short Title	ArthroCare Cartilage Trial (ACT)
Protocol Number	SM-2012-02
Study Design	Non-Inferiority, Adaptive Study Design
Study Duration	2 year post-operative follow-up
Study Center(s)	Up to 13 clinical sites
Number of Subjects	82 subjects randomized
Objectives	Primary: The primary objective is to evaluate clinical outcomes following Radiofrequency-Based Debridement or Mechanical Debridement for subjects requiring treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure Secondary: The secondary objectives are to evaluate imaging and additional clinical outcomes
Study Population	Male and non pregnant female subjects ≥ eighteen (18) years of age requiring a treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure
Study Intervention	Group I: Radiofrequency-Based Debridement: Quantum° 2 Controller plus Paragon T2° ICW or WEREWOLF° Controller plus FLOW 50° Wand **(study devices)**
Control Intervention	Group II: Mechanical Debridement **(control device)**
Randomization Scheme	Subjects will be assigned by a 1:1 schema
Intervention	Surgical intervention for a single medial femoral chondral lesion treatment plus partial medial meniscectomy procedure

Endpoints	Primary Endpoint: • Change in Knee and Osteoarthritis Outcomes Scores (KOOS) scores at Week 52 post-operative compared to baseline Secondary Endpoints: • Clinical Endpoints o Change in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores from baseline o Change in International Knee Documentation Committee (IKDC) Knee Examination Form scores from baseline o Change in KOOS scores from baseline at Weeks 6, 12, 24, 36 and 104 o Change in Visual Analogue Scale (VAS) scores from baseline o Change in SF-12 scores from baseline o Change in EQ-5D-5L scores from baseline o Subject Satisfaction at Weeks 52 and 104 • Imaging Endpoints o MRI assessments at Day 10, Weeks 52 and 104 o ICRS grade of chondral lesion at Day 10, Weeks 52 and 104
Safety Assessments	o Incidence of Adverse Events

4. TABLE 3: STUDY FLOWCHART AND FOLLOW-UP ASSESSMENTS

Procedure	Screening/ Baseline	Surgery	Post-Operative Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
Informed Consent	X[1]								
Medical History & Demographics	X								
Subject Eligibility Verification	X	X							
Physical Assessment - Knee	X		X	X	X	X	X	X	X
Magnetic Resonance Imaging (MRI)	X[2]		X					X	X
Weight bearing AP / Lateral / Merchant View	X								
Weight-bearing posteroanterior radiograph	X								
Standing Long Leg Alignment	X							X	
International Cartilage Repair Society classification (ICRS)		X[3]	X[4]					X[4]	X[4]
International Knee Documentation Committee (IKDC) [5]	X			X[6]	X	X	X	X	X
Visual Analogue Scale (VAS), knee pain	X		X	X	X	X	X	X	X
Knee Injury and Osteoarthritis Outcome Score (KOOS)	X			X	X	X	X	X	X
SF-12	X			X	X	X	X	X	X
EQ-5D-5L	X		X	X	X	X	X	X	X
Subject Satisfaction								X	X

Adverse Events		X	X	X	X	X	X	X	X
Post-operative Rehabilitation[7]			X	X					
Concomitant Medications	X		X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X

[1] Must occur prior to any study–specific procedures
[2] MRI must occur within 9 months of enrollment into this study confirming presence of a medial femoral chondral lesion and medial meniscal tear requiring a partial meniscectomy
[3] International Cartilage Repair Society (ICRS) classification will be used for intra-operative arthroscopic confirmation of the lesion grade
[4] International Cartilage Repair Society (ICRS) classification will be used for determination of lesion grade by MRI
[5] International Knee Documentation Committee (IKDC) Subject Knee Evaluation and Knee Examination Forms will be used
[6] IKDC Knee Examination Form - Subject dependent
[7] Post-operative Rehabilitation per Investigator standard of care

5. BACKGROUND INFORMATION

5.1 Introduction

Articular cartilage defects or chondral lesions are commonly detected during arthroscopy when treating knee pathology such as a torn meniscus or damaged anterior cruciate ligament (ACL). Three recent large studies consisting of 190, 1,000, and 25,124 patients each showed that between 60% and 70% of patients having arthroscopic knee surgery have concomitant chondral lesions (1-3). These lesions were found to occur most often in patients undergoing meniscal tear repair or anterior cruciate ligament repair and were usually found on the medial femoral condyle.

Focal chondral lesions observed during arthroscopy are usually addressed using any one of several different treatment options that are selected using a clearly defined algorithm (4). The treatment selected depends on the severity of the lesion, which is graded using a scheme such as the International Cartilage Research Society (ICRS) classification system (5). When chondral lesions are treated surgically, first line methods generally consist of debriding loose or worn articular cartilage, with the goal of stabilizing the lesion to prevent further degeneration. One method of treatment includes radiofrequency (RF) -based debridement. A prospective study by Voloshin et al. followed one hundred ninety-three patients that underwent bipolar radiofrequency–based chondroplasty over 38 months. Of these patients,

fifteen with a total of twenty-five defects were re-examined when undergoing repeat arthroscopy for recurrent or new injuries. Of the twenty-five lesions, only three demonstrated further deterioration of the cartilage defects after treatment with RF (6). Limited clinical data exists, however, evaluating the use of radiofrequency-based debridement for the treatment of chondral lesions compared to another commonly used treatment method, mechanical debridement. Owens and Busconi reported that women treated for isolated patellofemoral chondral lesions using a bipolar RF-based device tended to have better joint evaluation scores and demonstrated less incidence of crepitus at one and two years post-operatively than those receiving mechanical shaver-based treatment (7). In patients undergoing partial meniscectomy and having concomitant medial femoral condyle chondral lesions treated using mechanical debridement alone or mechanical and RF-based debridement, Barber and colleagues observed no significant differences between treatment groups in clinical outcomes through one year (8). Spahn et al. reported contrary findings to the Barber group when studying a similar patient cohort in Germany. In their prospective, randomized, controlled trial they found significantly better clinical results, as measured using the KOOS scores, Tegner scores, and qualitative recovery measures, in patients receiving mechanical and RF-based debridement compared to those receiving mechanical debridement alone (9).

Currently, it is not known if clinical outcomes following treatment of chondral lesions by mechanical debridement (i.e. mechanical shaver) or RF-based debridement may equal one another. The primary aim of the proposed study is to evaluate clinical outcomes following Radiofrequency-Based Debridement or Mechanical Debridement for subjects requiring treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure. Secondary aims include evaluating imaging and additional clinical outcomes.

5.2 Study Device

ArthroCare Corporation is a wholly-owned subsidiary of Smith & Nephew, Inc. ArthroCare Corporation is the legal manufacturer of the study devices. Smith & Nephew distributes the study devices.

The Quantum° 2 System and WEREWOLF° COBLATION° System are FDA cleared bipolar, radiofrequency electrosurgical systems designed for use in orthopaedic/arthroscopic surgical procedures.

The Quantum 2 Controller obtained FDA 510(k) clearance (K082666) on October 15, 2008, and Health Canada clearance (License #74846) on December 29, 2009. ARTHROWANDS°, which include the Paragon T2° ICW Wand, obtained FDA 510(k) clearance (K083306) on December 10, 2008, and Health Canada clearance (License #9285) on December 17, 2008. The System consists of the following components:

1. A bipolar radiofrequency Controller;
2. A reusable, non-sterile Foot Control;

2a. A reusable, non-sterile wireless Foot Control (optional);

3. A reusable, non-sterile Power Cord;
4. A reusable,, non-sterile Patient Cable (optional); and
5. A disposable, sterile ARTHROWAND Wand (sold separately)

The WEREWOLF° Controller and FLOW 50° Wand obtained FDA 510(k) clearance (K162074) on August 22, 2016. Health Canada clearance is pending. The System consists of the following components:

1. A bipolar radiofrequency Controller with Integrated Fluid Outflow Regulator;
2. A non-sterile, reusable wired Foot Control and Power Cord
3. Sterile, disposable, single-use COBLATION Wands

5.3 Mechanism of Action

Smith & Nephew distributes COBLATION devices for ablation, resection, and coagulation of soft tissue and hemostasis of blood vessels in arthroscopic and orthopaedic procedures.

The Paragon T2 ICW Wand is powered by the Quantum 2 Controller and the FLOW 50 Wand is powered by the WEREWOLF Controller. Both systems use a controlled radiofrequency-based plasma process (with the trademark 'COBLATION'). In this process, radiofrequency energy is used to excite the water molecules in a conductive medium, such as

an electrolyte (saline) solution, to generate excited radicals within precisely focused plasma. The energized particles in the plasma have sufficient energy to break molecular bonds (16-18), excising or dissolving (i.e. ablating) soft tissue at relatively low temperatures (typically 40ºC to 70ºC). This technology is a radiofrequency-based technique but its mechanism of action is a chemical process and not a function of the radiofrequency energy itself.

The Paragon T2 ICW Wand utilizes T2, or Temperature Technology, which facilitates optimal performance by providing a real-time visual indicator when the temperature exceeds the recommended 50°C. The FLOW 50 Wand utilizes the Ambient° feature which provides accurate (±3°C) real-time temperature monitoring of the intra-articular irrigating fluid.

These devices also provide the capability for hemostasis, typically delivered through devices that can also coagulate bleeding vessels.

6. OVERVIEW OF INVESTIGATIONAL PLAN

This is a prospective, double blinded, multi-center, randomized, controlled study with enrollment of 82 randomized subjects at up to 13 study sites. Study duration will be until the last subject enrolled reaches 104 weeks post-operative.

Subjects requiring arthroscopic treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure will be randomly assigned to one of the following device groups. The assignment will be based on a 1:1 ratio (Group I: Group II):

- Group I: Radiofrequency-Based debridement using the Quantum 2 Controller plus Paragon T2 ICW Wand or the WEREWOLF Controller plus FLOW 50 Wand **(study devices)**
- Group II: Mechanical Debridement **(control device)**

Study visits will be conducted at the following time points:

- **Visit 1**: Screening/Baseline (Day -21 to -1)

- **Visit 2**: Day 0- Surgery
- **Visit 3**: Day 10 (± 3 days)
- **Visit 4**: Week 6 (± 5 days)
- **Visit 5**: Week 12 (± 7 days)
- **Visit 6**: Week 24 (± 14 days)
- **Visit 7**: Week 36 (± 14 days)
- **Visit 8**: Week 52 (± 28 days)
- **Visit 9**: Week 104 (± 56 days)

The Study Flowchart and Follow-Up Assessments table (Table 3) outline the study procedures and timelines.

7. STUDY OBJECTIVES

7.1 Study Purpose

The purpose of this study is to evaluate changes in clinical and imaging outcomes following arthroscopic treatment of a single medial femoral chondral lesion plus partial medial meniscectomy by Radiofrequency-Based debridement or Mechanical Debridement in subjects ≥ eighteen (18) years of age.

7.2 Primary Objective

The primary objective is to evaluate clinical outcomes following Radiofrequency-Based Debridement or Mechanical Debridement for subjects requiring treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure.

7.3 Secondary Objective

The secondary objectives are to evaluate imaging and additional clinical outcomes.

8. STUDY ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is to evaluate the change in Knee and Osteoarthritis Outcomes Scores (KOOS) scores at Week 52 post-operative compared to baseline.

8.2 Secondary Endpoints

- Clinical Endpoints
  - Change in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores from baseline
  - Change in International Knee Documentation Committee (IKDC) Knee Examination Form scores from baseline
  - Change in KOOS scores from baseline at Weeks 6, 12, 24, 36 and 104
  - Change in Visual Analogue Scale (VAS) scores from baseline
  - Change in SF-12 scores from baseline
  - Change in EQ-5D-5L scores from baseline
  - Subject Satisfaction at Weeks 52 and 104
- Imaging Endpoints
  - MRI assessments at Day 10, Weeks 52 and 104
  - ICRS grade of chondral lesion at Day 10, Weeks 52 and 104

9. PROTOCOL

9.1 Study Design

This is a non-inferiority, prospective, double blinded, multi-center, randomized, controlled, adaptive study design with enrollment of 82 randomized subjects at up to 13 study sites. Study duration will be until the last subject enrolled reaches 104 weeks post-operative.

The study will be comprised of two parts:

Part I: Part I will require all Investigators perform 1 to 3 procedures using the Quantum 2 Controller plus Paragon T2 ICW Wand or the WEREWOLF Controller plus FLOW 50 Wand. Investigators must be qualified by training to perform procedures prior to use of either study device. This purpose of Part I will be to minimize variability with the recommended

directions for use established in the instructions for use (IFU). Part I subjects will be followed per protocol follow-up requirements, and will be included in the safety population only. These subjects will be additive (to the safety population) to the 82 randomized subjects planned as part of the primary evaluation in Part II.

Part II: Part II 82 randomized subjects. Each Investigator may initiate enrollment of subjects in this part of the study following completion of Part I requirements.
The Part II study implements a randomized adaptive study design, whereby an interim analysis will be conducted for sample size re-assessment. There is no intention of reducing the sample size as a result of this interim analysis; however, the sample size may be increased to either establish the non-inferiority and/or may be increased sufficiently to establish superiority depending on the results of the interim analysis.

9.2 Subject Recruitment and Screening

Subjects will be voluntarily recruited from the Principal Investigator or Sub-Investigator population and/or referring physicians.

Subjects who present requiring arthroscopic treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure will be screened to determine if they meet all inclusion and no exclusion criteria. If all entry criteria are achieved, the subject will be eligible to participate in the study. All general and indication-specific entry criteria must be met prior to study entry. Eligible subjects will be provided with an IRB/REB approved ICF for review and signature. Each subject will have a knee physical assessment, and study-related information will be collected.

All potential subjects screened for eligibility will be listed on the Screening and Enrollment Log. The Screening and Enrollment Log will document the date of screening, the results of screening, and the primary reason for excluding the subject (e.g., does not satisfy eligibility criteria or subject declined).

9.3 Study Duration and Follow-Up

Study duration will be until the last subject enrolled reaches 104 weeks post-operative treatment. Subjects will be assessed pre-operatively and return post-operatively at Day 10, Weeks 6, 12, 24, 36, 52, and 104. At each follow-up visit, the subject questionnaires will be administered and AEs and concomitant medication will be reviewed, if applicable. At Day 10, Weeks 52 and 104 post-operatively, the subjects will complete a MRI of the treated knee.

The Study Flowchart and Follow-Up Assessments table (Table 3) outlines study procedures and timelines.

10. SELECTION OF SUBJECTS

Subjects who meet all of the following criteria will be voluntarily recruited by participating Investigators:

10.1 Inclusion Criteria

Subjects MUST meet ALL of the following criteria to be included in the study:

1. Given written informed consent on the IRB/REB approved Consent Form specific to the study, prior to study participation
2. Is male or non pregnant female ≥ eighteen (18) years of age
3. MRI within 9 months of enrollment into this study confirming presence of a medial femoral chondral lesion and medial meniscal tear requiring a partial meniscectomy (as determined by the Investigator)
4. Must present with pain in the index knee of moderate or severe (> 30 mm) as measured by the VAS
5. Must be able to understand English (written and oral)
6. Must be available to come to all study related visits and is physically and mentally willing and able to comply with all post-operative evaluations
7. Must be in general good health (as determined by the Investigator) based on screening assessments and medical history

Intra-operative Inclusion Criteria

Subjects MUST meet ALL of the following criteria to be included in the study:

1. Arthroscopic confirmation of a lesion requiring treatment meeting the following parameters:
    a. Single, treatable chondral lesion, localized to the medial femoral condyle,
    b. ICRS Grade 2 with widely displaceable fibrillation or flaps or Grade 3A,
    c. $< 4cm^2$ in size

10.2 Exclusion Criteria

Subjects will be excluded from the study, if they meet ANY one (1) of the following criteria:

1. Body Mass Index (BMI) > 40 or index joint pain is due to BMI (as determined by Investigator)
2. Requires bilateral knee surgery
3. Any of the following conditions:
    a. active joint infections
    b. is immunocompromised, has Sickle Cell disease, has a primary bone disease (e.g., Paget's disease) or disorders that may adversely affect the healing process, or is terminally ill
    c. inflammatory rheumatoid arthritis or other systemic inflammatory arthritis (i.e., gout)
    d. metastatic and/or neoplastic disease
    e. infectious, highly communicable diseases (e.g., active tuberculosis or active hepatitis)
    f. coagulation disorder or patient is receiving anti-coagulants
    g. documented evidence of a history (e.g. liver testing) of drug/alcohol abuse within 12 months of enrollment into this study
    h. diagnosed with a behavioral condition which could affect their ability to accurately comply with the study (e.g. developmental delay, attention deficit disorder, and autism)

4. Any of the following conditions in the index limb or joint:
    a. Grade III or greater osteoarthritis as determined by AP radiograph (Kellgren-Lawrence classification)
    b. systemic steroid therapy or steroid intra-articular therapy within 4 weeks of enrollment into this study
    c. intra-articular viscosupplementation within 3 months of enrollment into this study
    d. osteomyelitis, septicemia, or other infections that may spread to other areas of the body
    e. fractures, osteocysts or osteolysis
    f. recurrent patellar instability (e.g., subluxation or dislocation)
    g. severe Varus or Valgus knee deformities (as determined by Investigator)
    h. symptomatic tear of the lateral meniscus
    i. avascular necrosis
    j. synovial disorders (e.g., pigmented villanodular synovitis)
    k. previous total or partial meniscectomy
    l. requires reconstruction or replacement of medial or lateral meniscus
    m. knee instability, malalignment, or patellar tracking dysfunction
    n. prior treatment for cartilage repair, including but not limited to ACI, Mosaicplasty and/or marrow stimulation procedures
    o. prior knee tendon and/or ligament repair or patellar surgery within 6 months of enrollment into this study
5. Any of the following conditions in the contralateral limb or joint:
    a. greater than minimal abnormality as shown by clinical exam and/or imaging
    b. scheduled or to be scheduled for surgery over the course of this study
    c. involvement causing abnormal ambulation and non-compliance with post-operative rehabilitation guideline
6. The subject has implanted metallic devices (insulin pumps, nerve stimulators, etc), medically implanted clips or other electronically, magnetically or mechanically activated implants that would contraindicate undergoing an MRI scan of the knee

7. The subject has claustrophobia that would inhibit their ability to undergo an MRI scan of the index knee
8. Receiving prescription narcotic pain medication for conditions unrelated to the index knee condition
9. Cardiac pacemaker or other electronic implant(s)
10. Pregnant and/or intending to become pregnant during this study period
11. Participated in a clinical study within 30 days of enrollment into this study, or who is currently participating in another clinical study.
12. Is a prisoner, or is known or suspected to be transient
13. Is involved with Worker's Compensation unrelated to the index knee
14. Is involved with health-related litigation

Intra-operative Exclusion Criteria

Subjects will be excluded from the study, if they meet ANY one (1) of the following criteria:

1. Has more than 1 chondral lesion requiring treatment
2. Requires concomitant procedures (i.e., anterior cruciate ligament repair, high tibial osteotomy), excluding partial medial meniscectomy
3. Has a medial meniscal tear not requiring treatment
4. Has a medial meniscal tear requiring a procedure other than partial meniscectomy
5. Has a lateral meniscal tear requiring treatment

10.3 Early Withdrawal of Subjects

10.3.1 When and How to Withdraw Subjects

Subjects may voluntarily withdraw from the study at any time for any reason. The Investigator(s) may elect at any time to withdraw a subject from the study for any reason unrelated to the study if such a decision is in the subject's best medical interest. Subjects who experience an AE may also voluntarily withdraw or be withdrawn if deemed in the subject's best medical interest. If a subject discontinues the study prematurely or is withdrawn by the Investigator(s), data collected up to the time of withdrawal will be used

if applicable for analysis. The primary reason for termination or discontinuation will be documented on the End of Study CRF. Subjects who are withdrawn for any reason from the study after intervention will not be replaced.

10.3.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent and refuse to complete the follow-up assessment, fail to adhere to protocol requirements, or die during the follow-up phase will be considered off-study at that time. Attempts will be made to retrieve any follow-up data, in particular, regarding possible AEs at the time of study discontinuation. If the Investigator(s) reports a subject as lost to follow-up, the Clinical Research Associate (CRA) will ensure that documentation is made regarding the reason(s) this has occurred and will ensure that every attempt is made by the Investigator(s) to contact the subject to determine subject status. Appropriate documentation will consist of at least two documented attempts at contact via telephone, followed by an attempt to contact via a registered US/Canada post letter.

10.3.3 Study Site Termination

A specific study site in this multi-center study may also warrant termination under the following conditions:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate;
- Failure of the Investigator to comply with ICH guidelines, IRB/REB policies and procedures and/or regulatory body(s) regulations;
- Knowingly submitting false information from the study site to the Sponsor or its designee, IRB/REB, and/or regulatory body(s), as applicable; or
- Insufficient adherence to protocol requirements.

10.4 Prior and Concomitant Therapy

Information on concomitant medications will be recorded on the Concomitant Medication CRF. Any medication used by the subject will be considered concomitant medication (e.g.,

aspirin, Tylenol, vitamins, dietary supplements, etc). Any changes in medication must be noted on the Concomitant Medication CRF.

Any other investigational drug or approved therapy for investigational use is not permitted during study participation.

11. STUDY PROCEDURES

11.1 Study Interventions

11.1.1 Single Medial Femoral Chondral Lesion Treatment plus Partial Medial Meniscectomy Procedure

A diagnostic arthroscopic evaluation will be conducted to confirm the area of treatment. If all arthroscopic eligibility criteria are met, the subject will be randomized to one of the following two treatments:

- Radiofrequency-Based Debridement (study devices)
- Mechanical Debridement (control device)

If randomized to Radiofrequency-Based Debridement, the subject will receive the Quantum 2 Controller plus Paragon T2 ICW Wand or the WEREWOLF Controller plus FLOW 50 Wand.

11.2 Outcome Measures

11.2.1 Subject Questionnaires

For examples of subject questionnaires, refer to **Appendix B**.

- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- International Knee Documentation Committee Assessment (IKDC) Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- Visual Analogue Scale (VAS), knee pain
- Subject Satisfaction

11.2.2 Physical Assessment

- Physical Assessment - Knee (warmth, swelling, skin changes, evidence of infection)
- IKDC Knee Examination Form

11.2.3 Magnetic Resonance Imaging (MRI)

All MRI assessments will consist of double reads completed by blinded radiologists. The following MRI assessments will be used to evaluate subjects at Day 10, Weeks 52 and 104 post-operatively.

- Quantitative and semi-quantitative assessment of knee morphology, including but not limited to:
  - Cartilage Morphology, Cartilage Signal, Osteophytes, Bone Marrow Edema, Subarticular Cysts, Effusion, Loose Bodies
  - Characterization of Cartilage
- International Cartilage Repair Score (ICRS)

11.2.3.1 Appropriateness for Measurements – MRI

MRI is increasingly being used in the clinical setting as a non-invasive tool for the diagnosis and evaluation of cartilage lesions in the knee. A variety of imaging sequences may be selected to optimize the contrast between the cartilage tissue and neighboring tissue making it more accurate than arthroscopic observation, which has a limited field of view. In addition, MR imaging, when performed with appropriate high contrast, high resolution pulse sequences, may provide quantitative information regarding specific dimensions of various tissues in the knee. Acquired MR images may be re-evaluated at a later date.

MR imaging will be performed according to established acquisition guidelines.

11.3 Visit Summary

11.3.1 Visit 1: Screening/Baseline (days -21 to -1)

All potential subjects screened for eligibility will be listed on the Screening and Enrollment Log. The Screening and Enrollment Log will document the date of screening, the results of screening, and the primary reason for excluding the subject (e.g., does not satisfy eligibility criteria or subject declined).

If all inclusion criteria and no exclusion criteria are met and the eligible subject agrees to participate in the study, he/she will be required to sign an IRB/REB approved ICF. After signing the ICF, each subject will have a knee physical assessment and study-related information will be collected.

The assessments to be performed at Visit 1 include, but are not limited to:

- Confirm written informed consent, prior to any screening procedures
- Inclusion/exclusion criteria
- Demographics (e.g., age, sex, work status, nicotine use)
- Concomitant medication, if applicable
- Medical and surgical history
- Physical Assessment – Knee
- IKDC Knee Examination Form
- Mechanism of injury
- Screening number assignment
- Confirm Visit 2 (surgery) scheduled within 1-21 days after screening

Imaging Assessment:

Pre-operative imaging include:

- Weight-bearing Anterior / Posterior
- Weight-bearing Lateral
- Merchant
- Weight-bearing posteroanterior radiograph
- Standing Long Leg Alignment
- MRI (within 9 months of enrollment into this study)

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain

11.3.2 Visit 2: Surgery (Day 0)

If the Investigator(s) discovers the presence of a condition at the time of surgery that would render the subject ineligible for study participation, the subject should be considered as an intra-operative failure and be discontinued from the study. The subject should receive the standard of care as determined by the Investigator(s).

The primary reason for termination or discontinuation will be documented on the End of Study CRF.

If the subject continues to meet eligibility, the data collected will include, but not be limited to:

- Subject randomization
- Date and time of surgery
- Device information
- Tourniquet time
- Duration of surgery (start and stop hh:mm from the first incision to the final closure)
- Anesthesia type and time of administration
- Adverse Events, if applicable
- Concomitant medication, if applicable

11.3.2.1 Surgical Procedure

- **Randomization**
  - The subject will be randomized to receive:
    - **study device, or**
    - **control device**

    if they continue to meet all of the following:
    - Single, treatable chondral lesion, localized to the medial femoral condyle,
    - ICRS Grade 2 with widely displaceable fibrillation or flaps or Grade 3A,
    - $< 4cm^2$ in size

    and
    - a medial meniscus tear requiring partial meniscectomy
- **End of Study**
  - Subjects will not be randomized and be considered off study if they meet **any one (1)** of the following intra-operative exclusion criteria:
    - Has more than 1 chondral lesion requiring treatment
    - Requires concomitant procedures (i.e., anterior cruciate ligament repair, high tibial osteotomy), excluding partial medial meniscectomy
    - Has a medial meniscal tear not requiring treatment
    - Has a medial meniscal tear requiring a procedure other than partial meniscectomy
    - Has a lateral meniscal tear requiring treatment
  - Subjects will not be randomized and be considered off study if they **do not** meet **any one (1)** of the following intra-operative inclusion criteria:
    1. Arthroscopic confirmation of a lesion requiring treatment meeting the following parameters:
       a. Single, treatable chondral lesion, localized to the medial femoral condyle,
       b. ICRS Grade 2 with widely displaceable fibrillation or flaps or Grade 3A,

c. < 4cm^2 in size

- An End of Study Case Report Form (CRF) will be completed

11.3.3 Visit 3: Day 10 Follow-Up (+/- 3 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- Admission/Discharge information
- Adverse Events, if applicable
- Concomitant medication, if applicable
  - Any changes in concomitant medication
- Compliance with Post-operative Rehabilitation Guideline

Imaging assessment:

Imaging includes:

- MRI

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- EQ-5D-5L
- VAS, knee pain

11.3.4 Visit 4: Week 6 Follow-up (+/- 5 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form - Subject dependent
- Adverse Events, if applicable
- Concomitant medication, if applicable
  - Any changes in concomitant medication
- Compliance with Post-operative Rehabilitation Guideline

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain

11.3.5 Visit 5: Week 12 Follow-Up (+/- 7 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form
- Adverse Events, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain

11.3.6 Visit 6: Week 24 Follow-Up (+/- 14 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form
- Adverse Events, if applicable
- Concomitant medication, if applicable

- Any changes in concomitant medication

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain

11.3.7 Visit 7: Week 36 Follow-Up (+/- 14 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form
- Adverse Events, if applicable
- Concomitant medication, if applicable
  - Any changes in concomitant medication

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain

11.3.8 Visit 8: Week 52 Follow-Up (+/- 28 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form

- Adverse Events
- Concomitant medication
    - Any changes in concomitant medication

Imaging assessment:

Imaging includes:

- Standing Long Leg Alignment
- MRI

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain
- Subject Satisfaction

11.3.9 Visit 9: Week 104 Follow-Up (+/- 56 day(s))

The data collected will include, but not be limited to:

- Physical Assessment - Knee
- IKDC Knee Examination Form
- Adverse Events
- Concomitant medication
    - Any changes in concomitant medication

Imaging assessment:

Imaging includes:

- MRI

Subject self-reported questionnaires:

Subjects will be asked to complete the following questionnaires:

- KOOS
- IKDC Subjective Knee Evaluation Form
- SF-12
- EQ-5D-5L
- VAS, knee pain
- Subject Satisfaction

11.3.10 Optional Follow-Up Visit, Unscheduled Visit Procedures

Subjects that have pre-scheduled surgical visits not involving the affected or contralateral limb (e.g., gallbladder removal, shoulder arthroscopy), and subjects that have additional visits beyond the study-scheduled visits and within the standard of care do not need documentation, unless associated with an AE (e.g., generalized AE or device/treatment-related AE).

11.3.11 Post-operative Rehabilitation Guideline

Guidelines for post-operative rehabilitation are included in the Investigator Site File.

12. STATISTICAL ANALYSIS

This section presents general information about statistical methodologies and concepts such as statistical power, sample size, randomization and a brief analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be provided as a separate document; i.e., the Statistical Analysis Plan (SAP).

12.1 Treatment Groups

The eligible subjects will be randomized to one of the following two treatment groups:

- Group I: Radiofrequency-Based debridement **(study devices)**
- Group II: Mechanical Debridement **(control device)**

If randomized to Radiofrequency-Based Debridement, the subject will receive the Quantum 2 Controller plus Paragon T2 ICW Wand or the WEREWOLF Controller plus FLOW 50 Wand. Investigators must be qualified by training to perform procedures prior to use of either study device.

12.2 Description of Study Endpoints

12.2.1 Primary Efficacy Endpoint

Change in Knee and Osteoarthritis Outcomes Scores (KOOS) scores at Week 52 post-operative compared to baseline.

12.2.2 Secondary Endpoints:

There are two sets of endpoints that are known and well established in this patient population, the clinical and imaging endpoints. Both of these will be assessed in this protocol.

- Clinical Endpoints
  - Change in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores from baseline
  - Change in International Knee Documentation Committee (IKDC) Knee Examination Form scores from baseline
  - Change in KOOS scores from baseline at Weeks 6, 12, 24, 36 and 104
  - Change in Visual Analogue Scale (VAS) scores from baseline
  - Change in SF-12 scores from baseline
  - Change in the EQ-5D-5L scores from baseline
  - Subject Satisfaction at Weeks 52 and 104
- Imaging Endpoints
  - MRI assessments at Day 10, Weeks 52 and 104
  - ICRS grade of chondral lesion at Day 10, Weeks 52 and 104

12.2.3 Safety Assessments

Safety will be assessed through reports of Adverse Events.

12.3 Sample Size Determination, Power calculation, and Rationale

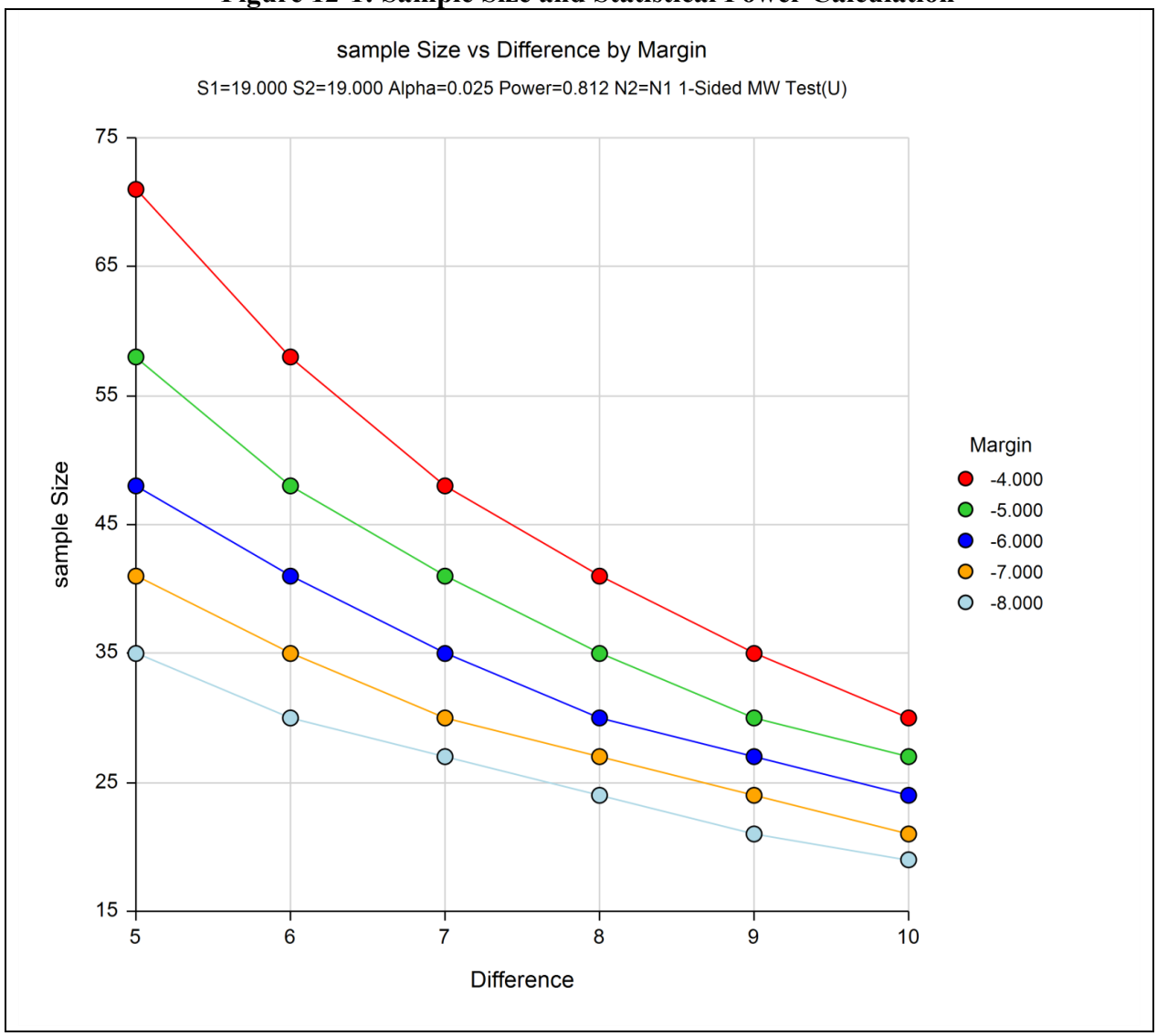
This study will be conducted in a two parts. There is no power calculation for the Part I study. In the Part II study subjects will be randomized to one of the two treatment groups in a 1:1 ratio.

A total of 82 subjects (41 in the study device group and 41 in the control device group) will be randomized in an effort to assure that seventy (70) subjects (i.e., 35 subjects per group) complete the study.

PASS version 2011, is used for this sample size and power calculation. The requirement of 70 subjects (35 active and 35 control) is based on achieving 80% statistical power to detect a non-inferiority margin difference of 8 points between the two groups (10). For the same 80% statistical power, and significance level (alpha) of 0.05 two-sided test; one may choose different number of subjects depending on the expected and observed KOOS score and the acceptance of the non-inferiority delta. These are depicted in Figure 12-1 below.

The discontinuation rate is predicted to be no more than 15%. To accommodate the potential discontinuations, 82 randomized subjects (41 in the study device group and 41 in the control device) are needed for this study.

Figure 12-1: Sample Size and Statistical Power Calculation



12.4 Randomization

This is a multi-center, randomized clinical study. The randomization will be by-site randomization to assure balanced number of subjects between the study devices and control device group in each investigational site.

The randomization will be in 1:1 ratio (i.e., study devices: control device). In each investigational site, subjects who are eligible for randomization will be randomized in a double-blind manner to a device.

12.5 Blinding

12.5.1 Subject Blinding

Subjects will be blinded to treatment assignment until they complete the course of the study. All efforts will be made to keep the subject blinded. Should a subject undergo subsequent arthroscopy for recurrent or new symptoms, withdraw from the study, or be terminated from the study, the blinded assignment will be revealed to the subject and the Investigator will provide care as standard and usual.

12.5.2 Study MRI Blinding

All MRI scans will be transferred to the study radiologists in DICOM format. All subject information will be masked to ensure blinding. The study radiologists reviewing the scans will also be blinded to the treatment received by the subject. MRI scans will be evaluated at Day 10, Weeks 52 and 104 post-operative treatment. All efforts will be made to keep the study radiologists blinded to treatment assignment information by restricting access to related information.

12.5.3 Interim Analysis (IA)

One interim analysis is planned to be conducted for this study. This interim analysis will be primarily for sample size recalculation of the Part II study. The study will not be stopped due to the efficacy results, and no hypotheses testing will be conducted in this IA to assess the differences between the two groups.

This interim analysis is planned to be conducted when 50% of subjects are randomized and completed the Week 24 post-operative follow up evaluations.
The interim analysis will be conducted under the auspices of an independent Data Safety Monitoring Board (DSMB).

There is no intention of decreasing the sample size; however, the sample size may be increased to either establish the non-inferiority and/or may be increased sufficiently to establish superiority depending on the results of the interim analysis.

12.5.3.1 Procedures for Interim Analysis

The data to be used in the interim analysis and the treatment assignment of each randomized subject will be given to the independent statistician. Using this data, the independent statistician will calculate the following metrics for the primary end point:

- difference in change in KOOS scores between the treatment groups
- change in KOOS score from baseline in Group I and the observed number of subjects in the group
- change in KOOS score from baseline in Group II and the observed number of subjects in the group
- dropout rate at the time of the IA
- statistical power of the study at the time of the Interim Analysis (using a conditional power approach)
- conditional power in this IA (CP) will be calculated according to the following formula (Chen 2004 [11]) using primary endpoint data from the ITT population.

$$CP(f_1,z_1) = \Phi \left\{ z_1 / \sqrt{f_1 (1-f_1)} - z_a / \sqrt{(1-f_1)} \right\}$$

Where:

- CP(f1,z1) is the conditional power at the IA
- **Φ{.}** is the cumulative distribution function of a standard Normal distribution ($\mu=0$, $\sigma^2 = 1$)
- f_1 is the fraction of patients enrolled and used in the interim analysis before decision of increasing the sample size
- z_α is the upper α quintile for standard Normal distribution
- z_1 is the standardized Normal

12.5.3.2 Rules and Method for Increasing Sample Size

The sample size will be adjusted only if the conditional power at the time of the Interim Analysis is 50% or more and less than 80%. The sample size will be recalculated based on the observed difference between the treatment groups.

If the conditional power is larger than 50%, then the sample size will be adjusted upward and no Type I error rate adjustment will be made to the final analysis.

If the conditional power is less than 50%, the Type I error rate will be inflated and statistical adjustment will be made to the final analysis, an adjustment to the final p-value will be made as follows:

$$\text{p-value} = 2\left[1 - \Phi\left\{\left| f_2^{\frac{1}{2}} z_1 + (1-f_2)^{\frac{1}{2}} z_2 \right|\right\}\right]$$

where:

P-value is the adjusted target p-value at the end of the study reflecting the adjustment for increasing the study size at the interim analysis

n_1, is the sample size at the time of the interim analysis ($n_1 = n_{gp1} + n_{gp2}$)

n_2 is the re-calculated sample size to be enrolled after the interim analysis

$f_2 = n_1 / (n_1+n_2)$ is the fraction of the newly planned sample size at the IA

z_1 is the observed z score at the time of the interim analysis

z_2 is the observed z value of the z score only based on the data collected after the interim analysis

12.5.4 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

12.6 Analysis Populations

12.6.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects. The Intent-to-Treat population will be the primary population for the analysis of the primary and secondary endpoints.

12.6.2 Per Protocol Population

The Per Protocol (PP) population is defined as all randomized subjects who were not associated with a major protocol violation.

12.6.3 Safety Population

The Safety population is defined as any subject receiving the device/treatment. This population will be used for the analysis of safety parameters. This population includes the subjects from both Parts I and II of the study.

12.7 Statistical Methods

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this study. No inferential statistics will be performed on the baseline and safety data summaries.

12.7.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by device/treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

12.7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics (i.e., medical history, AP/Lateral/ Merchant/ posteroanterior radiograph View, etc.) will be summarized by device/treatment group using appropriate descriptive statistics and/or presented as by-subject listing on the safety population.

12.7.3 Protocol Deviations

The deviations occurring during the clinical study will be summarized and/or presented as/by-subject listing.

12.7.4 Prior and Concomitant Medications

All prior and concomitant medications recorded in the Case Report Form will be coded using the most recent version of WHO Drug dictionary. Descriptive summaries, by device/treatment group, will be prepared using the coded term. All prior and concomitant medications recorded in the Case Report Form will be listed.

12.7.5 Efficacy Analyses

12.7.5.1 Primary Analysis

Primary Endpoint:

The primary analysis will be conducted on the Intent-to-treat (ITT) population. The change in Knee and Osteoarthritis Outcomes Scores (KOOS) from baseline will be compared between the device/treatment groups using Repeated Measures Analysis of Covariance.

Secondary Endpoints:

The secondary endpoints will be analyzed using Analysis of Covariance (ANCOVA) models, or logit model to assess the differences between the two device/treatment groups depending on the nature of the endpoint. The Baseline KOOS will be used as Covariates.

- Clinical Endpoints

- Change in International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form scores from baseline
- Change in International Knee Documentation Committee (IKDC) Knee Examination Form scores from baseline
- Change in KOOS scores from baseline at Weeks 6, 12, 24, 36 and 104
- Change in Visual Analogue Scale (VAS) scores from baseline
- Change in SF-12 scores from baseline
- Change in the EQ-5D-5L scores from baseline
- Subject Satisfaction at Weeks 52 and 104

- Imaging Endpoints
  - MRI assessments at Day 10, Weeks 52 and 104
  - ICRS grade of chondral lesion at Day 10, Weeks 52 and 104

12.7.5.2 Supportive Analysis

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the Per Protocol (PP) population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used.

12.7.6 Safety Analyses

The Safety population will be used for the analysis of safety outcomes. All safety assessments will be tabulated and no hypothesis testing will be conducted in this analysis. For continuous variables data will be summarized by device/treatment group using n, mean, standard deviation, median, minimum and maximum values. For categorical variables data will be summarized by device/treatment group using frequency and percentage.

12.7.6.1 Adverse Events / Adverse Device Effects

Adverse Events will be coded using most recent version of MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study device.

In addition, separate summaries of Serious Adverse Events will also be presented. The total number of subjects with at least one AE/ADE and the number of AEs/ADEs will be derived. If more than one AE/ADE with the same preferred term occurs within a subject during the study period, they will be counted only once for that subject using the worst reported severity and causal relationship to the intervention. AEs/ADEs will also be tabulated versus worst severity and worst relationship to the intervention.

Symptoms, AEs recorded before administration of intervention will only be presented in listings.

12.7.6.2 Physical Assessment - Knee

All knee physical assessment findings will be listed and/or summarized.

13. SAFETY AND ADVERSE EVENTS

13.1 Definitions

13.1.1 Adverse Event

An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study device, whether or not considered related to the study device.

13.1.2 Adverse Device Effect

ADEs are AEs caused by or related to the device.

13.1.3 Serious Adverse Events

Events are classified as serious if they meet any of the following criteria (in accordance with the recommendations of ICH [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):

- Results in death,
- Is life-threatening (NOTE: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect

Additionally, events are classified as serious if they meet any of the following criteria:

- Requires intervention to prevent permanent impairment/damage, or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.1.4 Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect is described as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

13.2 Recording of Adverse Events

At each contact with the subject, the Investigator must seek information on AEs through questioning. Information on all AEs should be recorded immediately in the source document and in the appropriate AE module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All AEs occurring during the study must be recorded in standard medical terminology. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. All unresolved AEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up, through the end of the study, or until it has been determined that the study intervention or participation is not the cause (whichever timing occurs first). Any Serious Adverse Event (SAE) that occurs until thirty (30) days after the study and is considered to be related to the study device or study participation should be recorded and reported immediately.

13.3 Reporting

13.3.1 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as from the initiation of any study treatment or randomization through the end of the study intervention follow-up.

13.3.2 Reporting Adverse Events

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this study device, whether or not considered related to the study device, shall be documented on the AE CRF, except those physical assessment findings that are considered to be clinically insignificant. All AEs meeting the above noted criteria reported by the subject or observed by the Investigator will be individually listed. The description of the event (confirmed diagnosis, if available), date of onset, date of resolution, severity and relationship to study device, action taken, outcome, and seriousness will be reported. The Investigator will evaluate all AEs as follows:

- ***CTCAE Grade (Intensity) Assessment***

The guidelines outlined in CTCAE v4.03 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 3: CTCAE v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

‡Unlike the AE outcome assessment (see Section 13.3.2), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v4.03: June 14, 2010

- ***Causality Assessment***

Adverse Events will be assigned a relationship (causality) to the study device/treatment. The Investigator will be responsible for determining the relationship between an AE and the study device/treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study device/treatment. Relationship of AEs to study device/treatment will be classified as follows:

- Not Related: Any reaction that does not follow a reasonable temporal sequence from administration of the study device AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

- Related: A reaction that follows a reasonable temporal sequence from administration of the study device AND that follows a known response pattern to the suspected device.

- ***Action Taken as a Result of the Event***

The action taken in terms of treatment provided will be as either: none, medication administered, therapy administered, surgery, study treatment unblinded, or other (with a specification).

- ***Outcome Assessment***

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, lost to follow-up or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

13.3.3 Reporting Serious Adverse Events and Incidents

For any **SAE**, the Principal Investigator must submit a completed AE CRF via email to the Sponsor's Medical Monitor, within 24 hours of becoming aware of the event and send the completed Serious Adverse Event/Unanticipated Adverse Device Effect (SAE/UADE) Report via email to the Sponsor's Medical Monitor within 48 hours. In addition, all IRB/REB reporting requirements will be followed.

The Principal Investigator shall make an accurate and adequate report of any **SAEs or Unanticipated Adverse Device Effects (UADE)**. The Principal Investigator shall document any such report on the appropriate CRF and email any initial or follow-up report to the Sponsor's Medical Monitor and to the IRB/REB (as applicable) that has reviewed and continues to review the study.

- **Pre-existing Condition:**
  A pre-existing condition, other than the condition being treated, is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study.

- **General Physical Assessment Findings:**
  At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of a SAE must be recorded and documented as a SAE.

- **Post-study Serious Adverse Event:**
  All unresolved SAEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up, through the end of the study, or until it has been determined that the study intervention or participation is not the cause (whichever timing occurs first). At the last scheduled visit, the Investigator should instruct each subject to report any subsequent event(s) until thirty (30) days after study completion that the subject or the subject's personal physician believes to be related to participation in the study. The Investigator should notify the Sponsor's Medical Monitor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation that is related to the study.

- **Hospitalization, Prolonged Hospitalization, or Surgery:**
  Any medical conditions that occurs after randomization and results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as a SAE if the condition meets the criteria for a SAE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as a SAE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the Investigator (e.g., secondary post-operative hemorrhage).

13.3.3.1 Investigator Reporting: Notifying the Sponsor

Any SAE or UADE must be reported to the Sponsor's Medical Monitor by submitting a completed AE CRF via email within 24 hours of becoming aware of the event:

MEDICAL MONITOR CONTACT INFORMATION

Joseph W. Krotec, MD
Chiltern International Ltd. / Theorem Clinical Research
1016 West Ninth Avenue
King of Prussia, PA 19406
Email: medicalsafety@theoremclinical.com
Phone: +1 (484) 832-8770

Within 48 hours after the initial report, the Investigator must provide further information via email to the Sponsor's Medical Monitor on the SAE or UADE in the form of a written narrative. This should include a copy of the completed SAE/UADE Report Form and any other related diagnostic information that will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the Sponsor's Medical Monitor. All identifiable reference to the

subject except for the subject screening number will be redacted from any report sent to the Sponsor's Medical Monitor.

13.3.3.2 Investigator Reporting: Notifying the IRB/REB

Investigators are responsible for safety reporting to their IRB/REB. Investigators are responsible for complying with their IRB/REB's reporting requirements for SAEs, though they must notify their IRB/REB within 10 working days of becoming aware of the event for any potential UADEs (21 CFR 812.150(a)(1)). The Sponsor or its designee will provide safety reports to the Investigators to assist with reporting to the IRB/REB's. Copies of each safety report and documentation of IRB/REB notification and receipt will be kept in the Trial Master File/Study Master File.

13.3.3.3 Reporting Deaths

The following describes the Investigator reporting requirements in the event of a death, considered a SAE, which occurs during the course of a study:

- Notify the Sponsor's Medical Monitor by submitting a completed AE CRF via email within 24 hours of becoming aware of the event,
- Provide the completed SAE/UADE Report Form via email to the Sponsor's Medical Monitor within 48 hours of the event,
- Notify the IRB/REB of the death per IRB/REB reporting requirements.

Should the Investigator determine the death to be device-related and unanticipated, it is considered an UADE, and the following Investigator reporting requirements should be followed:

- Notify the Sponsor's Medical Monitor by submitting a completed AE CRF via email within 24 hours of becoming aware of the event,
- Provide the completed SAE/UADE Report Form via email to the Sponsor's Medical Monitor within 48 hours of the event,
- Notify the IRB/REB of the death per IRB/REB reporting requirements, but no later than 10 days of becoming aware of the event.

13.3.4 Informed Consent Violation Reporting

If the Investigator uses the study device without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB/REB within 5 working days after the use occurs (21 CFR 812.150(a)(5)).

13.3.5 Protocol Deviation Reporting

The Investigator shall notify the Sponsor and the reviewing IRB/REB of any deviation from the protocol to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred (21 CFR 812.150(a)(4)). All other deviations from the protocol will be reported on the appropriate CRF and reported to the IRB/REB, if required. Every effort shall be made to comply with the requirements of the protocol to avoid deviations.

13.3.6 Progress Reports

The Investigator shall submit Progress Reports on the study to the Sponsor and the reviewing IRB/REB at regular intervals, but in no event less often than yearly (21 CFR 812.150(a)(3)).

13.3.7 Final Report

The Investigator shall, within 3 months after termination or completion of the study or the Investigator's part of the study, submit a Final Report to the Sponsor and the reviewing IRB/REB (21 CFR 812.150(a)(6)).

13.4 Unblinding Procedures

Data are to remain blinded per protocol throughout the study. However, unblinding of subjects will occur by the DSMB, data manager and/or statisticians in the event of a SAE that is deemed related to the study intervention. If time permits, the Investigator should make every attempt to contact the Sponsor and/or trial Medical Monitor before unblinding any

subjects' device/treatment. For emergent unblinding, appropriate study personnel must contact the Sponsor and the Medical Monitor as soon as possible after the incident to report the details surrounding the emergency unblind and to receive instruction on follow-up procedures.

13.5 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) consists of a group of individuals, appointed by the Sponsor or its designee, with pertinent expertise that will review accumulated data at the interim analysis from the study. The DSMB advises the Sponsor regarding the continuing safety of subjects and those yet to be voluntarily recruited to the study, as well as the continuing validity and scientific merit of the study. Unblinded data reviewed by the DSMB will be kept confidential and protected from inadvertent or inappropriate access by the Sponsor or its designee. Following review of data generated from the interim analysis, the DSMB may advise the Sponsor to continue, redesign, or stop the study.

13.6 Study Stopping Rules

The Sponsor may terminate the study at any study site, at any time, for any of the following reasons:

- Non-compliance to Good Clinical Practice (GCP) or protocol
- Failure to enroll subjects
- Major protocol deviations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Safety or performance considerations
- Recommendation made by the DSMB
- Administrative decision

13.7 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her study site. Safety monitoring will include careful assessment and appropriate reporting of AEs. Medical monitoring will include a regular assessment of the number and type of SAEs.

13.8 Assessment of Risks and Benefits

Any surgical procedure poses a potential risk, and the procedures undertaken as part of this study are no exception. There are always risks associated with any surgery or treatment and associated anesthesia, including death.

These risks have been minimized by establishing strict inclusion/exclusion criteria to assure only appropriate surgical candidates participate in the study. A diagnostic arthroscopy will be used to confirm that all inclusion criteria are met. In addition, only trained surgeons with expertise in radio-frequency based debridement and expertise in performing an arthroscopic chondral lesion debridement plus partial medial meniscectomy will participate in this study.

Participation in this study will not subject study participants to any additional risk other than that expected for other arthroscopic surgical procedures used to treat chondral defects. All study participants may benefit from having frequent physician visits and close observation. Additionally, the results of this investigation may benefit both physicians treating subjects and subjects diagnosed with a chondral lesion and meniscal defects by generating data regarding the safety and outcome of the procedure.

Subjects will be advised of the potential risks and benefits associated with this study in the IRB approved ICF.

13.8.1 Risks of Procedure

Possible risks that may occur post-operatively with an arthroscopic treatment of a single medial femoral chondral lesion plus partial medial meniscectomy procedure are defined as follows:

- Joint effusion
- Hematoma
- Adhesions or arthrofibrosis
- Hemarthrosis
- Reduced range of motion or gait status abnormality (temporary)
- Localized pain
- Sensation decrease at incision site
- Inflammation
- Infection
- Chondrolysis
- Fever
- Synovitis
- Deep Vein Thrombosis
- Treatment failure due to rehabilitation non-compliance
- Swelling and bruising
- Fracture
- Nerve injury
- Tendon Injury
- Delayed wound healing
- Vascular injury
- Conversion to mini-open or open procedure
- Secondary surgical intervention to address complications associated with surgery or treatment
- General risks associated with surgery and anesthesia

13.8.2 Risks of Study Device

Anticipated study device-related risks are identified below:

- Prolonged surgery time due to device breakage or malfunction
- Patient burn
- Inadvertent ablation

13.8.3 Benefits of Study Device

Potential benefits of the study device include:

- Minimal thermal penetration
- Precise and efficient tissue removal
- T2 (Temperature Technology) - facilities optimal performance by providing real-time visual indicator when the temperature exceeds the recommended 50ºC (indicator transitions from blue to white)
- Ambient feature - provides accurate (±3°C) real-time temperature monitoring of the intra-articular irrigating fluid

14. DATA HANDLING AND RECORD KEEPING

14.1 Confidentiality

All information and data concerning subjects or their participation in this study will be considered confidential and handled in compliance with the ICH E6 and all applicable regulations. Only authorized personnel, the Sponsor or its designee, and applicable regulatory bodies will have access to these confidential files. All data used in the analysis, reporting, and publication of this study will be maintained without identifiable reference to the subject.

The HIPAA (Health Insurance Portability and Accountability Act) Authorization adds to protections already provided by the elements of ICF and may be contained within the ICF document or as a separate document. The HIPAA document informs the subject that they can withdraw authorization to use data or samples not already submitted to the Sponsor or its designee and that the request must be in writing. If the subject allows samples to be used after withdrawal from the study, this permission may be withdrawn at a later date. The

HIPAA authorization specifies who may review confidential medical information and to whom test results will be submitted. It also describes that test results obtained solely for research will not be part of a subject's medical record.

In the event that a subject revokes authorization to collect or use personal health information, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use personal health information, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

14.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of source documents include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, subject files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the study.

The following data may be recorded directly in the CRF, which will then be considered as source data:

- IKDC Subjective Knee Evaluation Form
- IKDC Knee Examination Form
- KOOS
- VAS, knee pain
- SF-12
- EQ-5D-5L
- Subject Satisfaction Form
- Physical Assessment - Knee
- Imaging observations

14.3 Case Report Forms

The CRF is an integral part of the study and subsequent reports. The CRF provided by the Sponsor must be used to capture all study data recorded in the subject's medical record. The CRF must be kept current to reflect subject status during the course of the study. Only a subject screening number will be used to identify the subject. The Investigator must keep a separate log of subject names and medical record numbers (or other personal identifiers).

After obtaining written source document information from each subject at each visit, the study site will enter the data into the CRF (paper or electronic). The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol and local regulations on the conduct of clinical research as well as to ensure completeness, accuracy, and consistency of the data entered in the CRF.

At the study site, the monitor must have access to subject medical records, study-related records, and written source documentation needed to verify the entries on the CRFs. Final monitored and/or audited CRFs will be available at all times, unless specified in writing to the Sponsor. These CRFs must be reviewed and verified for accuracy by the Principal Investigator and signed off (via electronic and/or paper signature). A copy of the final CRFs will remain at the Investigator's study site at the completion of the study.

Pharmacoeconomic data relating to the surgery (i.e., operating room time, surgical time, blood loss), length of stay, admission, discharge, return to normal activities, medications, research center visits, and other related intervention and procedural costs and billing information may be collected when available for each group (study and control).

14.4 Data Management

Data management and handling will be conducted according to the study specific Data Management Plan in accordance with applicable guidelines.

14.5 Records Retention

Investigators are required to maintain all study documentation, including CRFs, ICFs, and adequate records for the receipt and disposition of the study according to the regulatory requirements and/or until notified by the Sponsor that the records may be destroyed. If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

15. STUDY MONITORING, AUDITING, AND INSPECTING

A monitor, whether an employee of the Sponsor or its designee, has the obligation to follow this study closely. In doing so, the monitor will visit the study sites at periodic intervals, in addition to maintaining necessary contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Quality assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format. The Sponsor audit reports will be kept highly confidential.

15.1 Study Monitoring

Monitoring of study progress and conduct will be ongoing. The study will be monitored throughout its active phase. The first monitoring visit during the active phase of the study will occur shortly after the first subject has been enrolled into the study at any particular study site. Subsequent monitor visits will occur as the frequency of enrollment dictates.

The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study-related facilities (e.g., pharmacy, operating room, etc) and has adequate space to conduct the monitoring visit. All data recorded during the study will be available for audit against source data and for

compliance with GCP (21 CFR Parts 11, 50, 54, 56, 812, ICH E6) and specific protocol requirements. The Principal Investigator will be responsible for the following:

- Monitoring study conduct to ensure that the rights and well-being of subjects are protected;
- Monitoring accuracy, completion, and verification of source documents; and
- Monitoring study conduct to ensure study compliance with the protocol/amendment(s), GCP, and applicable regulatory requirements.

15.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/REB, the Sponsor, government regulatory bodies, and institution compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, operating room, etc).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institution compliance and quality assurance offices.

16. ETHICAL CONSIDERATIONS

This study will be conducted according to the protocol, the US Code of Federal Regulations 21 CFR Part 50, 54, 56, and 812, the ethical principles of GCP as defined in ICH E6, and the ICH Guidelines. All aspects of this study will be conducted in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The decision of the IRB/REB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB/REB members or an IRB/REB assurance number to the Sponsor.

16.1 Protocol Amendments

All protocol amendments must be submitted to the IRB/REB and regulatory authorities, as required. A protocol amendment is generated by the Sponsor. The Investigator(s) is notified of the changes. The amended and/or revised protocol cannot be implemented until IRB/REB approval is received, as required. Protocol revisions that impact on subject safety, the scope of the study, or affect the scientific quality of the study must be approved by the IRB/REB and submitted to the regulatory authorities, as required, before implementation of such revisions to the conduct of the study.

The Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be subsequently notified. In the event of a protocol revision, the ICF may require revisions, which must also be approved by the IRB/REB.

16.2 Informed Consent

All subjects for this study will be provided an IRB/REB approved ICF describing this study and providing sufficient information for subjects to make an informed decision about participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/REB for the study. The formal consent of a subject, using the IRB/REB approved ICF, must be obtained prior to any study participation. The consent form must be signed by the subject and the Investigator and/or designated research professional obtaining the consent. A copy of the signed and dated ICF must be given to the subject, and the consent process must be documented in the source documentation. Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved ICF, and be provided with ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/REB review, and regulatory inspection. If an

amendment to the protocol changes the subject participation schedule or activity or increases the potential risk to the subject, the ICF must be revised and submitted to the IRB/REB for review and approval. The revised ICF must be used to obtain consent from a subject currently enrolled in the study if he/she is affected by the amendment, as deemed necessary by the reviewing IRB/REB. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the IRB/REB approval.

17. INVESTIGATOR TRAINING

17.1 Investigator Training

The Sponsor will select only Investigator(s) with extensive experience in performing arthroscopic knee procedures. Training on the protocol will be provided prior to the start of the study. The protocol will be reviewed with the Investigator(s) and their study personnel at the Site Initiation Visit. In addition, all Investigators will be required to perform 1 to 3 procedures using the Quantum 2 Controller plus Paragon T2 ICW Wand or the WEREWOLF Controller plus FLOW 50 Wand (Part I). The purpose of these procedures will be will be to minimize variability relating to the technique recommended in the IFU. These subjects will be followed per protocol and analyzed for safety findings only.

17.2 Training of Staff

The Investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved and that new information of relevance to the performance of this study is forwarded to the staff involved.

18. PUBLICATION PLAN

Authorship and contents of the publication shall be discussed between each Principal Investigator at the study centers participating in this study and the Sponsor. The Sponsor shall serve as the coordinator of multi-center study disclosures and, in the event of a disagreement among the investigators, the Sponsor shall determine, in its sole discretion, the resolution of any such dispute. The Sponsor shall be furnished copies of any proposed multi-center publication or disclosure, including, without limitation, disclosures in papers or abstracts or at research

seminars, lectures, professional meetings, or poster sessions, at least 90 days prior to the proposed date for submission for publication or disclosure. During such 90-day period, the Sponsor shall have the right to review and require modification of such publication to assure the accuracy of the contents thereof and to delete Sponsor Confidential Information therefrom. In addition, upon the Sponsor's written request during the foregoing 90-day period, the proposed submission for publication or disclosure shall be delayed for a period not to exceed ninety (90) days from the date of such request to permit the Sponsor to file patent applications or to otherwise seek intellectual property protection related to information contained in such publication or disclosure.

It is also agreed that no presentations or publications will be authorized individually or by subgroups participating in the Study without the consent of the Sponsor prior to publication of the pooled data; provided however that in no event shall any Institution or Investigator involved in this Study be restricted from submitting a publication independently after the expiration of 365 days from the completion of the multi-center study.

19. INSTITUTIONAL REVIEW BOARD / RESEARCH ETHICS BOARD

Before initiation of the study, the Investigator must obtain approval of the protocol, ICF, CRFs, and any advertisement for subject recruitment from an IRB/REB complying with the provisions specified in 21 CFR Part 56 or ICH GCP, as applicable, and pertinent government regulations.

A copy of written IRB/REB approvals of the protocol, ICF, CRFs, and any advertising for subject recruitment (if applicable) must be provided to the Sponsor or its designee prior to initiation of the study. The approval letter must be signed by the IRB/REB chairman or designee, identify the IRB/REB name and address, identify the protocol by title and/or protocol number, and include the date that approval was granted. The letter must also contain a statement that the IRB/REB complies with the requirements in 21 CFR Part 56 for a study conducted under ICH or GCP, as applicable.

The Investigator is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not exceeding one year or otherwise specified by the IRB/REB.

20. REFERENCES

1. Figueroa D, Calvo R, Vaisman A, Carrasco MA, Moraga C, Delgado I. Knee chondral lesions: incidence and correlation between arthroscopic and magnetic resonance findings. *Arthroscopy* 2007; 23(3):312-315.

2. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy* 2002; 18(7):730-734.

3. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee* 2007; 14(3):177-182.

4. Sgaglione NA, Miniaci A, Gillogly SD, Carter TR. Update on advanced surgical techniques in the treatment of traumatic focal articular cartilage lesions in the knee. *Arthroscopy* 2002; 18(2 Suppl 1):9-32.

5. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am* 2003; 85-A Suppl 2:58-69.

6. Voloshin I, Morse KR, Allred CD, Bissell SA, Maloney MD, DeHaven KE. Arthroscopic evaluation of radiofrequency chondroplasty of the knee. *Am J Sports Med* 2007; 35(10):1702-1707.

7. Owens BD, Stickles BJ, Balikian P, Busconi BD. Prospective analysis of radiofrequency versus mechanical debridement of isolated patellar chondral lesions. *Arthroscopy* 2002; 18(2):151-155.

8. Barber FA, Iwasko NG. Treatment of grade III femoral chondral lesions: mechanical chondroplasty versus monopolar radiofrequency probe. *Arthroscopy* 2006; 22(12):1312-1317.

9. Spahn G, Klinger HM, Mückley T, Hofmann GO. Four-year results from a randomized controlled study of knee chondroplasty with concomitant medial meniscectomy: mechanical debridement versus radiofrequency chondroplasty. *Arthroscopy* 2010; 26(9 Suppl):S73-80.

10. Roos M. Ewa, Lohamander Stephan L, The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. BioMed Central 2003; 1:64, page 5 of 8

11. Chen JYH, Demets DL, and Lan KKG ‘ Increasing the Sample Size when unblinded interim results is promising,’ Statistics in Medicine 23 (2004) 1023- 1038.

21. APPENDICIES

21.1 Appendix A - Draft Informed Consent

21.1.1 US Sites- Draft Informed Consent

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title: A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions

Protocol No.: SM-2012-02

Investigator:

Sub-Investigator(s):

Sponsor: Smith & Nephew, Inc.
1450 E. Brooks Road
Memphis, TN 38116
US

☐ **Introduction**: Before agreeing to participate in this research study, it is important that you read and understand this consent form. This form provides all the information we think you will need to know in order to decide whether you wish to participate in the study. If you have any questions after you read through this form, ask your questions to the study doctor or study personnel. You should not sign this form until you are sure you understand everything on this form. You may also wish to discuss your participation in this study with your family doctor, a family member, or a close friend. It is required that you sign this consent form before the study doctor or study personnel can begin any study procedures.

It is important that you answer any questions, to the best of your ability, which your study doctor may ask with respect to your health history and any medications you may be taking. This is done in order to prevent any unnecessary harms to you should you decide to participate in this study.

☐ **Purpose of the Study:** You are being asked to participate in this research study because you require an arthroscopic knee procedure for the treatment of a chondral lesion and torn meniscus. This study will evaluate 2 different treatments, Mechanical Debridement (i.e., a mechanical shaver that removes areas of damaged tissue) and Radiofrequency Debridement (i.e., electrical energy that removes areas of damaged tissue), used to repair the chondral lesion in your knee. Your torn meniscus will be treated per standard of care by your study doctor.

All of the Mechanical Debridement and Radiofrequency Debridement devices being used in this study have obtained clearance by the U.S. Food and Drug Administration (FDA) for commercial use and are currently being used on the market.

The study doctor would normally use any one of the methods, Mechanical Debridement or Radiofrequency Debridement, to treat your knee, but right now it is not known if one of these methods is better than the other. This study is being conducted to see whether Radiofrequency Debridement is as safe and effective as Mechanical Debridement in patients with knee problems such as yours.

This study will involve up to 3 Part 1 patients per study doctor and a total of 82 Part 2 patients 18 years of age and over, who will participate in this study at up to 13 medical centers across the United States and Canada.

☐ **Study Device Description:** The Quantum◇ 2 Controller plus Paragon T2◇ ICW and the WEREWOLF◇ Controller plus FLOW 50◇ Wand are device systems manufactured by ArthroCare and distributed by Smith & Nephew. Both systems are designed for use in orthopaedic/arthroscopic surgical procedures. These devices will be used to perform the Radiofrequency Debridement.

The study devices use electrical energy to precisely dissolve (remove) damaged tissue at relatively low temperatures (typically 40°C to 70°C).

☐ **Description of the Study:** If you are enrolled in the study, your participation will last 104 weeks (2 years). You will have to visit the study site a total of 9 times during the study, including the time you come in for your surgery.

The study will be conducted in two (2) parts:

- Every study doctor is required to complete 1 to 3 **Part 1** subjects. If you are included in Part 1 of the study, you will be treated with one of the Radiofrequency Debridement devices. The information collected will be evaluated for safety of the study device.
- **Part 2** will include an additional 82 subjects who will be assigned to one of two groups in order to compare the treatments. These groups are selected by chance, as if by tossing a coin. You have one in two chances of being placed into one of the following treatment groups:

    - Mechanical Debridement, or
    - Radiofrequency Debridement (study devices)

    The information collected in Part 2 will be evaluated for safety and effectiveness of the study device. If you are included in Part 2 of the study, you will not know what group you have been assigned to and therefore what treatment you received until 104 weeks (2 years) after your surgery, at the end of the study.

Visit 1: If you choose to participate in this study, you will be evaluated to determine if you are a good candidate for the study. The study personnel will perform the following procedures to find out if you qualify for the study:

- Ask general questions about your health and current medications
- Perform a knee assessment
- Have you complete study questionnaires regarding your pain, function, and general health

If you fulfill all criteria for the study, you will be assigned for surgery.

Visit 2 – Surgery: During surgery, the following will take place:

- You will be administered standard anesthesia
- The study doctor will make several small incisions in your knee in order to perform the arthroscopic surgery
- After your torn meniscus is treated, the study treatment portion will begin and you will receive the assigned treatment
- The areas of incision will be closed

Immediately following surgery, you will have a bandage and dressing on your treated knee. You may be given a prescription for pain medication to use if you have pain following the surgery. You may also be prescribed a standard physical therapy regimen. These are the same procedures used for any knee surgery.

If, during the surgery, your study doctor determines that your condition no longer meets the requirements for the study you will not be able to complete the study. In this case, you will not be asked to undergo additional study visits and will be treated according to the standard of care normally given by your doctor for your condition.

The study personnel will explain the pre-surgical and surgical procedures to you in greater detail and answer any questions you have.

Visits 3 – 9: You will see your study doctor for follow-up after surgery at day 10 (Visit 3), 6 weeks (Visit 4), 12 weeks (Visit 5), 24 weeks (Visit 6), 36 weeks (Visit 7), 52 weeks (Visit 8), and 104 weeks (Visit 9). At each follow-up visit, you will be asked general questions about your health and will complete study questionnaires regarding your pain, function, and general health. You will be free to decline answering any questions that you do not feel comfortable answering. It is anticipated that the questionnaires will take 20 minutes to complete at each visit.

At Visits 4, 5, 6, 7, 8, and 9 the study personnel will perform a knee assessment, which will take up to 10 minutes to complete.

At Visits 3, 8, and 9, a MRI will be taken of your treated knee. An MRI is a magnetic resonance image that will show the interior area of your knee following surgery. It is anticipated that the MRI will take up to 1 hour to complete at each of these visits. Your MRIs may be re-evaluated at a later date.

In total, there are 5 extra visits that are not standard follow-up for this type of procedure (i.e. Visits 5, 6, 7, 8, and 9). MRIs are not usually taken at any follow-up visits for arthroscopic knee procedures. In addition, questionnaires may not be completed as standard follow-up. These extra visits and procedures are being done in this study to provide additional information on the safety and effectiveness of Radiofrequency Debridement.

Pharmacoeconomic data such as information relating to the surgery (i.e., operating room time, procedures performed), work status, medications, study site visits, rehabilitation and other related treatment and procedural costs and billing information may be collected when available for each treatment group (Mechanical Debridement and Radiofrequency Debridement).

☐ **Potential Harms (Injury, Discomforts, or Inconvenience):** As with any arthroscopic knee surgery involving anesthesia there are potential risks and complications, including: dizziness, fainting, difficulty breathing, fluid buildup on knee (joint effusion), bruising of soft tissue (hematoma), scar tissue (adhesions), painful restriction of joint motion (arthrofibrosis), bleeding into the knee joint (hemarthrosis), reduced range of motion or abnormal walking (gait status abnormality) (temporary), localized pain, sensation decrease at incision site, inflammation of knee, infection, breakdown of articular cartilage (chondrolysis), fever, inflammation of the knee joint (synovitis), deep vein blood clot (deep vein thrombosis), treatment failure due to rehabilitation non-compliance, swelling of the knee, bruising of the knee, break in bone (fracture), nerve injury, tendon injury, delayed wound healing, vascular injury, conversion to

mini-open or open procedure vs. arthroscopic procedure and/or additional surgery to fix problems associated with the first surgery.

The potential medical risks associated with the study device are prolonged surgery time due to device breakage or malfunction, patient burn, and/or inadvertent tissue removal.

Your study doctor is experienced in this type of surgery, but the results of this surgery cannot be guaranteed. It is possible that the surgery will not reduce the pain or disability felt before surgery. In addition, the pain or disability may be worse after the surgery. It is possible that by being in the study, you can have problems and/or side effects not know at this time. There is some element of this risk in all surgeries, whether or not you receive the study device.

If you choose to take part in this study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the study, that might cause you to change your mind about continuing in the study. You may be asked to sign a new consent form if this occurs.

Participating in more than one study may increase risks to you and may affect study results. You should tell your study doctor if you are considering joining another study.

☐ **Women as Study Subjects:** If you are a woman and are pregnant you cannot be in this study. If a woman is pregnant or nursing a child when she has medication associated with surgery there may be risks to the unborn baby or nursing child.

If you think that you are pregnant during the study, you must tell the study doctor immediately. If you become pregnant before the surgery, you will be removed from the study.

☐ **Potential Benefits:** You may not benefit directly from participating in this study. If you choose to participate in the study, your condition may or may not improve. The potential benefits of the study device are minimal thermal penetration and precise and efficient tissue removal. The information collected in this study to determine the safety and effectiveness of Radiofrequency Debridement may benefit future patients undergoing arthroscopic knee surgery.

☐ **Treatment Options:** If you choose not to participate in this study, there are other treatments available to you. These include receiving the treatment that is routinely offered by this clinic/hospital for a chondral lesion and torn meniscus or not have any treatment at all. These alternatives may have similar and/or additional risks and precautions. Your doctor will have additional information on the alternative treatments.

If you choose to participate in this study, you will be asked not to have another surgical treatment for your knee, unless you have recurring or new pain and/or symptoms, until the 104th week (2 year) visit is complete.

☐ **Confidentiality and Privacy:** All persons associated with this study, including study doctors, coordinators, nurses and delegates (hereby referred to as “study personnel”) and the

sponsor (Smith & Nephew) or its designee are committed to respecting your privacy. No other persons will have access to your personal health information or other identifying personal information without your consent, unless required by law.

The study information collected will be part of what is called your "personal health information" and is identifying information about you that relates to your health or the provision of health care services to you. Your personal health information will include the information from the procedures described in this consent form, as well as other information about you, such as your name and address.

Any personal health information collected or other information related to you will be coded by screening numbers to ensure that persons outside of the study will not be able to identify you. The study personnel are in control of the screening number code key, which is needed to connect your personal health information to you. Our guidelines include the following:

- All information that identifies you, both paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access.
- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- No information identifying you will be allowed off site in any form. Examples include your hospital or clinic charts, copies of any part of your charts, or notes made from your charts.

It is important to understand that despite these protections being in place, there continues to be the risk of unintentional release of information. The study personnel will protect your records and keep all the information in your study file confidential to the greatest extent possible. The chance that this information will be accidentally released is small.

By signing this form, you are authorizing access to your medical records by the study personnel, authorized representatives (i.e., study monitor) of the sponsoring company, the Institutional Review Board (IRB), and by government regulatory authorities (i.e., the US Food and Drug Administration (FDA), the Department of Health and Human Services, and/or regulatory agencies from other countries). This authorization does not have an expiration date. Such access will be used for the purpose of verifying the authenticity and accuracy of the information collected for the study and for checking patient safety, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal regulations, including the Health Insurance Portability and Accountability Act (HIPPA) protect your personal information. They also give you the right to control the use of your personal information (including personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study. However, if you decide to be in this study or choose to withdraw from it, your right to look at or copy your personal information related to this study will be delayed until after the research study is completed.

Photographs may be taken of your knee before, during, and after the surgery; however, your identity will not be revealed.

By FDA regulations, the study sites and the sponsor will keep your study records for at least 2 years from the conclusion of the study. Your study records will then be destroyed in a secure manner once the retention period has elapsed.

A description of this research study will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

☐ **Study Results**: The results of this study may be presented at conferences, seminars or other public forums, and published in journals, but at no time will you be identified. No information will be used in these presentations that would disclose your identity as a study subject. The analyzed data may also be used to plan for future research studies or to prepare reports or marketing applications to regulatory agencies.

☐ **Participation and Withdrawal:** Participation in any research study is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at this study site. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at this study site. If you decide to withdraw your consent to participate in this study, you must write a letter to the study doctor.

The sponsor, the study doctor, the FDA, or the IRB may withdraw you from the study without your consent under the following circumstances:

- to protect your health and safety,
- failure to comply with study procedures,
- failure to later consent to any changes made in the study plan, or
- the study is terminated for any reason.

If you withdraw from the study, the data collected for you up to that time will be used to maintain the integrity of the study, but no more data on you will be collected. You will also be asked to return for a final visit for safety concerns and standard clinical care.

☐ **Cost:** All costs that are part of your usual medical care, such as your surgery and physical therapy will be charged to your insurance company if you have such coverage. You will be responsible for all costs that are not paid by your insurance company. You should check with your insurance company before you enroll in this study. If you have no health insurance you will be held responsible for paying all costs of the study.

Costs which are not associated with standard treatment, such as costs of MRI required specifically for this research study, will be paid for by the sponsor.

While you are in the study, you may still need to get regular medical care. You will still have to pay for the costs of your regular medical care that are not a part of this study. To find out more about costs, you can ask the study doctor or study personnel.

☐ **Compensation for Injury:** In no way does signing this form waive your legal rights nor release the study doctor(s), the study personnel, the sponsor (Smith & Nephew) or this study site from their legal and professional responsibilities.

If you experience an injury or illness during the course of the study, you should seek medical treatment from a doctor, or treatment center of your choice, and promptly notify your study doctor.

In the event that any illness or injury is determined to be related to the study procedure, your study doctor will provide essential medical treatment. You will not be charged for reasonable medical expenses required to treat the injury or illness if your study doctor has determined that the injury or illness is directly related to the study procedure and is not the result of a pre-existing condition caused by accidental re-injury or because you have not followed your study doctor's directions.

If you have any questions about this, please ask the study doctor or study personnel.

☐ **Potential Costs/Reimbursements:** You will be compensated $60 (per visit) for Visits 1, 4, 5, 6, and 7 and $100 (per visit) for Visits 3, 8, and 9 that you complete. This will total $600 over the course of the study and is to compensate you for your time and any travel expenses associated with your participation in this research study.

☐ **Source of Funding for the Study:** Funding for this research study will be provided by the sponsor (Smith & Nephew).

☐ **Institutional Review Board Contact:** If you have any questions regarding your rights as a research subject in this study, you may contact *name* at *xxx-xxx-xxxx.*

☐ **Consent:** This consent form is only part of the process of informed consent. It should give you the basic idea of what the research study is about and what your participation will involve. It is not consent for surgery. You will be asked to sign a separate consent form for surgery. Your continued participation should be as informed as this initial consent so you should feel free to ask for clarification or new information throughout your participation in the study.

A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at this study site for me and for other members of my family. As well, the potential risks, harms, and discomforts have been explained to me, and I also understand the benefits of participating in the research study.

I understand that I have not waived my legal rights nor released the study doctors, or involved institutions, from their legal and professional duties. I know that I may ask now, or in the future, any questions that I have about the study or the research procedures. I have been assured that those records relating to me, and my care, will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information.

I hereby freely and voluntarily consent to participate, and I will be given a signed copy of this consent form.

_____
Name of Subject (please print)

_____ _____
Signature of Subject Date

_____
Name/Status of Individual obtaining Consent (please print)

_____ _____
Signature of Individual obtaining Consent Date

21.1.2 Canadian Site- Draft Informed Consent

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title: A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions

Protocol No.: SM-2012-02

Investigator:

Sub-Investigator(s):

Sponsor: Smith & Nephew, Inc.
1450 E. Brooks Road
Memphis, TN 38116
US

☐ **Introduction**: Before agreeing to participate in this research study, it is important that you read and understand this consent form. This form provides all the information we think you will need to know in order to decide whether you wish to participate in the study. If you have any questions after you read through this form, ask your questions to the study doctor or study personnel. You should not sign this form until you are sure you understand everything on this form. You may also wish to discuss your participation in this study with your family doctor, a family member, or a close friend. It is required that you sign this consent form before the study doctor or study personnel can begin any study procedures.

It is important that you answer any questions, to the best of your ability, which your study doctor may ask with respect to your health history and any medications you may be taking. This is done in order to prevent any unnecessary harms to you should you decide to participate in this study.

☐ **Purpose of the Study:** You are being asked to participate in this research study because you require an arthroscopic knee procedure for the treatment of a chondral lesion and torn meniscus. This study will evaluate 2 different treatments, Mechanical Debridement (i.e., a mechanical shaver that removes areas of damaged tissue) and Radiofrequency Debridement (i.e., electrical energy that removes areas of damaged tissue), used to repair the chondral lesion in your knee. Your torn meniscus will be treated per standard of care by your study doctor.

The Mechanical Debridement devices and the Radiofrequency Debridement device system Quantum◇ 2 Controller plus Paragon T2◇ ICW have obtained clearance by Health Canada (HC) for commercial use and are currently being used on the market. The Radiofrequency Debridement device system WEREWOLF◇ Controller plus FLOW 50◇ Wand has not obtained clearance by HC for commercial use. The WEREWOLF◇ Controller plus FLOW 50◇ Wand will only be used in medical centers in the United States and not in Canada.

The study doctor would normally use any one of the methods, Mechanical Debridement or Radiofrequency Debridement, to treat your knee, but right now it is not known if one of these methods is better than the other. This study is being conducted to see whether Radiofrequency Debridement is as safe and effective as Mechanical Debridement in patients with knee problems such as yours.

This study will involve up to 3 Part 1 patients per study doctor and a total of 82 Part 2 patients 18 years of age and over, who will participate in this study at up to 13 medical centers across the United States and Canada.

☐ **Study Device Description:** The Quantum◇ 2 Controller plus Paragon T2◇ ICW and the WEREWOLF◇ Controller plus FLOW 50◇ Wand are device systems manufactured by ArthroCare and distributed by Smith & Nephew. Both systems are designed for use in orthopaedic/arthroscopic surgical procedures. The Quantum◇ 2 Controller plus Paragon T2◇ ICW device will be used at the Canadian sites to perform the Radiofrequency Debridement.

The study devices use electrical energy to precisely dissolve (remove) damaged tissue at relatively low temperatures (typically 40°C to 70°C).

☐ **Description of the Study:** If you are enrolled in the study, your participation will last 104 weeks (2 years). You will have to visit the study site a total of 9 times during the study, including the time you come in for your surgery.

The study will be conducted in two (2) parts:

- Every study doctor is required to complete 1 to 3 **Part 1** subjects. If you are included in Part 1 of the study, you will be treated with Radiofrequency Debridement. The information collected will be evaluated for safety of the study device.
- **Part 2** will include an additional 82 subjects who will be assigned to one of two groups in order to compare the treatments. These groups are selected by chance, as if by tossing a coin. You have one in two chances of being placed into one of the following treatment groups:

    - Mechanical Debridement, or
    - Radiofrequency Debridement (study device).

    The information collected in Part 2 will be evaluated for safety and effectiveness of the study device. If you are included in Part 2 of the study, you will not know what group you have been assigned to and therefore what treatment you received until 104 weeks (2 years) after your surgery, at the end of the study.

Visit 1: If you choose to participate in this study, you will be evaluated to determine if you are a good candidate for the study. The study personnel will perform the following procedures to find out if you qualify for the study:

- Ask general questions about your health and current medications
- Perform a knee assessment
- Have you complete study questionnaires regarding your pain, function, and general health

If you fulfill all criteria for the study, you will be assigned for surgery.

Visit 2 – Surgery: During surgery, the following will take place:

- You will be administered standard anesthesia
- The study doctor will make several small incisions in your knee in order to perform the arthroscopic surgery
- After your torn meniscus is treated, the study treatment portion will begin and you will receive the assigned treatment.
- The areas of incision will be closed

Immediately following surgery, you will have a bandage and dressing on your treated knee. You may be given a prescription for pain medication to use if you have pain following the surgery.

You may also be prescribed a standard physical therapy regimen. These are the same procedures used for any knee surgery.

If, during the surgery, your study doctor determines that your condition no longer meets the requirements for the study you will not be able to complete the study. In this case, you will not be asked to undergo additional study visits and will be treated according to the standard of care normally given by your doctor for your condition.

The study personnel will explain the pre-surgical and surgical procedures to you in greater detail and answer any questions you have.

Visits 3 – 9: You will see your study doctor for follow-up after surgery at 7-13 days (Visit 3), 6 weeks (Visit 4), 12 weeks (Visit 5), 24 weeks (Visit 6), 36 weeks (Visit 7), 52 weeks (Visit 8), and 104 weeks (Visit 9). At each follow-up visit, you will be asked general questions about your health and will complete study questionnaires regarding your pain, function, and general health. You will be free to decline answering any questions that you do not feel comfortable answering. It is anticipated that the questionnaires will take 20 minutes to complete at each visit.

At Visits 4, 5, 6, 7, 8, and 9 the study personnel will perform a knee assessment, which will take up to 10 minutes to complete.

At Visits 3, 8, and 9, a MRI will be taken of your treated knee. An MRI is a magnetic resonance image that will show the interior area of your knee following surgery. It is anticipated that the MRI will take up to 1 hour to complete at each of these visits. Your MRIs may be re-evaluated at a later date.

In total, there are 5 extra visits that are not standard follow-up for this type of procedure (i.e. Visits 5, 6, 7, 8, and 9). MRIs are not usually taken at any follow-up visits for arthroscopic knee procedures. In addition, questionnaires may not be completed as standard follow-up. These extra visits and procedures are being done in this study to provide additional information on the safety and effectiveness of Radiofrequency Debridement.

Pharmacoeconomic data such as information relating to the surgery (i.e., operating room time, procedures performed), work status, medications, study site visits, rehabilitation and other related treatment and procedural costs and billing information may be collected when available for each treatment group (Mechanical Debridement and Radiofrequency Debridement).

☐ **Potential Harms (Injury, Discomforts, or Inconvenience):** As with any arthroscopic knee surgery involving anesthesia there are potential risks and complications, including: dizziness, fainting, difficulty breathing, fluid buildup on knee (joint effusion), bruising of soft tissue (hematoma), scar tissue (adhesions), painful restriction of joint motion (arthrofibrosis), bleeding into the knee joint (hemarthrosis), reduced range of motion or abnormal walking (gait status abnormality) (temporary), localized pain, sensation decrease at incision site, inflammation of knee, infection, breakdown of articular cartilage (chondrolysis), fever, inflammation of the knee joint (synovitis), deep vein blood clot (deep vein thrombosis), treatment failure due to rehabilitation non-compliance, swelling of the knee, bruising of the knee, break in bone

(fracture), nerve injury, tendon injury, delayed wound healing, vascular injury, conversion to mini-open or open procedure vs. arthroscopic procedure, and/or additional surgery to fix problems associated with the first surgery.

The potential medical risks associated with the study device are prolonged surgery time due to device breakage or malfunction, patient burn, and/or inadvertent tissue removal.

Your study doctor is experienced in this type of surgery, but the results of this surgery cannot be guaranteed. It is possible that the surgery will not reduce the pain or disability felt before surgery. In addition, the pain or disability may be worse after the surgery. It is possible that by being in the study, you can have problems and/or side effects not know at this time. There is some element of this risk in all surgeries, whether or not you receive the study device.

If you choose to take part in this study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the study, that might cause you to change your mind about continuing in the study. You may be asked to sign a new consent form if this occurs.

Participating in more than one study may increase risks to you and may affect study results. You should tell your study doctor if you are considering joining another study.

☐ **Women as Study Subjects:** If you are a woman and are pregnant you cannot be in this study. If a woman is pregnant or nursing a child when she has medication associated with surgery there may be risks to the unborn baby or nursing child.

If you think that you are pregnant during the study, you must tell the study doctor immediately. If you become pregnant before the surgery, you will be removed from the study.

☐ **Potential Benefits:** You may not benefit directly from participating in this study. If you choose to participate in the study, your condition may or may not improve. The potential benefits of the study device are minimal thermal penetration and precise and efficient tissue removal. The information collected in this study to determine the safety and effectiveness of Radiofrequency Debridement may benefit future patients undergoing arthroscopic knee surgery.

☐ **Treatment Options:** If you choose not to participate in this study, there are other treatments available to you. These include receiving the treatment that is routinely offered by this clinic/hospital for a chondral lesion and torn meniscus or not have any treatment at all. These alternatives may have similar and/or additional risks and precautions. Your doctor will have additional information on the alternative treatments.

If you choose to participate in this study, you will be asked not to have another surgical treatment for your knee, unless you have recurring or new pain and/or symptoms, until the 104th week (2 year) visit is complete.

☐ **Confidentiality and Privacy:** All persons associated with this study, including study doctors, coordinators, nurses and delegates (hereby referred to as “study personnel”) and the

sponsor (Smith & Nephew) or its designee are committed to respecting your privacy. No other persons will have access to your personal health information or other identifying personal information without your consent, unless required by law. If you choose to participate in this study, your personal doctor may be informed.

The study information collected will be part of what is called your "personal health information" and is identifying information about you that relates to your health or the provision of health care services to you. Your personal health information will include the information from the procedures described in this consent form, as well as other information about you, such as your name and address. The study information collected on you will leave the country.

Any personal health information collected or other information related to you will be coded by screening numbers to ensure that persons outside of the study will not be able to identify you. The study personnel are in control of the screening number code key, which is needed to connect your personal health information to you. Our guidelines include the following:

- All information that identifies you, both paper copy and electronic information, will be kept confidential and stored and locked in a secure place that only the study personnel will be able to access.
- Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices.
- No information identifying you will be allowed off site in any form. Examples include your hospital or clinic charts, copies of any part of your charts, or notes made from your charts.

It is important to understand that despite these protections being in place, there continues to be the risk of unintentional release of information. The study personnel will protect your records and keep all the information in your study file confidential to the greatest extent possible. The chance that this information will be accidentally released is small.

By signing this form, you are authorizing access to your medical records by the study personnel, authorized representatives (i.e., study monitor) of the sponsoring company, the Research Ethics Board (REB), and by government regulatory authorities (i.e., Health Canada (HC), the US Food and Drug Administration (FDA), the Department of Health and Human Services, and/or regulatory agencies from other countries). Such access will be used for the purpose of verifying the authenticity and accuracy of the information collected for the study and for checking patient safety, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal and Provincial Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA 2000) and the Personal Health Information Protection Act (PHIPA 2004) of Ontario, protect your personal information. They also give you the right to control the use of your personal information (including personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study. However, if you decide to be

in this study or choose to withdraw from it, your right to look at or copy your personal information related to this study will be delayed until after the research study is completed.

Photographs may be taken of your knee before, during, and after the surgery; however, your identity will not be revealed.

By HC regulations, the study sites and the sponsor will keep your study records for 25 years from the conclusion of the study. Your study records will then be destroyed in a secure manner once the retention period has elapsed.

A description of this research study will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

☐ **Study Results**: The results of this study may be presented at conferences, seminars or other public forums, and published in journals, but at no time will you be identified. No information will be used in these presentations that would disclose your identity as a study subject. The analyzed data may also be used to plan for future research studies or to prepare reports or marketing applications to regulatory agencies.

☐ **Participation and Withdrawal:** Participation in any research study is voluntary. If you choose not to participate, you and your family will continue to have access to customary care at this study site. If you decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at this study site. If you decide to withdraw your consent to participate in this study, you must write a letter to the study doctor.

The sponsor, the study doctor, HC, the FDA, or the REB may withdraw you from the study without your consent under the following circumstances:

- to protect your health and safety,
- failure to comply with study procedures,
- failure to later consent to any changes made in the study plan, or
- the study is terminated for any reason.

If you withdraw from the study, the data collected for you up to that time will be used to maintain the integrity of the study, but no more data on you will be collected. You will also be asked to return for a final visit for safety concerns and standard clinical care.

☐ **Compensation for Injury:** In no way does signing this form waive your legal rights nor release the study doctor(s), the study personnel, the sponsor (Smith & Nephew) or this study site from their legal and professional responsibilities.

If you experience an injury or illness during the course of the study, you should seek medical treatment from a doctor, or treatment center of your choice, and promptly notify your study doctor.

In the event that any illness or injury is determined to be related to the study procedure, your study doctor will provide essential medical treatment. You will not be charged for reasonable medical expenses required to treat the injury or illness if your study doctor has determined that the injury or illness is directly related to the study procedure and is not the result of a pre-existing condition caused by accidental re-injury or because you have not followed your study doctor's directions.

If you have any questions about this, please ask the study doctor or study personnel.

☐ **Potential Costs/Reimbursements:** You will be compensated $60 (per visit) for Visits 1, 4, 5, 6, and 7 and $100 (per visit) for Visits 3, 8, and 9 that you complete. This will total $600 over the course of the study and is to compensate you for your time and any travel expenses associated with your participation in this research study.

☐ **Source of Funding for the Study:** Funding for this research study will be provided by the sponsor (Smith & Nephew).

☐ **Research Ethics Board Contact:** If you have any questions regarding your rights as a research subject in this study, you may contact *name* at *xxx-xxx-xxxx.*

☐ **Consent:** This consent form is only part of the process of informed consent. It should give you the basic idea of what the research study is about and what your participation will involve. It is not consent for surgery. You will be asked to sign a separate consent form for surgery. Your continued participation should be as informed as this initial consent so you should feel free to ask for clarification or new information throughout your participation in the study.

A Prospective, Double Blinded, Multi-Center, Randomized, Controlled Trial to Evaluate Mechanical Debridement vs. Radiofrequency-Based Debridement in the treatment of Articular Cartilage Lesions

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at this study site for me and for other members of my family. As well, the potential risks, harms, and discomforts have been explained to me, and I also understand the benefits of participating in the research study.

I understand that I have not waived my legal rights nor released the study doctors, or involved institutions, from their legal and professional duties. I know that I may ask now, or in the future, any questions that I have about the study or the research procedures. I have been assured that those records relating to me, and my care, will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information.

I hereby freely and voluntarily consent to participate, and I will be given a signed copy of this consent form.

_____
Name of Subject (please print)

_____ _____
Signature of Subject Date

_____
Name/Status of Individual obtaining Consent (please print)

_____ _____
Signature of Individual obtaining Consent Date

21.2 Appendix B – Draft Subject Questionnaires

21.2.1 International Knee Documentation Committee (IKDC)

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
International Knee Documentation Committee (IKDC)	X			X	X	X	X	X	X

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Your Full Name_____

Today's Date: _____/_____/_____ (Day / Month / Year) Date of Injury: _____/_____/_____ (Day / Month / Year)

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

4❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
3❑ Strenuous activities like heavy physical work, skiing or tennis
2❑ Moderate activities like moderate physical work, running or jogging
1❑ Light activities like walking, housework or yard work
0❑ Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	10	9	8	7	6	5	4	3	2	1	0	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	10	9	8	7	6	5	4	3	2	1	0	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

4❑ Not at all
3❑ Mildly
2❑ Moderately
1❑ Very
0❑ Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

4❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
3❑ Strenuous activities like heavy physical work, skiing or tennis
2❑ Moderate activities like moderate physical work, running or jogging
1❑ Light activities like walking, housework, or yard work
0❑ Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

0❑ Yes 1❑ No

7. What is the highest level of activity you can perform without significant giving way in your knee?

4❑ Very strenuous activities like jumping or pivoting as in basketball or soccer
3❑ Strenuous activities like heavy physical work, skiing or tennis
2❑ Moderate activities like moderate physical work, running or jogging
1❑ Light activities like walking, housework or yard work
0❑ Unable to perform any of the above activities due to giving way of the knee

Page 2 – 2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
3❑Strenuous activities like heavy physical work, skiing or tennis
2❑Moderate activities like moderate physical work, running or jogging
1❑Light activities like walking, housework or yard work
0❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	4❑	3❑	2❑	1❑	0❑
b.	Go down stairs	4❑	3❑	2❑	1❑	0❑
c.	Kneel on the front of your knee	4❑	3❑	2❑	1❑	0❑
d.	Squat	4❑	3❑	2❑	1❑	0❑
e.	Sit with your knee bent	4❑	3❑	2❑	1❑	0❑
f.	Rise from a chair	4❑	3❑	2❑	1❑	0❑
g.	Run straight ahead	4❑	3❑	2❑	1❑	0❑
h.	Jump and land on your involved leg	4❑	3❑	2❑	1❑	0❑
i.	Stop and start quickly	4❑	3❑	2❑	1❑	0❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Couldn't perform daily activities 0❑ 1❑ 2❑ 3❑ 4❑ 5❑ 6❑ 7❑ 8❑ 9❑ 10❑ No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities 0❑ 1❑ 2❑ 3❑ 4❑ 5❑ 6❑ 7❑ 8❑ 9❑ 10❑ No limitation in daily activities

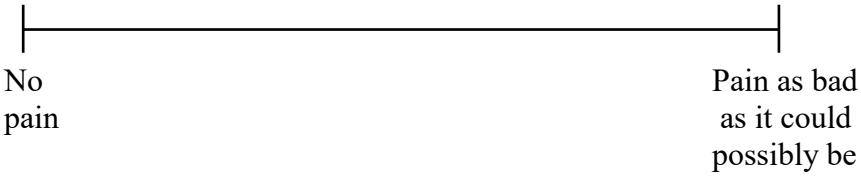
21.2.2 Visual Analog Scale (VAS), knee pain

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
Visual Analogue Scale (VAS), knee pain	X		X	X	X	X	X	X	X

Visual Analog Scale

How severe is your pain today? Please place a vertical mark on the line below to indicate how bad you feel your pain is today.

Visual Analogue Scale (VAS)*



*A 10-cm baseline is recommended for VAS scales.
From: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research & Quality, Rockville, MD; pages 116-117.

21.2.3 Knee Injury and Osteoarthritis Outcome Score (KOOS)

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
Knee Injury and Osteoarthritis Outcome Score (KOOS)	X			X	X	X	X	X	X

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

21.2.4 SF-12

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
SF-12	X			X	X	X	X	X	X

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the follov result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

21.2.5 EQ-5D-5L

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
EQ-5D-5L	X		X	X	X	X	X	X	X

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

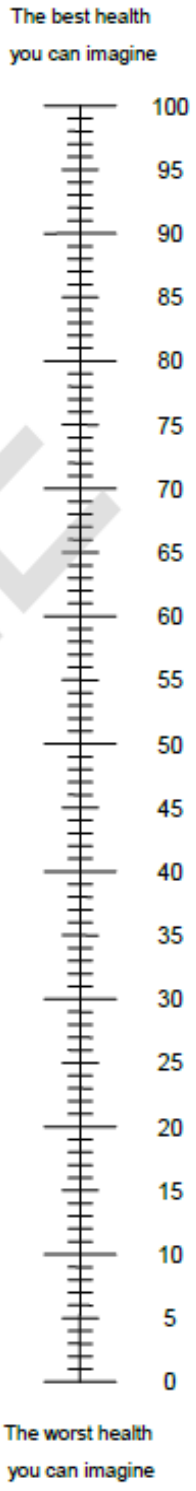
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



21.2.6 Subject Satisfaction

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -21 to -1	Day 0	Day 10 ±3 Days	Wk 6 ± 5 Days	Wk 12 ± 7 Days	Wk 24 ± 14 Days	Wk 36 ±14 Days	Wk 52 ±28 Days	Wk 104 ±56 Days
Subject Satisfaction								X	X

Subject Satisfaction

"All things considered (such as your pain level and functionality prior to treatment versus after treatment), how satisfied are you with the results of your treatment for your knee pain?"

- ☐ Extremely satisfied
- ☐ Very satisfied
- ☐ Somewhat satisfied
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied
- ☐ Extremely dissatisfied