The VENUS Clinical Study

(**V**erifying the **E**ffectiveness of the **NU**surface® **S**ystem)
Clinical Investigation Plan (CIP)

A multi-center, prospective, randomized, interventional, superiority clinical study

Protocol Reference Number:
00249

Revision Number:
J

Date:
9 November 2015

ClinicalTrials.gov Identifier:
NCT02108496

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FDA IDE Number:
G120182

REVISION HISTORY

Revision	Description of changes	Date
A	First issue	26 July 2012
B	Second issue, submitted in IDE Supplement 001: • Change of study title to «The VENUS Clinical Study» • Added Signature page • Updated definitions of terms used in the study plan • Changed Incl / Excl criteria according to FDA letter • WOMET patient questionnaire added • Par 2.5.6. Updated MRI review procedure by independent radiologist • Par. 4.1.3 Negative Imaging Outcomes updated • Par. 5.3.6 Enrollment period extended to 36 months • Par. 6.1.1 modified • Par 6.1.6 modified • Par 12 Adverse Events, Adverse Device Effects updated • Par. 13.1 Study stopping rules added	23 April 2013
C	Third issue, submitted in IDE supplement 001a: • Changed Incl / Excl criteria according to FDA letter • Updated list of abbreviations and definitions • Automatic Study Success changed to Provisional Study Success • Par. 2.2.1 updated • Par. 2.3.2 updated • Par. 3.1 updated • Par. 5.3.1 and 5.3.2 updated according to FDA letter • Par. 5.3.6 updated • Par. 6.1.1 updated • Par. 6.1.4 Definition of Overall Success modified • Par. 6.1.7 updated • Appendix E updated	24 June 2013
D	Fourth issue, submitted in IDE supplement 002: • Modified exclusion criteria no. 7 at page 11 and par. 5.3.2 • Par. 3 modified • Par. 13.1 modified • Par. 14 modified • Appendix D modified	5 Sept 2013
E	Fifth issue, submitted in IDE amendment: • Updated wording in Par 2.5.1, 2.5.4, 2.7.1, 4.2.2, 5.2.2, 5.3.1, 5.3.3, 5.3.6, 6.5.5, 6.6., • Par 7.4 modified • Par 5.5 modified • Par 11 modified • Par 13.4 modified • Appendix A modified table	11 Oct 2013
F	Sixth Issue, submitted in IDE Supplement 005	22 Nov 2013

	• add Staged study text and clarification wording throughout such as in 5.3.4, 6.5.5.1	
G	Add 10 Dec 2013 CMS Final Rule Wording about reimbursement	6 Dec 2013
H	Eight issue, submitted as Supplement 006: • Add text clarifying MRI use for determining primary endpoint • Add text clarifying definition of Overall Success, Provisional PRO • Removed specific reference to sizes of implants available • Appendix B updated with Declaration of Helsinki text as amended during the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 • Appendix C updated to mention latest surgical technique • Appendix F: text revised to provide option to use MRI equipment higher than 3 Tesla	22 Jan 2014
I	Clarify language concerning MRI images and update surgical technique: • Par. 2.5.1 modified • Par 2.5.6 modified • Appendix A updated • Appendix D updated • Appendix E modified	15 Dec 2014
J	Correct typographical errors in version I: • Para 2.5.1 reference changed to 1.5.1 and slightly reworded for clarity • Para 2.5.6 reference changed to 1.5.6 • Appendix D reference changed to Appendix C	9 Nov 2015

SIGNATURE PAGE

Confidentiality Statement

The information contained in this document, especially unpublished data, is the property of the sponsor of this clinical investigation, Active Implants LLC. It is therefore provided to you in confidence as an investigator, potential investigator, consultant, or Regulatory Authority or their representative, for review by you, your staff, and an Independent Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor, except to the extent necessary to obtain informed consent from those persons to whom the study treatments may be administered.

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TERMS AND DEFINITIONS

ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
BMI	Body Mass Index
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DSMB	Data and Safety and Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IKDC	International Knee Documentation Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
KOOS	Knee injury and Osteoarthritis Outcome Score
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
PI	Principal Investigator
PCU	Polycarbonate-Urethane
PRO	Patient Related Outcome
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
UHMWPE	Ultra High Molecular Weight Polyethylene
VAS	Visual Analog Scale
VENUS	Verifying Effectiveness of NUsurface® System
WOMET	Western Ontario Meniscal Evaluation Tool

For this study protocol, the following terms and definitions apply:

1. **Adverse event** is any untoward medical occurrence in a subject whether device related or not which occurs during the course of the clinical trial.

2. **Adverse device effect** is any untoward and unintended response to a medical device including insufficiencies or inadequacies in instructions for use or deployment of the device.

3. **Automatic Study Failure** is, in the Investigational Arm (also referred to as Group), a device removal or MRI detection of a dislocation or device fracture. In the non-surgical control an automatic study failure is any post-intervention surgery of the index knee, as triggered by objective measurement of the KOOS pain score being equal or less than the baseline value after 3 or more months of treatment.

4. **Bailout or Screening Failure** is an enrolled study patient that is excluded from the study by the investigator before treatment begins or a bailout during surgery in the investigational arm because the patient was found not to fulfill all of the inclusion criteria or has one of the exclusion criterion (e.g. Outerbridge Grade 4 lesion on the medial femoral condyle or tibial plateau greater than 0.5 cm^2 or 8 mm in diameter)

5. **Dislocation** is the displacement (more than 50% of the device length) of the NUsurface device from its implanted position between the medial femoral condyle and the medial tibial plateau.

6. **Dropout** is an enrolled study patient that freely decides to withdraw from the clinical investigation before or after receiving the study treatment.

7. **Intervention or treatment** is the event in time when a study patient receives either the investigational device or when the non-surgical treatment begins. Pre-intervention or pre-treatment evaluation is also known as baseline.

8. **Meniscectomy** is the surgical excision of part of a meniscus:
   - 8.1. **Partial Meniscectomy** is a meniscectomy where less than or equal to two-thirds (≤67%) of the meniscus is removed.
   - 8.2. **Subtotal Meniscectomy** is a meniscectomy where 67% to ~95% of the meniscus is removed.
   - 8.3. **Total Meniscectomy** is a meniscectomy where ~95% or more of the meniscus is removed.

9. **Post-Implantation Surgery Terms (Secondary Surgical Interventions):**
   - 9.1. **Other surgical intervention** this category includes other surgeries the patient incurs while enrolled in the study that are unrelated to the implanted device, e.g. appendectomy.
   - 9.2. **Subsequent Return to Operating Room** - Anything that causes the patient to be returned to the OR and surgery not performed (e.g. manipulation under anesthesia).
   - 9.3. **Re-operation** is any study-related post-implantation return of the patient to the operating room for a subsequent knee surgery on the knee receiving the NUsurface device, e.g. infection (device-related or not) or lateral meniscus surgery.

     NOTE Re-operation should only be listed if it is not classified by Terms 9.4 or 9.5 below.
   - 9.4. **Revision** is any post-implantation surgery in which the position or the soft tissue around the originally implanted NUsurface device is changed or altered and the device is not removed or replaced.

9.5. **Removal** is the physical removal the NUsurface implant from the patient whether the device is replaced with another NUsurface implant or not (note: if the device is removed due to a non-device related infection, the data will be analyzed separately).

NOTE Post-implantation surgeries will be categorized in only one of the above categories. Categories 10.1 to 10.5 are mutually exclusive meaning that any post-implantation surgery will not be in more than one category. Removals of the NUsurface implant are automatically considered Failures in the study. If the device is replaced, these patients will continue to be followed based on the previously scheduled follow-up schedule, and will be analyzed separately. These replaced patients will still be considered a Failure in the study.

10. **Provisional PRO** is the primary Patient Related Outcome of KOOS that pending passage of all other success/fail parameters would make the patient an Overall Success. Exact details of how KOOS success is determined are contained in the Statistical Plan (see also par 6.5 of the present study protocol).

11. **Serious adverse event is an** adverse event that

- Led to death
- Led to serious deterioration in the health of a subject that
  - Resulted in a life threatening illness or injury
  - Resulted in a permanent impairment of a body structure or a body function
  - Required in-patient hospitalization or prolongation of existing hospitalization
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

NOTE A hospitalization for a pre-existing condition or unrelated condition to the index knee, or a procedure required by the study plan, without a serious deterioration in health, is not considered to be serious adverse event.

12. **Serious adverse device effect** is adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

13. **Subluxation** is a partial displacement or misalignment of the NUsurface device relevant to the medial femoral condyle and the medial tibial plateau (e.g. in a sagittal view, the posterior aspect of the device is located on top of the 2-4mm posterior wall of the medial meniscus).

14. **Surgery** is a clinical procedure carried out in the operating room under anesthesia by the study investigator under direct visualization of the index knee through incision of the skin and capsule.

Title: The **VENUS** (**V**erifying the **E**ffectiveness of the **NU**surface® **S**ystem) Clinical Study

Type of Study: A multi-centered, prospective, randomized, interventional, superiority study

Size of Study: The planned full pivotal study consists of 124-128 patients randomized between the NUsurface® device and control Arms (Groups) at a 1:1 ratio (62-64 in each Group). However, this number may be adjusted up or down depending upon the results of a planned protocol decision making interim analysis. Stage I of the study consists of 32-33 in each group.

Population: Both men and women, age 30 and 75 years (inclusive), meeting all the inclusion criteria and none of the exclusion criterion.

Number of Sites: In the US Stage I of the study will be at up to 8 to 10 sites and Stage II at up to 15-20.

Study Duration Estimate:

Up to 36 months of recruitment (~0.1 NUsurface patients/month/site) plus an additional 24 months of follow-up for a total of up to 60 months or more.

Description of Intervention:

Patients will be randomized to receive either the NUsurface® Meniscus implant, or be treated with the non-surgical Standard of Care.

Study Rationale: The rationale for performing this clinical study is to gather clinical data to evaluate the safety and effectiveness of the NUsurface device compared to the Standard of Care.

Study Data Elements:

Primary Data Elements:

The primary endpoint components of the study are as follows:

- Effectiveness: Change in KOOS Pain and KOOS Overall (Average of the 5 KOOS Subscales) relative to baseline at 24 months
- Investigational Group Device-Related Secondary Surgical Interventions: The device related secondary surgical interventions of the NUsurface® Meniscus Implant during the 24 month visit post-operative period.
- Control Group Post-Intervention Surgical Procedures: The treatment failures of the control group are defined as any surgery on the index knee medial compartment up to and including the 24 month visit.

Each of these components of Overall Success will be analyzed separately, but their analyses will not affect the 0.05 type I error rate (threshold p-value of 0.05 for significance) for the test of the primary superiority hypothesis.

Secondary Data Elements:

- Safety: Adverse events in either Group occurring at a rate of 5% or more at any post-treatment follow-up period will, if applicable, be statistically compared between study groups. Examples of safety measurements are:
    1. Incidence rate of all adverse events through the 1.5, 3, 6, 12, and 24-month post-treatment period.
    2. Incidence rate of secondary (or primary for the non-surgical control patients) surgical intervention through the 1.5, 3, 6, 12, and 24-month post-treatment period.
    3. Device-related complication is defined as a complication found to be caused by the device and device malfunctions (including severity), as assessed at each post-op period.

Inclusion Criteria: In the opinion of the investigator, if ALL of the following 9 conditions are applicable for the index knee, then the patient is included if he/she:

1. Had > 6 months ago a medial partial meniscectomy as confirmed by patient history and MRI
2. Has a KOOS Pain of ≤ 75 (100 being the highest attainable and no pain)
3. Is between age 30 and 75 years (inclusive) at the time of study treatment
4. Has neutral alignment ± 5º of the mechanical axis, i.e., the angle formed by a line drawn from the center of the femoral head to the medial tibial spine and a line drawn from the medial tibial spine to the center of the ankle joint
5. Has ≥ 2 mm intact medial meniscal rim capable of being fitted with a NUsurface® device AND is also recommended for the baseline non-surgical (and, if likely to receive benefit, any injection) therapies to be administered in the study.
6. Is willing to be entered into either arm of the study: implanted with the NUsurface device OR treated with the recommended control arm therapies.
7. Is able to do the study required follow up visits, questionnaires, X-rays, and MRI's
8. Is able to read and understand the English language
9. Is able and willing to understand and sign the study Informed Consent Form

Exclusion Criteria: If ANY of the following 35 conditions are applicable, then the patient is excluded if he/she:

1. Has a symptomatic knee because of a tear that could be addressed by a repeat partial meniscectomy leaving > 4 mm of medial meniscus rim
2. Has evidence of a Outerbridge Grade IV cartilage loss on the medial tibial plateau or femoral condyle that potentially could contact a NUsurface implant (e.g., a focal lesion > 0.5 cm^2 correlating to a circular defect of > 8 mm in diameter)
3. Has complete disruption of the posterior root attachment of the meniscus
4. Has lateral compartment pain and Grade III or Grade IV Outerbridge cartilage score in the lateral compartment
5. Has a varus or valgus knee deformity > 5º requiring a tibial or femoral osteotomy

6. Has a laxity level of more than Grade II (IKDC), primary or secondary to an injury of the anterior cruciate ligament (ACL) and/or posterior cruciate ligament (PCL) and/or lateral collateral ligament (LCL) and/or medial collateral ligament (MCL)
7. Has significant trochlear dysplasia, patellar instability or symptomatic patellar malalignment
8. Has patellar compartment pain and Grade III or Grade IV Outerbridge cartilage score in the patellar compartment.
9. Compared to a normal knee, has obvious radiological evidence of medial femoral squaring, anatomical variance in the medial tibial plateau, or irregularly shaped cartilage surface
10. Had an ACL reconstruction performed < 9 months prior to study treatment
11. Has a BMI > 32.5 at the start of study treatment
12. Decides to receive (if eligible and an option) allograft medial meniscus transplantation
13. Received any type of prosthetic knee implant made of artificial non-resorbable plastic, metal or ceramic, not including the NUsurface® Meniscus Implant
14. Has a knee flexion contracture > 10º
15. Has flexion < 90º
16. Had a previous medial femoral condyle surgery (not including microfracture) or High Tibial Osteotomy (HTO)
17. Has insufficiency fractures or avascular necrosis of the medial compartment
18. Has an active infection or tumor (local or systemic)
19. Has any type of knee joint inflammatory disease including Sjogren's syndrome
20. Has neuropathic knee osteoarthropathy, also known as Charcot joint
21. Has any medical condition that does not allow possible arthroscopy of the knee
22. Has neurological deficit (sensory, motor, or reflex)
23. Is currently involved in another investigation of the lower extremity
24. Anticipates having another lower extremity surgery during the study period
25. Is contraindicated for hyaluronic acid injections (i.e., patients with known hypersensitivity [allergy] to hyaluronan [sodium hyaluoronate] preparations); patients having knee joint infections or skin diseases or infections in the site of possible injections
26. Is contraindicated for corticosteroid injections (i.e., patients with allergy to any of the components or with idiopathic thrombocytopenic purpura)
27. Has received any corticosteroid knee injections ≤ 3 months prior to study treatment
28. Has chondrocalcinosis
29. Is on immunostimulating or immunosuppressing agents
30. Has ipsilateral or contralateral lower limb joint conditions that may affect ambulation or KOOS (e.g. have a leg length discrepancy > 2.5 cm [1 inch], causing a noticeable limp)
31. Is a female who is lactating, expecting, or is intending to become pregnant during the study period
32. Is an active smoker

33. Is mentally incapacitated (incapable of appraising or controlling conduct) or have mental disability (e.g., dementia or Alzheimer's)
34. Is a prisoner
35. Is a patient who has economic incentive not to improve

Treatment and Follow-up Schedule:

Baseline, treatment, 6 weeks, 3, 6, 12, and 24 months. Patients will continue to be followed annually until all treated patients reach 24 months. Although a two-year study, long-term follow-up for safety and effectiveness may occur.

Effectiveness: The effectiveness of the NUsurface Meniscus Implant relative to the standard of care will be evaluated at the 1.5, 6, 12, and 24 months post-intervention periods using the KOOS Pain Subscale, KOOS Overall Scale, and VAS Scale. The IKDC evaluations will be performed at 6, 12, and 24 months relative to baseline.

Success Criteria: To be an Overall Success, the patient must have all of the following, relative to baseline at 24 months:

1) $KOOS_{pain} \geq 86.1$ **AND** $KOOS_{overall} \geq 86.2$ at 24 months, **OR**
   a. a ≥ 20 point improvement in the $KOOS_{pain}$ scale (with a minimum KOOS Pain Score of ≥ 40 at 24 months), relative to baseline, **AND**
   b. a ≥ 20 point improvement in the $KOOS_{overall}$ (the average of all 5 subscales compared to pre-op) relative to baseline, **AND**
2) For each group:

   Investigational Group: No device removal **AND** no negative imaging outcomes showing device dislocation or symptomatic subluxation greater than 50% of the device length at either 12 or 24 months

   Control Group: No post-treatment surgical intervention of the index knee compartment.

Statistical Analyses: According to the Statistical Plan, the superiority of the investigational device over the standard of care control will be tested by comparing the ratio of Overall Success in each arm.

Supplemental Analyses: At the completion of the study additional analyses outside of the primary scope of the study objectives will be performed and analyzed. These results will be used for literature comparisons, for future regulatory submissions, and for quality of life and reimbursement analyses

1. *Comparison to Literature;*
2. *Effectiveness will be shown by:*
   1) Assessing the effectiveness of the NUsurface® Meniscus Implant through the first 24-month post-intervention period
   2) Evaluating the changes in knee pain from baseline through the 24-month post-intervention period (using the pain scales).
   3) Evaluating changes in patient function from baseline through the 24-month post-intervention period (using the IKDC and/or KOOS forms).

4) Evaluating changes in quality of life from baseline through the 24-month post-intervention period.

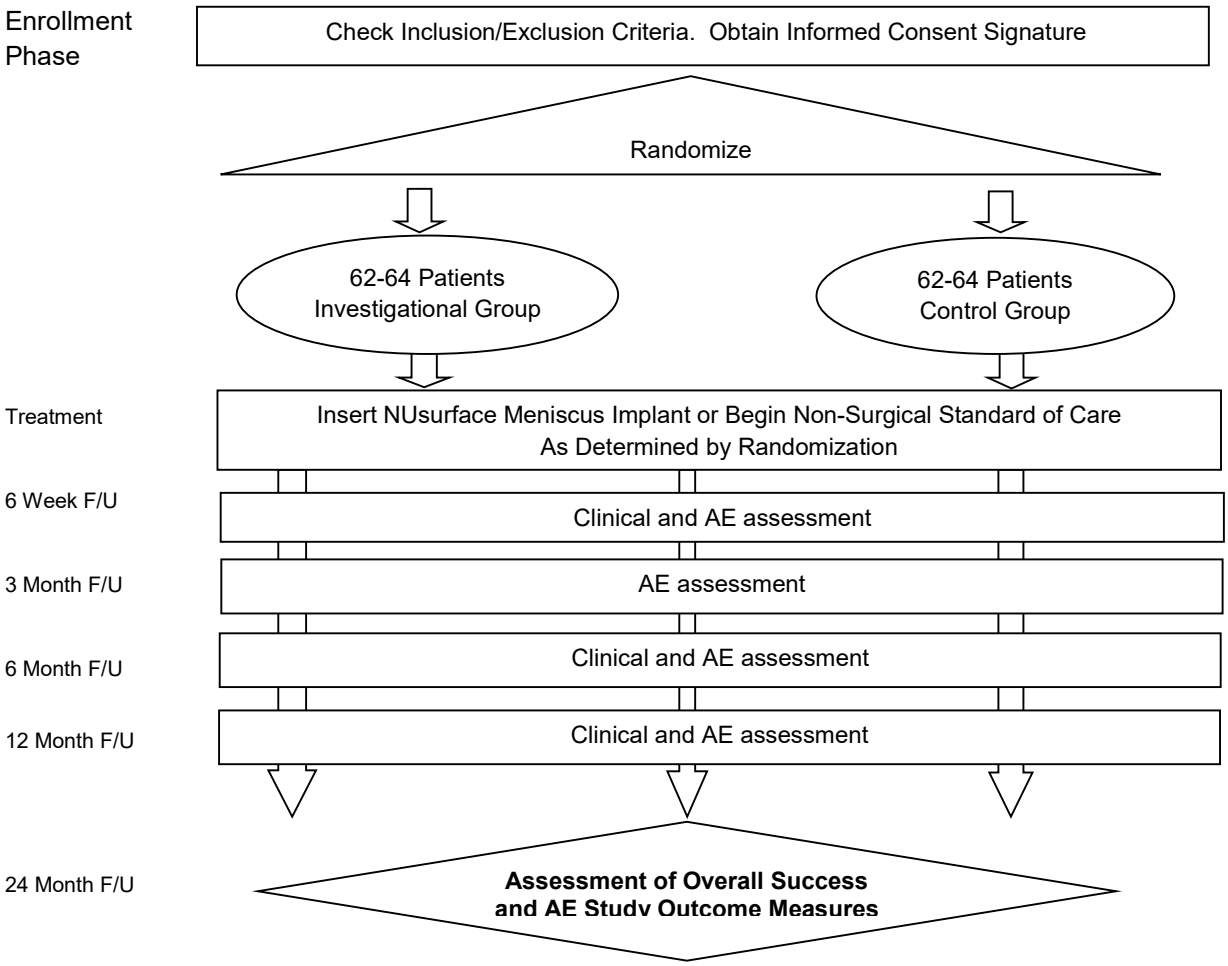
3. *Additional Analyses:*
MRI analysis of the cartilage and knee condition at 12 and 24 months will be performed relative to the 1.5 month baseline. Additional analyses of the effect of prior surgeries, prior non-surgical treatment(s), type of tears, etc. on outcome data may be performed as described in the statistical plan.

4. *Quality of Life;*
To assess the Quality of Life the EQ-5D and WOMET forms will be used pre-intervention (baseline), at 6, 12, and 24 months. From this analysis, Quality-Adjusted Life Year (QALY) will be calculated.

5. *Reimbursement;*
Cost of episode of care, hospital costs, and rehabilitation charges will be gathered for reimbursement analysis purposes.

Schematic of Study Design:

Enrolled in Study	NUsurface	62-64	NUsurface Meniscus Implant
	Control	62-64	Non-Surgical Standard of Care



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Investigators and investigation sites

A current list of investigators and investigational sites will be provided upon request to the Sponsor. Any new sites will be submitted to the FDA by means of an IDE Supplement.

1 IDENTIFICATION AND DEVICE DESCRIPTION

1.1 Intended use

The NUsurface® Meniscus Implant is intended for use in patients with medial compartment pain that have had a previous partial medial meniscectomy.

1.2 Population and study indications

1.2.1 Population

The planned pivotal trial will be conducted in 124-128 patients who meet all of the inclusion criteria and none of the exclusion criterion. A total of 62-64 Investigational Group patients will receive the NUsurface device, with the 62-64 Control Group patients receiving the standard of care. This study size may be modified when 16 patients in each group reach 2 years and an interim analysis is performed. Stage I of the study consists of 32-33 in each group. Stage II (the remainder) will be added after FDA approval.

1.3 Device description and Materials

1.3.1 Device Design Goals

The following goals were defined as essential requirements in the design of a meniscal implant similar to the general concept of the interpositional device, which is to replace the function of a normal meniscus.

a) Mimic load distribution of natural meniscus

b) Mimic intra-capsular movement of natural meniscus

c) Help reduce pain and restore function for patients suffering from meniscal tears/insufficiency

d) Be implanted with a minimally invasive approach

e) Need no bone resection nor suture attachment

f) Have a relatively short rehabilitation

1.3.1.1 Design Rationale

The resulting device, called the NUsurface® Meniscus Implant, is conceptually analogous to the structural characteristics of the natural meniscus where a highly orientated collagen fiber network supports the large hoop stresses to produce better distribution of contact pressures within the knee joint [9-13]. The NUsurface Meniscus Implant is a Polycarbonate-Urethane (PCU)-based device reinforced with high tensile Ultra High Molecular Weight Polyethylene (UHMWPE) fibers. The product is available in different sizes, left and right, and with trials so as to allow the surgeon several size options for implantation.

1.3.1.2 The Treatment Gap

The majority of surgical treatment options are designed primarily to treat younger patients, most often suffering from traumatic tears rather than degenerative tears that are most common in people 30 years old

and older. Because of poor regenerative capabilities usually found in these patients, surgeons are reluctant to choose any of surgical treatment options. On the other hand, more aggressive procedures like Unicompartmental Knee Arthroplasty or Total Knee Arthroplasty are used in older patients (65+) with more severe condition of the cartilage, e.g., grade IV Outerbridge (OB) or exposed bone, many of whom have three-compartmental disease. Thus, a “treatment gap” exists for middle aged patients with mild to moderate osteoarthritis and meniscal insufficiency.

1.3.2 Device description

The NUsurface device is offered in multiple left and right sizes. Radiopaque trials of the same sizes are also offered.

Figure 1 Photograph of NUsurface® Meniscus Implant

The bulk material of the NUsurface Meniscus Implant device is made of medical grade polycarbonate-urethane (PCU) reinforced circumferentially with embedded Dyneema Purity® UHMWPE fibers. After preparing the knee with an arthroscopic approach, the device is designed to be inserted through a minimal arthrotomy incision and to be positioned between the medial tibial and femoral condylar cartilage of the patient. The NUsurface device is a single use device.

Materials:

Polycarbonate urethane (PCU) (Medical Grade)	Implant bulk material
Dyneema Purity® Fibers (Medical Grade) UHMWPE	Reinforcement fiber inside the PCU

The NUsurface device is made of Bionate® 80A polycarbonate-urethane (PTG, Berkley, CA), tested for biocompatibility according to ISO 10993. This material has been used to make numerous implants in humans for nearly 20 years. The fiber used for reinforcement is a special form of ultrahigh molecular weight polyethylene (UHMWPE), distributed under the brand named Dyneema Purity® fiber (DSM Biomedical, Heerlen, Netherlands). UHMWPE has been used in orthopedics for joint replacement for over 50 years. This particular fiber version has also been tested for biocompatibility according to ISO 10993.

1.3.3 Materials of construction

Bionate® 80A polycarbonate-urethane (PCU) is a tough polymer with a relatively low elastic modulus (10-100 MPa, [2]). This material is one of the most extensively tested plastic biomaterials in orthopedics. This material has been shown to have biocompatibility and biostability equal to, or better, than other plastic materials currently on the orthopaedic implant market [3-5]. In addition, PCU has been used extensively in

other clinical, non-orthopaedic applications such as vascular grafts, artificial heart valves, and pace maker leads.

PCU is an attractive material for a meniscal implant application since it is pliable, yet durable, and offers excellent mechanical and hydrophilic properties that are comparable to those of natural meniscus and cartilage [2, 6-8]. Specifically, the natural meniscus is an orthotropic material [1, 6]. By circumferentially reinforcing the PCU with high strength UHMWPE fibers (Dyneema Purity® fibers from DSM Biomedical) the NUsurface Meniscus Implant can mimic the orthotropic properties of the normal meniscus.

1.4 User training requirements

Prior to each study site activation, Active Implants, the Sponsor, will provide or arrange for training relevant and pertinent to the involvement of personnel conducting study activities, investigator responsibilities, as well as device training on usage and handling of device under investigation. Study-specific training will be provided prior to the investigation site activation.

1.5 Device specific and Control Group procedures

1.5.1 Pre-study screening for both study Groups

Each patient considered possibly eligible will be asked to participate in the study and sign a consent form prior to any study related examination. Patients will have a complete history and general physical exam performed. Baseline health assessment will include: prior surgeries and medical interventions, complete medical history and concomitant medication treatment.

An MRI of the knee is needed to determine study eligibility. An MRI taken at another site can be used and if none is available can be taken pre-enrollment according to the site's routine method. These MRI's can be used to determine if the patient is provisionally a study candidate. If so, then a more detailed MRI of the patient's knee taken according to the method described in Appendix E is needed to confirm study eligibility and establish a baseline MRI. This baseline study MRI will need to be repeated if older than 6 months prior to the start of treatment. The baseline MRI will be reviewed by an independent radiologist to confirm eligibility. By signing the Informed Consent Form, the patient gives his/her consent to allow a third party review of all their MRI images.

Radiographic images (see Appendix A for the complete list) of the index knee will be taken at screening to allow initial evaluation of the cartilage status, lower limb alignment and will be used prior to surgery to select the initial trial size that will be used in surgery.

1.5.2 Intra-operative procedures for the Investigational Group

For the investigational group, the operative procedure may be performed either under general or regional (spinal or epidural) anesthesia at the anesthesiologist's discretion. Patients will be positioned the same as for a standard arthroscopic procedure and closure of the wound will follow the standard procedure for an arthrotomy.

The following data will be recorded during the operation:

- medial meniscus description.
- any articular cartilage pathology.

- any other knee joint abnormality.
- operation duration and length of incision.
- adverse reactions.
- surgery/anesthesia time

Please refer to the surgical technique (Appendix C) for detailed instructions on the implantation of the device.

1.5.3 Post-intervention procedures for both study groups

See Appendix D for the rehabilitation protocol for both treatment groups. Post-treatment medications, treatment will be performed according to investigator's normal practice.

1.5.4 Follow-up procedures for both study groups

Post-treatment evaluations will be carried out immediately post op for the investigational group, and at 1.5 months, 3 months, 6 months, 12 months, and 24 months for both groups. Each patient will be seen annually until the last patient has completed 24-month follow-up. Patients will continue to be followed annually until all treated patients reach 24 months. Although a two-year study, long-term follow-up for safety and effectiveness may occur.

Patients in either Group who are automatic failures (e.g., dislocation or infection followed by removal in the Investigational Group, and surgery on the index knee after being randomized to the Control Group) will be followed at their regularly scheduled time until the end of the study. Patients in the Investigational Group that had the device removed will continue to be studied because those patients would have been exposed to the investigational device. Patients in the Control Group who fail by receiving surgery (with the type of surgery being captured) will be followed so as to gather adverse event information to aid in the interpretation of the adverse event data in the Investigational Group. None of the failures will be analyzed for effectiveness after they fail. Instead each will be analyzed for safety through the capture of adverse events.

1.5.5 Validated Questionnaires for both study Groups

1.5.5.1 KOOS and IKDC

The KOOS (Knee injury and Osteoarthritis Outcome Score) and IKDC (International Knee Documentation Committee) forms are validated knee evaluation forms for assessing knee related injuries and treatments [14]. These forms provide a comprehensive evaluation of the patients' pre-intervention and post-intervention condition including activity levels, pain, swelling, locking, stability, support, sports activity, and quality of life assessment. The KOOS form consists of 7 questions about symptoms, 9 questions related to pain, 17 questions related to function in daily activities, 5 questions related to function in sports activities, and 4 questions related to Quality of Life. All 42 questions have 5 possible answers. These forms are to be filled out by the patient at baseline and at 1.5, 6, 12, and 24 months (Appendix A).

The IKDC form includes a demographic form, current health assessment form, subjective knee evaluation form, knee history form, surgical documentation form, and knee examination form. The knee history form and surgical documentation form are provided for convenience. Completion of all of the IKDC forms at baseline and the subjective knee evaluation form at 6, 12, and 24 months (Appendix A) is required per the protocol.

1.5.5.2 VAS

The Visual Analog Scale (VAS) is a validated measurement tool for patient assessment of pain [15]. This scale uses a 10cm baseline, where the patient marks where on the line that they are currently feeling related to pain. One end of the line represents “no pain,” while the other end of the line represents, “Pain as bad as it could possibly be.” This scale is used at baseline and at 1.5, 6, 12, and 24 months (Appendix A).

1.5.5.3 EQ-5D

The EQ-5D is a standardized instrument for use as a measure of health outcome. This tool consists of five questions, and a 20cm scale for assessing pain. This instrument is used at baseline and at 6, 12, and 24 months (Appendix A).

1.5.5.4 WOMET

The Western Ontario Meniscal Evaluation Tool is a validated, disease-specific tool for use in evaluating health-related quality of life (HRQOL) for patients with meniscal pathology. This scale will be used at baseline and at 6, 12, and 24 months (Appendix A).

1.5.6 Post-Intervention MRI of the knee for both study Groups

Post-intervention MRI images will be taken at 1.5, 12, and 24 months according to the MRI protocol described in Appendix E. During the course of the study, each site will be asked to send copies of all MRI’s to a central location for independent analysis by a board certified musculoskeletal radiologist who will review for adverse events and performed analyses comparing the 12 and 24 month images to the 1.5 month and baseline.

1.5.7 Device Regulatory Status

The NUsurface® Meniscus Implant has not been approved by the FDA. This study is being performed under an Investigational Device Exemption (IDE) to gather data that would support a pre-market approval or other regulatory application.

2 RISKS AND BENEFITS OF THE STUDY DEVICE AND CLINICAL INVESTIGATION

2.1 Anticipated clinical benefits

Both the study device and surgical procedure and non-surgical Control Group may be beneficial to the patient by:

- Reducing pre-intervention knee pain as determined by the KOOS Pain Sub-scale.
- Improving the KOOS Symptoms, QoL, ADL, and Sports/Rec Sub-scales and KOOS Overall.

2.2 Anticipated adverse device effects and residual risks associated with the study device

1) The risks associated with any knee surgery are also possible for those patients randomized to the Investigational Group of the study. In addition to these normal risks, the NUsurface device may have the additional possible risks:

- Bending or breakage of the components or bone
- bending, fracture, breakage, or dislodgement (failure) or movement of the implant from position;
- device separation that may result in loose or free-floating fibers or particles inside your knee joint or get inside the tissues surrounding your knee
- device-generated noise, clicking,
- motion sensation
- reaction to the materials used or to wear debris created
- inflammation or swelling of your knee (synovitis)
- remodeling or deposits around the implant
- infection
- loss of or restriction in motion of the knee
- knee instability in the case of erosion of soft tissue stabilizing structures around the knee due to device implantation/dislocation/malposition/extraction/infection
- nerve disorder (peripheral neuropathies), nerve damage, neurovascular injury or compromise, circulatory compromise
- allergic reaction
- permanent, irreversible damage to knee cartilage
- permanent damage to the collateral ligament of the inside of the knee (medial collateral ligament) while shaving the medial meniscus cartilage tissue
- unknown systemic side effects of debris from device
- inability to implant device at the time of surgery
- chronic pain
- late complications that are currently unknown (destruction of the knee joint)
- late infections
- sepsis
- presence of the device may make subsequent surgery more difficult and may require removal
- additional surgery (revision) because of a failing device, or revision to an alternate procedure due to a poor outcome
- device breakage during removal in case of a subsequent surgery
- scarring (fibrosis) which may interfere with knee function or make revision more difficult
- unknown effects of systemic uptake of breakdown products and remote disposition in other tissues/organs (lymph nodes, liver/kidney)

3 STUDY DATA ELEMENTS

3.1 Primary Data Elements

The primary data element components of the Overall Success are as follows:

3.1.1 Effectiveness:

The KOOS Pain Subscale and KOOS Overall (Average of the 5 KOOS Subscales) relative to baseline — all at 24 months.

3.1.2 NUsurface Device Related Complications:

The device related complications of the NUsurface Meniscus Implant during the 24-month post-operative period in regard to secondary surgical intervention of the NUsurface device.

3.1.3 NUsurface Negative Imaging Outcomes

Negative imaging outcomes such as device dislocation and/or device fracture will be considered as automatic study failures in the Investigational Group.

3.1.4 Non-Surgical Control Post-Intervention Surgical Procedures:

The automatic treatment failures of the Control Group during the first 24-month period are any surgical intervention of the index knee.

Each of these individual components of Overall Success will be analyzed separately, but their analyses will not affect the 0.05 type I error rate (threshold p-value of 0.05 for significance) for the test of the primary superiority hypothesis.

3.2 Secondary Data Elements

3.2.1 Safety

Adverse events in either Group occurring at a rate of 5% or more at any post intervention follow-up period will be compared between study groups. Examples of safety measurements are:

1) Incidence rate of all adverse events through the 1.5, 3, 6, 12, and 24 month post-intervention periods.
2) Incidence rate of secondary (or primary for the non-surgical controls patients) surgical interventions through the 1.5, 3, 6, 12, and 24 month post-intervention periods.
3) Device-related complication is defined as a complication found to be caused by the device and device malfunctions (including severity), as assessed at each post-op period.

3.2.2 Effectiveness:

The effectiveness of the NUsurface® Meniscus Implant relative to the non-surgical standard of care will be evaluated at the 1.5, 6, 12 post-intervention periods using the KOOS Pain Subscale, KOOS Overall scale, and VAS scale. The effectiveness of the IKDC outcome will be evaluated at 6, 12, and 24 months relative to baseline.

4 DESIGN OF THE CLINICAL INVESTIGATION

4.1 General Introduction

The purpose of the study is to test whether the NUsurface Meniscus Implant meaningfully improves health outcomes of the appropriately selected target patient population, which includes Medicare age subjects. The protocol design meets the current Medicare study requirements, answers questions of importance and potential benefit to Medicare and its beneficiaries, and does not only test toxicity or disease pathophysiology in healthy individuals.

The scientific rationale for the study is well supported by available scientific and medical literature. The study results will not duplicate existing knowledge, even for the control group since the study evaluates the time course health outcomes of non-surgical treatments already in common clinical use. The study design is methodologically appropriate and the anticipated number of enrolled subjects is adequate to answer the *bona fide* clinical research questions being studied.

The study will be in compliance with all applicable U.S. Federal regulations concerning the protection of human subjects, clinical trials, and Institutional Review Boards found in 21 CFR Parts 50, 56, and 812 and/or 45 CFR Part 46. The study will be conducted according to appropriate standards of scientific integrity such as those set by the International Committee of Medical Journal Editors and will be registered on the National Institutes of Health's National Library of Medicine's ClinicalTrials.gov website by the Sponsor prior to treatment of the first study subject. The website will be updated when the results of the pre-specified outcomes, whether positive or negative, are published following the requirements of the International Committee of Medical Journal Editors. It is intended that a full report of the outcomes of the study will be made public no later than 3 years after the end of data collection and that the publication will be hastened if the study is terminated early. The Sponsor is capable of successful completion of the study and will have the supporting infrastructure to assure protocol adherence and that the intended patient protections are in place.

The study protocol inclusion/exclusion criteria are not expected to exclude the recruitment of traditionally underrepresented patient populations. The study results are expected to be generalizable to the entire study population from age 30 to 75 inclusive, including the Medicare population (age 65-75 inclusive) and determine whether Medicare aged patients may benefit from the intervention. Age, disability, or Medicare/Medicaid eligibility are not known to have any effect on the results and even if such an effect is found to exist, the randomized study design causes the effect equally in both treatment arms of the study, thus allowing the effect of the NUsurface Meniscus Implant to be determined.

The study design is a multi-center, prospective, randomized, interventional, superiority clinical trial. The IDE pivotal study will be conducted at multiple centers, with no center enrolling more than 35% of the total number of patients. The patients will be randomized between the Investigational and Control Groups at a 1:1 ratio (62-64 in each Group).

The pivotal study has been designed to demonstrate safety and effectiveness, and measure device-related complications of the device relative to baseline and standard of care controls.

4.2 Study device and control

The patients enrolled in this study will be randomized between the Investigational and Control Groups at a 1:1 ratio. The patients randomized to the Investigational Group will receive the NUsurface® Meniscus Implant. The patients randomized to the Control Group of the study will receive Non-Surgical Care (the current standard of care for this patient population, explained in further detail in Section 5.2.2).

4.2.1 If randomized to the Investigational Group:

Surgery is scheduled after final evaluations of inclusion/exclusion criteria and informed consent are checked. If confirmed, the NUsurface® Meniscus Implant will be implanted using the recommended surgical technique and rehabilitation protocol as well as the investigator's standard post-op protocol for meniscectomy.

4.2.2 If randomized into the Control Group:

Based upon a review of the medical literature, the most appropriate treatment for patients randomized to the Control Group is non-surgical care It is anticipated that the patients randomized to the Control Group will have better early results than the Investigational Group initially primarily because of the absence of a surgery from which to recover.

To standardize this Control Group treatment across all sites, a treatment algorithm has been established based on literature and input from clinicians in this field. Each patient randomized to the Control treatment will begin care with a list of Pharmacological and Non-surgical Treatment Options (known as the Baseline Treatment). These treatment options can be administered throughout the length of the study. The investigator has flexibility to start and/or stop these acceptable treatments at his/her discretion (as long as there is a minimum of 3 months of documented Baseline Treatment during the course of the study).

Baseline- Pharmacological and Non-surgical Treatment Options

Options Allowed in this Study

- Non-prescription drugs, creams, vitamins, and supplements
- Prescription or Non-Prescriptions NSAIDs
- Non-weight bearing and/or open chain physical therapy or self-administered exercise
- The following weight bearing exercises: cycling, elliptical, and/or leg presses or other physical therapy directed closed chain exercises
- Ice or heat therapy
- Compression sleeves, braces, crutches, and/or canes for the index knee
- Body weight reductions
- Limitations in activities
- Shoe inserts or other types of orthotic devices

Options Not Allowed in this Study

- Platelet Rich Plasma (PRP Injections)
- Acupuncture
- Any other treatment device that does not have regulatory approval for use
- Any surgical treatment requiring taking the patient to an operating room to cut into the index knee

In addition to these Baseline Treatment Options, two additional treatment modules are available to the investigator to treat the Control Group:

Module A- Intra-Articular Injections with Corticosteroids

Intra-articular injection of a corticosteroid, such as 40mg of Triamcinolone (e.g. Aristocort or Kenalog). If joint effusion is present, consider aspiration prior to injection.

This module is a minimum two-month period. Steroid injections can be repeated and evaluated at the investigator's discretion. No corticosteroids may be administered within 6 months of the 24 Month follow-up visit.

Module B- Intra-Articular Injections with Hyaluronic Acid (HA)

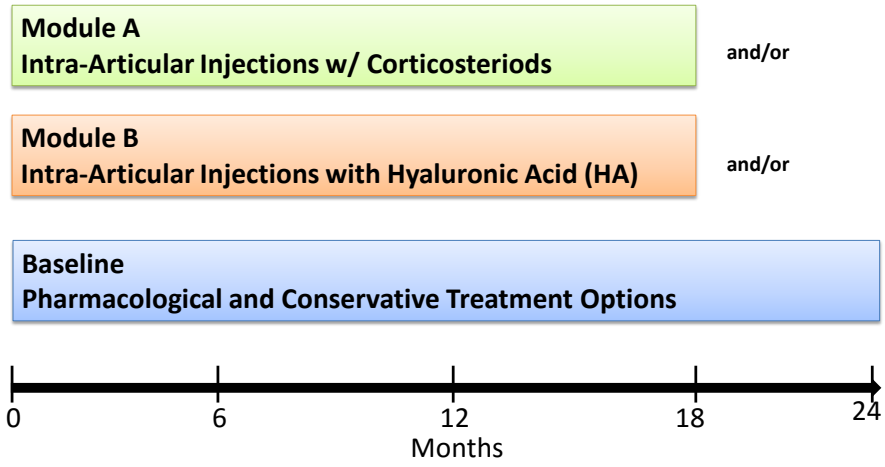
Intra-articular injection of a hyaluronic acid treatment, such as SYNVISC® HA Injections. If joint effusion is present consider aspiration prior to injection.

This module is a minimum two-month period. HA injections can be repeated and evaluated at the investigator's discretion. No HA may be administered within 6 months of the 24 Month follow-up visit.

Patients may enter the study starting with Baseline and/or either Module

- Baseline only
- Baseline + Module A
- Baseline + Module B
- Baseline + Module A + Module B

Palliative Treatment Algorithm for Control Patients in the NUsurface® Randomized Study



Note: If there are any questions regarding whether a treatment should or should not be considered for the non-surgical standard of care control patients, the site should contact Dr. Elliott Hershman, the Medical Director of the Study.

Control Patients will not be eligible to receive the NUsurface device so as to prevent any bias towards failing in order to receive the study device.

4.3 Subject

4.3.1 Inclusion criteria

In the opinion of the investigator, if ALL of the following 9 conditions are applicable for the index knee, then the patient is included if he/she:

1) Had > 6 months ago a medial partial meniscectomy as confirmed by patient history and MRI
2) Has a KOOS Pain of ≤ 75 (100 being the highest attainable and no pain)
3) Is between age 30 and 75 years (inclusive) at the time of study treatment
4) Has neutral alignment ±5º of the mechanical axis, as measured from the angle formed by a line drawn from the center of the femoral head to the medial tibial spine and a line drawn from the medial tibial spine and the center of the ankle joint
5) Has ≥ 2 mm intact medial meniscal rim capable of being fitted with a NUsurface® device AND is also recommended for the baseline non-surgical (and, if likely to receive benefit, any injection) therapies to be administered in the study.
6) Is willing to be entered into either arm of the study: implanted with the NUsurface device OR treated with the recommended control arm therapies.
7) Is able to do the study required follow-up visits, questionnaires, X-rays and MRI's
8) Is able to read and understand the English language
9) Is able and willing to understand and sign the Informed Consent Form

4.3.2 Exclusion criteria

In the opinion of the investigator, if ANY of the following 35 conditions are applicable for the index knee, then the patient is excluded if he/she:

1. Has a symptomatic knee because of a tear that could be addressed by a repeat partial meniscectomy leaving > 4 mm of medial meniscus rim
2. Has evidence of a Outerbridge Grade IV cartilage loss on the medial tibial plateau or femoral condyle that potentially could contact a NUsurface implant (e.g., a focal lesion > 0.5 cm^2 correlating to a circular defect of > 8 mm in diameter)
3. Has complete disruption of the posterior root attachment of the meniscus
4. Has lateral compartment pain and Grade III or Grade IV Outerbridge cartilage score in the lateral compartment
5. Has a varus or valgus knee deformity > 5º requiring a tibial or femoral osteotomy
6. Has a laxity level of more than Grade II (IKDC), primary or secondary to an injury of the anterior cruciate ligament (ACL) and/or posterior cruciate ligament (PCL) and/or lateral collateral ligament (LCL) and/or medial collateral ligament (MCL)
7. Has significant trochlear dysplasia, patellar instability or symptomatic patellar misalignment
8. Has patellar compartment pain and Grade III or Grade IV Outerbridge cartilage score in the patellar compartment.
9. Compared to a normal knee, has obvious radiological evidence of medial femoral squaring, anatomical variance in the medial tibial plateau, or irregularly shaped cartilage surface
10. Had an ACL reconstruction performed < 9 months prior to study treatment
11. Has a BMI > 32.5 at the start of study treatment

12. Decides to receive (if eligible and an option) allograft medial meniscus transplantation
13. Received any type of prosthetic knee implant made of artificial non-resorbable plastic, metal or ceramic, not including the NUsurface® Meniscus Implant
14. Has a knee flexion contracture > 10º
15. Has flexion < 90º
16. Had a previous medial femoral condyle surgery (not including microfracture) or High Tibial Osteotomy (HTO)
17. Has insufficiency fractures or avascular necrosis of the medial compartment
18. Has an active infection or tumor (local or systemic)
19. Has any type of knee joint inflammatory disease including Sjogren's syndrome
20. Has neuropathic knee osteoarthropathy, also known as Charcot joint
21. Has any medical condition that does not allow possible arthroscopy of the knee
22. Has neurological deficit (sensory, motor, or reflex)
23. Is currently involved in another investigation of the lower extremity
24. Anticipates having another lower extremity surgery during the study period
25. Is contraindicated for hyaluronic acid injections (i.e., patients with known hypersensitivity [allergy] to hyaluronan [sodium hyaluoronate] preparations); patients having knee joint infections or skin diseases or infections in the site of possible injections
26. Is contraindicated for corticosteroid injections (i.e., patients with allergy to any of the components or with idiopathic thrombocytopenic purpura)
27. Has received any corticosteroid knee injections ≤ 3 months prior to study treatment
28. Has chondrocalcinosis
29. Is on immunostimulating or immunosuppressing agents
30. Has ipsilateral or contralateral lower limb joint conditions that may affect ambulation or KOOS (e.g. have a leg length discrepancy > 2.5 cm [1 inch], causing a noticeable limp)
31. Is a female who is lactating, expecting, or is intending to become pregnant during the study period
32. Is an active smoker
33. Is mentally incapacitated (incapable of appraising or controlling conduct) or have mental disability (e.g., dementia or Alzheimer's)
34. Is a prisoner
35. Is a patient who has economic incentive not to improve

4.3.3 Subject withdrawal or discontinuation

Patients can withdraw from the study for any of the following reasons:

1. Patient requests early discontinuation.
2. Patient becomes Non-Compliant
3. Patient is lost to follow up.

Upon request, the patient can withdraw from the study at any time. The reason for withdrawal will be investigated and carefully documented in the Patient's Medical file and the appropriate section of the Case Report Forms. When a patient withdraws or is withdrawn from the study, the final evaluation and the follow up will be performed as completely as possible (to the extent to which the patient agrees to). In addition, any comments (spontaneous or elicited) or complaints made by the patient or any other physician not

related to the study but taking care of the patient subsequently will be carefully recorded in the Patient's Medical File and related section of the Case Report Forms.

Withdrawn patients will continue to be followed up for 7 days for AE occurrences and for 30 days for SAE occurrences.

Clinical data collected up until the moment of withdrawal will be used for analysis as defined in the current study protocol.

4.3.4 Point of Enrollment vs. Treatment

Point of enrollment is defined as the time at which a subject signs and dates the Informed Consent Form. Point of treatment is defined as the date of surgery or start of control therapy if the patient is not a bailout or screening failure.

4.3.5 Duration of the clinical investigation

If there is no gap in enrolment between Stage I and Stage II, it is anticipated that it will take up to 36 months to enroll 62-64 patients in each arm from the participating sites. Any gap in beginning of Stage II enrolment will be additive. Follow-up duration is 24 months resulting in a study duration of up to 60 months or more. Although the participation in the trial by the patients is planned to end at 24 months, investigators will be asked to continue to follow all subjects annually until the last patient enrolled has completed 24-month follow-up.

4.3.6 Number of subjects

62-64 in each study group. Stage I will be 32-33 in each group.

4.3.7 Enrollment period

Up to 36 months.

4.3.8 Bailout

If the patient was randomized and the treatment not started for any reason (bailout or screening failure), new patients may be recruited to complete the patient treatment goal according to the method described in the Statistical Plan.

4.4 Procedures

4.4.1 Clinical evaluations

The clinical evaluation procedures for this study are summarized in Section 2.5. Additionally, a time table summarizing follow-up visits and the necessary evaluations at each time point are found in Appendix A.

4.5 Case Report Forms

Case report forms are provided in a uniform design, each form heading requires identification of the hospital, patient and investigator and each visit is to be dated. Patient Reported Outcomes included in the Case Report Forms will serve both as source documentation and case report forms. Completed CRF's will

be reviewed and signed by the Principal Investigator (or designee). The CRF shall be kept on site until the Sponsor or its representative performs verification of all data. Faxes of the CRFs that have been filled out may be sent to the Sponsor and/or its Representative throughout the study.

Note: As forms are reprinted the CRF's may change slightly throughout the study for the sake of layout, clarity, or eliminating redundancy. If such a modification happens during the course of the study, the protocol will not be amended.

Investigators shall provide access to the hospital files and any other medical source document containing patient's study/medical information, to the Sponsor or its representative for them to perform source document verification and monitoring.

Investigators shall provide support to the Sponsor or its representative during the investigation to allow collection of fully scientific valid data.

5 STATISTICAL CONSIDERATIONS

Complete details of the study Statistical Plan are contained in a separate document. The following is a summary of its contents.

5.1 Statistical design

The NUsurface® Meniscus Implant Randomized Study is a multi-center, prospective randomized, interventional clinical trial to test the hypothesis that the NUsurface implant is superior to the non-surgical standard of care in treating the target population. Patients who meet the inclusion/exclusion criteria will be assigned by balanced randomization into one of two groups. This guarantees, at least on average, that patient characteristics such as gender, weight, percent left knee, and baseline pain, will be similar in the two groups.

For the NUsurface® Meniscus VENUS IDE study, the following hypothesis of superiority will be tested: At two years after treatment, recipients of the NUsurface® Meniscus Implant will have a higher probability of the binary "Overall Success" outcome than recipients of the Non-Surgical Standard of Care. The null hypothesis is the converse: At two years after treatment, the probability of Overall Success will not be greater in NUsurface® Meniscus Implant recipients. (Campbell 1993)

5.2 Randomization Ratio

Giving potential patients a 1 to 1 randomization ratio (50:50 chance) of receiving either the NUsurface® device or non-surgical standard of care suggests "equipoise," i.e., either Arm of the study is acceptable and both have an equal chance of success.

5.3 Confirmation of Demographic Homogeneity and Baseline Pain Scores Between the Two Groups of the Study

Baseline balance of the Investigational and Control Groups will be checked. As appropriate, comparisons between the two treatment groups will be made using Student's t (e.g. for age and BMI at treatment), chi-square (e.g., for gender and treated side), and Cochran-Mantel-Haenszel chi-square tests for variables, if any, with ordinal values such as "none, mild, moderate, severe."

5.4 Poolability of Data

At the conclusion of the study, as described in the statistical plan, the sites will be compared for poolability of the data to identify any sites with unusual or significant inhomogeneity in the NUsurface Meniscus Implant minus Standard of Care difference of the Overall Success outcome. The between-treatment *difference* of the outcomes will be examined for homogeneity across sites; it is not problematic if individual sites have elevated or lower success rates for both study groups. If the results show the data are poolable, they will be pooled.

5.5 Definition of Patient Overall Success / Overall Failure

Each patient at 24 months will be classified individually as either an Overall Success or Overall Failure in this study. Figure 2 shows the flowchart to be used to determine the success/failure status of each patient.

Individual patient Overall Success is defined as follows: at 24 months post treatment, to be an Overall Success the patient must meet all of the following:

	Investigational Group	Control Group
Overall Success	Provisional PRO **AND** Positive MRI **AND** No device removal	Provisional PRO **AND** No surgical intervention to index knee for 24 months
Overall Failure	Negative PRO KOOS **OR** Negative MRI **OR** Device removed/replaced for any reason	Negative PRO KOOS **OR** Any surgical intervention to index knee during 24 months of study

Where:

- **Provisional PRO** is defined as**:**

$KOOS_{pain} \geq 86.1$ **AND** $KOOS_{Overall} \geq 86.2$ at 24 Months

OR

$KOOS_{pain}$ Δ (improvement from Baseline) ≥ 20 points at 24 Months **AND** $KOOS_{Overall}$ $\Delta \geq 20$ points at 24 Months **AND** $KOOS_{pain} \geq 40$ points at 24 Months

- **Negative PRO KOOS** is defined as**:**

$KOOS_{pain} < 86.1$ **OR** $KOOS_{Overall} < 86.2$ at 24 Months

AND

$KOOS_{pain}$ Δ (improvement from Baseline) ≤ 19 points at 24 Months **OR** $KOOS_{Overall}$ $\Delta < 20$ points at 24 Months **OR**

$KOOS_{pain} < 40$ points at 24 Months

- **Positive MRI** is defined as MRI images taken at 12 OR 24 Months that show the device in one piece and not subluxed more than 50% of the device length (dislocated)
- **Negative MRI** is defined as MRI images taken at 12 OR 24 Months that show the device fractured in two (or more) pieces and/or subluxed more than 50% of the device length (dislocated)

Further justification of the above Overall Success definitions is contained in section 6.1.5. However, these definitions yield a composite of patient pain, function, activity, and quality of life, while requiring that the patient either not have the device removed or, if a non-surgical control patient, not need surgery.

5.5.1 Study Arm Overall Success

Each Study Arm Overall Success Proportion at 24 months is defined as:

$$\frac{no.(Overall\ Success\ Patients)}{no.(Overall\ Success\ Patients) + no.(Overall\ Failure\ Patients)}$$

The two study arm success proportions will be compared as defined in the Statistical Plan for superiority.

5.5.2 Justification for Composition of Overall Success/Failure

Overall Success or Failure for each patient is determined using a composite of variables. To be a success each patient must meet pre-defined KOOS goals and not be an automatic study failure. These two factors mean the Overall Success variable represents a composite measurement reflecting all aspects of the study. KOOS has five sub-scales: symptoms, pain, activities of daily living, sports/recreation, and quality of life. To use KOOS as a part of the definition of Overall Success/Failure means that for the patient to be a Provisional Overall Success is if the 5 different components improve on average ≥ 20 points. KOOS Pain

has an entrance criterion (≤ 75), a definition of success if KOOS Pain for the patient is ≥ 86.1 at 24 months, and a minimum KOOS Pain Score of ≥ 40 at 24 months at 24 months as a requirement. An additional part of the composite nature of the Overall Success/Failure criteria is that negative MRI outcomes showing device fracture or subluxation greater than 50% of the device length or a post-treatment surgical intervention will cause the patient to become an automatic Overall Failure.

5.5.2.1 The Significance of the 20-point KOOS Improvement

A 10-point improvement in KOOS is considered by Roos [16] the inventor of KOOS, to be the Minimal Clinically Important Difference (MCID). The MCID does not however, guarantee that the results are "clinically important." The AAOS Guideline, "Treatment of OA of the Knee (Non-Arthroplasty)" (2008), states that in order for results to be "clinically important" they need to show significant improvement from baseline. Therefore, for the IDE study a more challenging KOOS success criterion of two times the MCID (20 points) has been selected for determining that a patient has a clinically important KOOS success. Further details of how KOOS success is determined can be found in the Statistical Plan. Further justification of the use of ≥ 20 points in KOOS as part of the definition of Overall Success is contained in Appendix F to the study protocol. In summary, 20 points is a natural dividing point to a 100 point scale that contains 5 parts and has 5 answers with each 20 points representing a level of knee disability. Requiring a ≥ 20 point improvement in KOOS means that to be a success, a patient, regardless of his or her pre-treatment or baseline level, would be required to have an increase of one knee disability level. For all these reasons, having a ≥ 20 point KOOS improvement be a success criterion (one level improvement in disability level) was viewed as an appropriate requirement for determining a successful, clinically important difference in KOOS outcome.

Once calculated, the percent Overall Success at 24 months for the two Groups of the study will then be compared by a one degree of freedom chi-square test with significance defined by a p-value of 0.05 or less as described in the statistical plan.

5.5.3 Modified Intent-to-Treat (ITT) Analysis

The primary analysis will be guided by a modified Intent-to-Treat (ITT) analysis as described in the statistical plan for the IDE.

5.5.4 Interim Analysis of the Data

Hypothesis testing and a decision-making interim analysis about sample size and whether to proceed with the study will be performed when 16 patients in each group reach 2 years.

Interim reviews of the data may be performed at time points other than at the above predetermined point of the study. However, these interim reviews will not be used for making decisions about the study's primary effectiveness hypothesis.

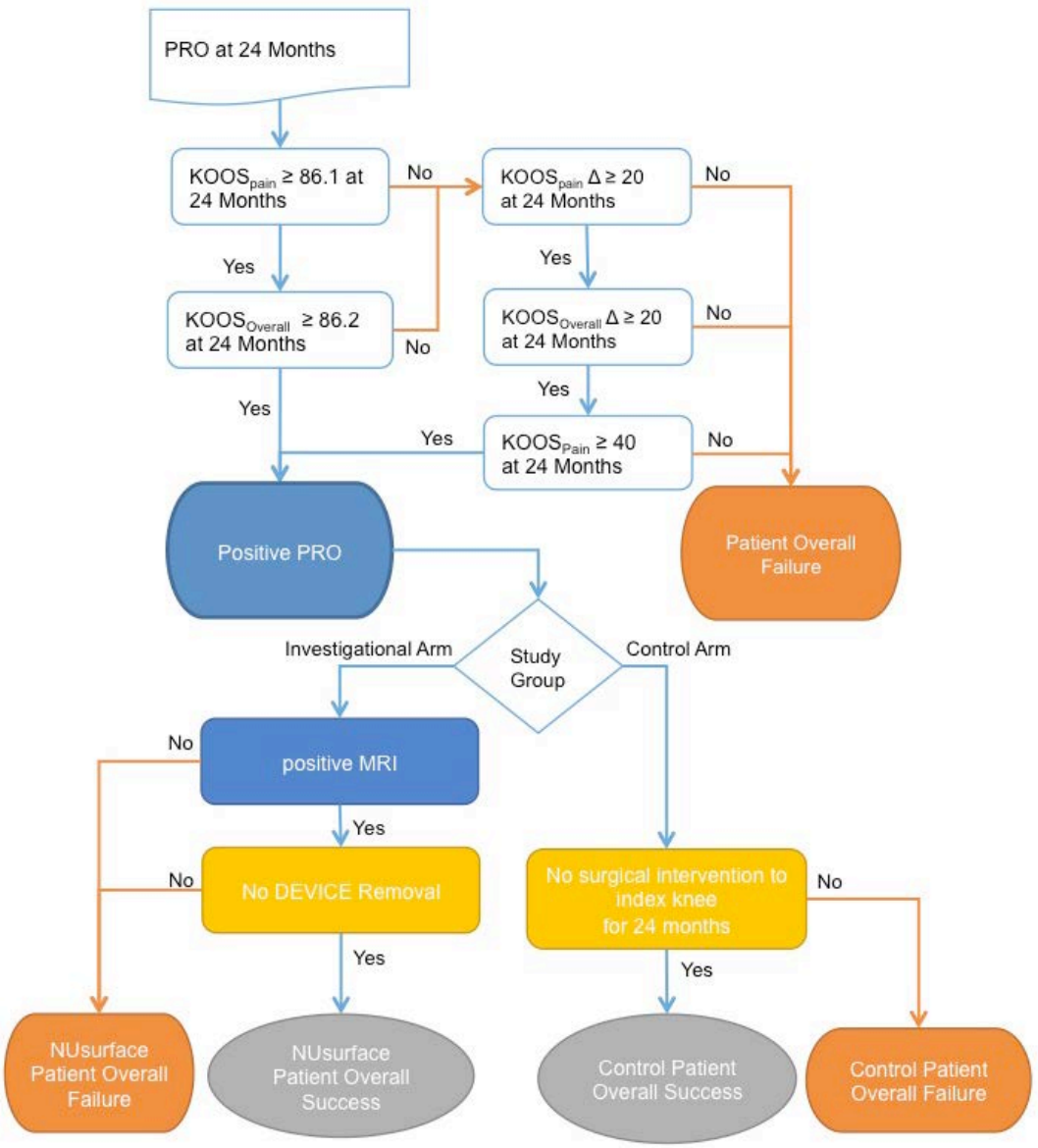


Figure 2 Patient Overall Success/Failure flowchart to be used in the NUsurface VENUS study protocol.

5.5.5 Study Data Elements:

5.5.5.1 Primary Statistical Data Elements

The primary statistical data element components of the Overall Success are as follows:

- Effectiveness: The KOOS Pain Subscale and KOOS Overall relative to baseline — all at 24 months as described in 6.5.

Investigational Group Device-Related Secondary Surgical Interventions or Negative MRI finding: The device related secondary surgical interventions of the NUsurface® Meniscus

- Implant during the 24-month post-operative period and negative MRI images as defined in 6.5.
- Control Group Post-Treatment Surgical Procedures: The treatment failures of the Control Group are defined as any surgery on the index knee medial compartment during the 24-month post-operative period.

The results will be analyzed according to the Statistical Plan for the study.

5.5.5.2 Secondary Statistical Data Elements

- Safety: Adverse events in either Group occurring at a rate of 5% or more at any post-treatment follow-up period will be statistically compared, if applicable, between study groups. Examples of safety measurements are:
  1. Incidence rate of all adverse events through the 1.5, 3, 6, 12, and 24-month post-treatment period.
  2. Incidence rate of secondary (or primary for the control group patients) surgical interventions through the 1.5, 3, 6, 12, and 24-month post-treatment period.
  3. Device-related adverse event are defined as a complication caused by the device and/or a device malfunction (including severity), as assessed at each post-op period.

- Effectiveness: The effectiveness of the NUsurface® Meniscus Implant relative to the non-surgical standard of care will be evaluated at the pre-op, 1.5, 6, and 12-month post-intervention periods using KOOS Pain and KOOS Overall. The effectiveness of the IKDC will be evaluated at 6, 12 and 24 months relative to baseline. The effectiveness of Pain VAS outcomes will be evaluated at 1.5, 6, 12, and 24 months relative to baseline.

5.5.6 Additional Statistical Analyses

Additional secondary analyses of the data obtained in this study may be performed and are described in the Statistical Plan for this study. For example, the sub-group of the Medicare age population (age ~65-75 inclusive) will be statistically analyzed to determine whether Medicare age patients benefited from the intervention of the investigational device and whether their results were poolable with, and therefore not statistically different from, the study group as a whole.

5.6 Statistical Power and Sample Size

The statistical power of the study is 80%. The calculated full sample size is 62-64 subjects in each study arm.

6 DATA MANAGEMENT

6.1 Patient Identification and Confidentiality

Patients will be identified on all CRF's by a unique reference referred to as a patient identifier. CRF's are confidential documents and will only be available to the Sponsor and its consultants/representatives, the Investigator, and if requested by any advisory committee and regulatory authorities. The Principal Investigator for each center will maintain as part of the study file a list identifying all patients entered into the study and their patient identifier reference and their informed consents.

6.2 Case Report Forms (CRFs)

The CRF's contain confidential material. Specific instructions to complete the CRF's shall be provided to the Investigator and other site personnel as appropriate.

The Investigator is responsible for reporting appropriately and in a legible manner the requested information in the CRF's.

The Sponsor or its representative shall verify the data entered into the CRF's against hospital source documents to ensure accuracy and completeness of the data, prior to retrieving the CRF's, from the study center.

6.3 Monitoring

The Sponsor or its representative will visit the study center periodically during the study to ensure adherence to the study plan, accurate data recording on the CRF's and to monitor recruitment rates and adherence to follow-up schedules. The Investigator shall permit and assist this person to carry out verification of completed CRF's against data in the source documents.

The Sponsor or its representative will be notified about any problems relating to facilities, technical equipment or medical staff at the study center. During the study monitors shall check that appropriate written informed consents have been obtained. The Sponsor or its representative shall also be responsible for notifying such deficiencies in writing to the related study center's principal Investigator and convene with the study center personnel appropriate and timely corrective actions.

During the monitoring visit the Monitor will perform a review of study eligibility, Inclusion/Exclusion criteria, any reports of device malfunction, any events meeting the criteria for serious adverse event reporting as well as safety and performance endpoints. Additional reviews will be performed as warranted by the findings of previous monitoring visits. Key variables (demographics, inclusion/exclusion criteria and safety) on the CRFs will be compared with each patient's source documents. Any discrepancies will be noted and resolved.

6.4 Source documentation

Regulations require that Investigators maintain information in the study patient's medical records, which corroborate data collected on the CRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the sponsor and/or regulatory inspections:

- Medical history/physical condition of study patient before involvement in the study sufficient to verify protocol entry criteria.
- Medical record documenting that informed consent was obtained for the patient's participation in the study.
- Description of the device implantation procedure (Material used, drugs administered during the procedure, date, time, radiographic findings).
- Dated and signed noted for each study patient visit including results of examination.
- Description of AEs and follow-up of the AEs (minimal event description, severity, onset date, duration, relation to NUsurface device, outcome and treatment for device).
- Notes regarding concomitant medications taken during the study (including start and stop dates).
- Patient Reported Outcomes, such as the KOOS, IKDC, EQ-5D, Pain VAS and WOMET questionnaires will be considered both as Source Data and CRFs.
- It is allowed by the study sites to make use of study related worksheets to collect the source data required by the study protocol
- The monitors (or CRAs) are allowed to support the site research staff to develop study specific worksheets to be used for source data collection purposes
- Study patient's condition upon completion or withdrawal from the study.

6.5 Audit and supervision

Investigator sites and study documentation may be subject to Quality Assurance audits during the course of the study. In addition, inspections may be conducted by regulatory bodies at their discretion, during and after study completion.

6.6 Database management

A validated system will be used to analyze the database for the final PMA submission.

6.7 Record retention

The Sponsor will maintain copies of correspondence, data, shipment of devices, adverse device effects, and other records related to the clinical trial. All study records and report will remain on file at sites for a minimum of 2 years after completion of the study, and will further be retained in accordance with local and international guidelines as identified in the clinical study agreement. Study records are to be discarded only upon notification by the Sponsor. The Investigator must contact the study Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be contacted if the Investigator plans to leave the Investigational Site.

7 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The Investigator and the Sponsor will agree to any changes to this study plan, prior to its implementation. Any study plan amendment is required to be submitted for information/consideration to the reviewing IRB and the appropriate regulatory authority.

IRB approval will be requested for any change to this study plan, which could affect the safety of the subjects, the scope or design of the study, an increase of number of subjects treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

Minor procedural changes or clarifications will be implemented by Study File Notes and documented at the Sponsor and at Site, if appropriate.

8 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the Study Plan.

Investigators are required to obtain prior approval from the sponsor before deviating from the Study Plan, except when necessary to protect the life or physical well-being of a patient in an emergency. Such approval will be documented in writing and maintained in the study files. Prior approval is generally not expected in situations where circumstances are beyond Investigator's control (e.g. patient did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation.

Deviations shall be reported to the study sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the patient in an emergency. Patient specific deviations will be reported on the Protocol Deviation Form in the CRF. Non-patient specific deviations will be reported to the sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with the reviewing IRB reporting policies and procedures.

Regulations (ISO 14155) require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

9 DEVICE ACCOUNTABILITY

9.1 Device Accountability

The NUsurface® meniscus implant device used in this study is not approved by the FDA for commercial use. This study is being performed under an Investigational Device Exemption and the implant inventory needs to be accounted and traced. The NUsurface implant devices should only be used for treating patients

in the IDE study. Documentation of the device accountability will be kept at each site and used in the close-out of the study to verify the location or disposition of all investigational inventories.

9.2 Receipt of Supplies

Each site is responsible for taking care of any study related inventory.

9.3 Storage

At each study site, all study supplies will be stored in a safe area to prevent unauthorized access.

9.4 Unused Supplies

At the conclusion of the study, a final inventory will be performed, with the number of unused NUsurface devices. At the Sponsor's request, the Investigator shall return to the Sponsor any remaining supply of the device or dispose of the device as the Sponsor directs.

10 INFORMED CONSENT PROCESS

After explaining the rationale for and the details, aims and objectives of the study, the risks and benefits of alternative treatments, and the extent of a patient's involvement, the Investigator or their designee must obtain from patients a written informed consent for their inclusion in the study. All patients must sign and date the informed consent.

The Investigator or his designee is responsible for ensuring that no patient is subject to any IDE study-related activity before the patient has given his/her written informed consent. For this reason, the Investigator or their designee has to sign and date the informed consent document.

A copy of the fully signed informed consent document is to be given to the patient.

The informed consent process or the patient's participation in the clinical trial shall be documented in the patient's medical records.

All information provided to patients including any advertisements for the investigation within the trial center or in the public press needs approval of both the Sponsor and IRB prior to being presented to the patients under any format.

11 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

11.1 Definition of Adverse Event (AE) / Adverse Device Effect (ADE)

An AE/ADE is any adverse event change from the subject's baseline condition, i.e. any unfavourable and unintended sign including an abnormal laboratory finding, symptom or disease, which is considered to be

clinically relevant by the physician, that occurs during the course of the clinical investigation, whether or not considered related to the medical device.

Adverse Event /Adverse Device Effect include:

- Exacerbation of a pre-existing disease,
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition,
- Disease or medical condition detected or diagnosed after treatment (with/without the medical device) even though it may have been present prior to the start of the clinical investigation,
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the clinical investigation,
- Events considered by the investigator to be related to clinical investigation-mandated procedures,
- Abnormal assessments, e.g., EKG and physical examination findings, must be reported as AEs/ADEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the clinical investigation,
- Laboratory test abnormalities must be reported as AEs/ADEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the clinical investigation lead to interruption or permanent discontinuation of medical device (or treatment).

AEs/ADEs do not include:

- Pre-planned interventions (or treatment) or occurrence of endpoints specified in the CIP are not considered AEs/ADEs, if not defined otherwise,
- Medical or surgical procedure, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE/SADE narrative,
- Pre-existing disease or medical condition that does not worsen,
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons,
- Misuse of either medical device or concomitant medication without any signs or symptoms.

11.2 Serious Adverse Events (SAEs) / Serious adverse device effects (SADEs)

A Serious Adverse Event (SAE) / Serious adverse device effect is defined as any AE/ADE fulfilling at least one of the following criterion:

- leads to a death,
- leads to a serious deterioration in the health of the subject that
    - resulted in a life-threatening illness or injury,

- resulted in a permanent impairment of a body structure or a body function,
- required in-patient hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

- is an important medical event that may not immediately result in death, be life-threatening, or require hospitalization but may be considered as SAEs/SADEs when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

Life threatening 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 that hypothetically might have caused death if it were more severe.

11.2.1 Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room. An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE/SADE and should be reported as an AE/ADE only:

- Treatment on an emergency or out subject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

11.2.2 SAEs /SADEs related to study-mandated procedures

Such SAEs /SADEs are defined as SAEs/SADEs that appear to have a reasonable possibility of causal relationship (i.e. a relationship cannot be ruled out) to study-mandated procedures (excluding administration of medical device) such as discontinuation of subject's previous treatment or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

11.3 Severity of adverse events/adverse device effects

The severity of clinical AEs /ADEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE/ADE worsens during medical device administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE /ADE resolves spontaneously or may require minimal therapeutic intervention;

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE/ADE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE/ADE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE/ADE (SAE/SADE) may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe synovitis). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations (SAE/SADE).

11.4 Relationship to study treatment

For each event, the investigator and the Sponsor independently will assess the causal relationship between the treatment (medical device or control treatment) and the AE/ADE (SAE/SADE) using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE/ADE (SAE/SADE):

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study treatment
- Is biologically implausible and does not follow known response pattern to the suspect medical treatment (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Possible related

- Follows a reasonable temporal sequence form administration of the study treatment.
- May follow a known response pattern to the study treatment (if response pattern is previously known).
- Could not be reasonable not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable.

Definitely related

- Follows a reasonable temporal sequence form administration of the study treatment.
- Follows a known response pattern to the study treatment (if response pattern is previously known).

In the event that the investigator and the Sponsor disagree on the relationship, the Medical Director will make the final decision.

11.5 Reporting procedures

11.5.1 Reporting procedures for AEs/ADEs

A dedicated form is designated to AEs/ADEs in the case report form. The following details must thereby be entered:

- Description of event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Pattern (once, continuous, intermittent)
- Serious (no / yes), according to the definitions provided onto the form
- Unexpected (no / yes)
- Relation to medical device (unrelated, possibly related, definitely related)
- Relation to procedure (unrelated, possibly related, definitely related)
- Action taken (none, medication given, medical procedure, withdrawal from study, change of the control treatment program, other)
- Outcome (resolved, improved, unchanged, worsened, patient death)

Patients will be carefully monitored during the study for possible adverse events. Any adverse events observed will be investigated by the Investigator. Appropriate treatment of the patient will be initiated and future follow up will continue.

The Investigator will attempt to assess the involvement of the study device (where applicable) in the adverse event. All observations and study findings, including the nature and severity will be documented on the appropriate case report forms.

Additionally, if the study device is removed, please contact the Sponsor immediately to determine the necessary course of action (see also par 12.5.2).

11.5.2 Reporting procedures for SAEs/SADEs

In the event of a SAE/SADE, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the principal investigator immediately. The following details should be at least available:

- Patient initials and number
- Patient data: date of birth, sex, study group, index knee, relevant medical history and current medical condition, device size and lot no. (if applicable)
- A full description of the SAE/SADE occurred
- Start Date, if event is on-going or eventual stop Date
- Severity (mild, moderate, serious)

- Location of occurrence (home, hospital, other)
- Relation to device (none, possible, definitely)
- Relation to procedure (none, possible, definitely)
- Outcome:
    - Patient recovered with no lasting harm,
    - The symptom(s) persisted but did not require medical / surgical treatment
    - The symptom(s) persisted and required medical / surgical treatment
    - Patient died
- Criterion of seriousness:
    - Patient death
    - Led to serious deterioration in health of the patient that:
        - Resulted in permanent impairment of a body function or to a body structure
        - Resulted in medical or surgical intervention to prevent permanent impairment
        - Resulted in in-patient hospitalization or prolongation of existing hospitalization
        - Resulted in a life-threatening illness or injury
- Medication and procedures used to treat the event
- Laboratory and radiology data (if applicable / available)

The written report is intended (if required) to be completed in two different time points:

- Initial report: Informs about what has happened (AE/ADE assessed as serious), if there is a relationship to the medical device and which action was set.
- Follow up-Report: informs about the outcome

The Investigator or designee will report all serious adverse events and adverse device effects to the Sponsor by telephone or fax within three working days (contact details on par 12.5.2). The Investigator or designee will provide a detailed written report within 7 working days. Serious adverse events need to be reported to the IRB. All other adverse events will be captured on the form for the next scheduled visit. The Sponsor will discuss with the Investigator, and perhaps the Data and Safety Monitoring Board (DSMB) as appropriate, these serious adverse events.

11.5.3 Emergency contact details

Name	Richard Treharne, PhD
Title	Vice President – Clinical & Regulatory
Institution	Active Implants LLC
Address	5865 Ridgeway Center Parkway, Suite 218 38120 Memphis, TN – U.S.A.
Phone Number	+1 901 762-0352 Ext 20
Fax Number	+1 901 767-4205
E-mail	rick.treharne@activeimplants.com

12 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

As determined by the Medical Director, the Sponsor, the DSMB, the FDA, and/or pre-determined stopping rules described in 13.1, the clinical study may be suspended or terminated if study subjects experience too many serious adverse events as a result of the direct failure of the device.

In the case of a suspension the Sponsor will immediately stop all patients' recruitment and will consult with the IRB, with the company consultants and with the study Investigators whether the study may continue or should be terminated.

12.1 Study Enrollment Suspension Rules

To prevent unreasonable risk to patient health and to allow for adequate patient protection, IDE study enrollment suspension rules are part of the protocol. These enrollment suspension rules are in place to protect the health, safety, and welfare of future study enrollment patients in the event that device-related safety issues are detected, one or both study treatment arms demonstrates a clinically significant worsening of pain, or new safety risk information is discovered during the course of the study.

This protocol allows three different levels of review of the clinical results--any one of which may trigger suspension of further enrollment of study patients. The first level is the Sponsor's pre-determined rules that would cause automatic suspension of further enrollment of new patients in either or both arms of the study. The second level is a review by the DSMB. At any time, regardless of the Sponsor's pre-determined rules, the DSMB, based upon their medical judgment, can suspend further enrollment. The third level of review is FDA which after review of the Sponsor's reports of NUsurface patients can ask for a suspension of further NUsurface patient enrollment.

If any of these three review levels causes a suspension of enrollment, an investigation of cause and risk prevention mitigation would be started. After review of the results and with DSMB approval and FDA consent, enrollment may be re-started.

12.2 Sponsor's Device-Related Safety Thresholds for Automatic Enrollment Suspension:

The Sponsor's threshold for immediate automatic suspension of further patient enrollment if either of the following two device-related safety issues is detected:

- Greater than 19 (>30% of 64 NUsurface implant patients) NUsurface device removals for any reason automatically suspends further enrollment of patients into the NUsurface arm of the study at ≤ 12 or ≤ 24 months if full enrollment is not yet completed.
- Greater than 16 (>25% of 64 NUsurface implant patients) NUsurface dislocations (whether diagnosed clinically, at removal, or by MRI imaging) will automatically suspend further

enrollment of patients into the NUsurface arm of the study at ≤ 12 or ≤ 24 months if full enrollment is not yet completed.

12.3 DSMB Suspension of Further Patient Enrollment:

The Data and Safety Monitoring Board (DSMB) may suspend further enrollment of study patients in either arm of the study at any time. The DSMB can consider whether the removals were device-related or not, whether the number of re-sizing cases is too high, and/or whether the removal of the device for other reasons (e.g. persistent pain) is/are a sufficient reason for triggering a suspension of further enrollment. The DSMB can also review cases of tears of the NUsurface device detected by MRI imaging that may not necessarily be considered a device-related safety issue as a reason for suspension of patient enrollment.

The DSMB will also review the cases of infection and try to determine of whether they were device-related or not, superficial or deep, early or late, common from skin or rare, above the same or below the infection rate seen for other implants (estimated to be no more than 2 in a 64 patient implant study), and make a medical judgment based upon all the known facts about whether further NUsurface enrollment should continue and/or changes in sterile protocol or antibiotic prophylactic treatment be recommended.

If it occurs during the study, the DSMB will also review any worsening of pain in patients as a whole from either arm of the study. Each set of 8 patients that reach 12 months follow-up will have their KOOS Pain average scores compared to their baseline scores. If a clinically significant increase in pain (>10 points lower on the KOOS Pain scale) is detected, then a review by the DSMB of whether to suspend further enrollment for that arm of the study would be performed.

The DSMB would also review any significant safety information discovered during study via device usage, non-clinical testing, or any other source and determine whether a suspension of further enrollment of either arm of the study is warranted.

In all of the above cases, the DSMB would use its medical judgment after an investigation of the particular facts to determine whether patient enrollment suspension, if not yet complete, should occur. If any of the above events occurs, the DSMB will be convened and a unanimous recommendation can stop further enrollment of new patients in the NUsurface and/or Control arms of the study. In instances where the DSMB has suspended study enrollment of one or both arms and an investigation determines that the suspension is no longer necessary, enrollment may be resumed upon a unanimous vote by the DSMB, which may include a recommendation to modify the protocol inclusion/exclusion criteria or other parts of the study protocol. The FDA would be notified of any such DSMB actions.

12.4 FDA Suspension of Further NUsurface Enrollment

During the IDE, the FDA will be provided annual reports on May 24th of each year. Those interim reports will contain information on all study patients and adverse events. The Sponsor will also provide the FDA with additional quarterly reports (on Aug 24, Nov 24, and Feb 24 of each year beginning after the first investigational device implantation in the U.S.) on all known adverse events for the IDE patients implanted with the NUsurface device. Based upon their review of all the adverse events, rates, and timing, the FDA will decide whether to discontinue or suspend enrollment on any future planned investigational subjects. The FDA will also decide when and if Stage II of the clinical study can begin.

13 PATIENT COMPENSATION

To prevent inducement, all patients will not be compensated for participation in the study. However, at long-term follow-up points the patients may be reimbursed for expenses incurred for returning for follow-up visits.

14 STUDY OBLIGATIONS

The study obligations for the Sponsor and the Investigator will be reviewed with the Investigator prior to the start of the study.

15 LIABILITY AND INSURANCE CONDITIONS

In case of any damage or injury occurring to a patient that is caused by the NUsurface device, the Sponsor has insurance coverage. A copy of this policy is on file at the Sponsor and in the Investigator Site File.

16 REVIEW PROCESS

16.1 Declaration of Helsinki

The study will be conducted according to the guidelines established in the Declaration of Helsinki (Appendix B). Patients will be free to withdraw from the study at any stage without prejudice to their subsequent treatment.

16.2 Institutional Review Board (IRB) Approval

The final version of the study investigation plan with the consent forms will be submitted to an appropriately constituted IRB by the Investigator prior to the commencement of the study. A copy of the IRB opinion/approval will be provided to the Sponsor, and provided to the FDA by way of IDE Supplement, prior to initiating the investigation in a particular center.

The Investigator will submit the appropriate documentation if any necessary extension or renewal of the IRB approval must be obtained. In particular major design changes of the device, amendments to the study investigation plan, the informed consent, or other written information provided to patients, and/or study procedures directly affecting the patient must be approved in writing by the IRB and FDA.

The Investigator shall report in writing to the IRB, any Serious Adverse Event whether device related or not according to the IRB required timelines but no longer than 10 days after the event's occurrence.

The Investigator will report to the IRB any new information that may affect the safety of the patients or the conduct of the investigation. Written summaries of the investigation status shall be sent by the Investigator to the IRB annually or more frequently as requested.

Upon completion of the investigation, the Investigator shall provide the IRB with a brief report of the outcome of the investigation as required by the local IRB.

17 WITHDRAWAL OF SPONSOR

Sponsor will withdraw from Sponsorship of the investigation at any site if

- major non-adherence to the study investigation plan is occurring.
- it is anticipated that the patient recruitment will not be adequate to meet the trial objectives.
- the Sponsor is no longer in business

In case Sponsor withdraws, follow-up for the patients already entered into the study will continue per the protocol.

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SUPPLEMENTS/APPENDICES

Appendix A- Study Timetable

Appendix B- Ethical Principles for Medical Research Involving Human Patients

Appendix C- Recommended NUsurface® Surgical Technique

Appendix D- Suggested Rehabilitation Program

Appendix E- Knee MRI Protocol for the NUsurface® Meniscus Implant

Appendix F- KOOS Disability Level Categories

Appendix A

Recruitment is expected to be completed within 18-36 months from local approval of the study. Study evaluation continues until 24 months of follow up has occurred with the last patient entered into the study. The following table is the study timeline evaluation methods. The Inter-op form and fluoroscopy only apply to those patients randomized to the investigational group.

Evaluation Method	Baseline	Treatment	1.5 Mo	3 Mo (**)	6 Mo	12 Mo	24 Mo	Add'l visits"
Assessments								
Screening	✓							
Treatment		✓						
3 Mo Questionnaire **				✓				
24 Mo Questionnaire							✓	
Patient Reported Outcomes								
KOOS	✓		✓		✓	✓	✓	✓
IKDC ^	✓				✓	✓	✓	
Pain VAS	✓		✓		✓	✓	✓	
WOMET	✓		✓		✓	✓	✓	
EQ-5D	✓		✓		✓	✓	✓	
Clinician Assessment								
Physical Examination	✓	✓	✓		✓	✓	✓	✓
Imaging								
Weight bearing (standing) A/P / Lat radiography*	✓							
45° Weight-bearing A/P knee x-ray (Rosenberg)	✓							
Merchant view knee x-ray	✓							
MRI index knee +	✓		✓			✓	✓	
Intra-op Fluoroscopy index knee		✓□						

*A 91-cm (36-inch) or 130-cm (51-inch) Standing Anteroposterior X-ray including the Hip and Ankle may be needed pre-intervention to check for alignment. (NOTE: For these cases a bilateral X-ray is preferred but not required.)

** According to potential investigators, partial meniscectomy or the non-surgical standard of care patients are not routinely seen at 3 months and may be evaluated by phone call.

^ SKEF is the Subjective Knee Evaluation Form of the IKDC and is used post-intervention.

+ MRI Scans performed at baseline and post-intervention (1.5, 12, 24 months) should be performed according to Appendix E

□ intra-operative fluoroscopy will be performed only to patients randomized in the study arm receiving the NUsurface device

At each visit, the doctor should document any adverse events as well as any medical intervention.

For the purposes of this study, patients seen from 6 weeks +/- 2 weeks from the baseline treatment date will be considered in the 1.5 month interval, 3 months +/- 2 weeks in the 3 month interval, 6 months +/- 1 month in the 6 month interval, 12 months +/- 2 months in the 12 month interval, 24 months +/- 2 months in the 24 month interval, 36 months +/- 2 months in the three year interval, and 48 months +/- 2 months in the four year interval. All patients reaching the 24 month interval will continue to be evaluated annually until the last patient entered when enrollment is stopped, reaches the 24 month time point. All follow-up visits that fall outside of these windows will be noted in the CRFs for that patient. Longer term follow-up may be performed, but these results will not affect the primary endpoint and determinations at 24 months.

Appendix B

WMA Declaration of Helsinki
Ethical Principles of Medical Research Involving Human Patients

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

B. General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be

evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

C. Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

D. Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E. Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F. Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

G. Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

H. Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the

study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in bio banks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I. Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

J. Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

K. Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

L. Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix C

RECOMMENDED NUsurface® SURGICAL TECHNIQUE

The recommended NUsurface® surgical technique can be found in Active Implants Document no. WI-00027, entitled: NUsurface® Meniscus Implant Training Manual. Version G available in December 2014 or later should be used and followed. However, in case of future amendment to the surgical technique, the document will be submitted to the FDA and/or other applicable regulatory bodies for their review and approval. All investigators will be immediately notified of the changes, after approval is granted.

Appendix D

Suggested* Rehabilitation Program for Investigational Patients

A. Immediate post-operative period (0 to appr. 7 days)

[1] Compression bandage
[2] Locking straight-leg knee immobilizer for ambulation (such as the DonJoy Trom or equivalent)
[3] Weight bear as tolerated (Cane or crutches)
[4] Remove immobilizer 3-4 times per day for active range of motion exercises
[5] Straight leg raising exercises three times per day
[6] Quadriceps setting exercises three times per day
[7] Ice to control swelling and inflammation

B. Post-treatment (appr. from day 7 to 14)

[1] Discontinue knee immobilizer.
[2] Continue measures to control inflammation and swelling
[3] Advance range of motion (active, active-assisted, and passive)
[4] Full weight bearing without assistive device as tolerated
[5] Continue early quadriceps exercises

C. Post-treatment (appr. from day 14 onwards)

[1] Stationery bicycle with seat high to encourage extension
[2] Straight leg abduction/adduction exercises
[3] Closed chain exercises

D. Post-treatment (appr. from week 6 onwards)

[1] Open chain exercises if well tolerated

All patients must be instructed about all post-operative restrictions, particularly those related to occupational and/or excessive loading activities. The following table lists the recommended, recommended with experience, and not recommended activities:

Recommended	Recommended with Experience	NOT recommended
Low-impact aerobics	Cycling	Racquetball / Squash
Bowling	Hiking	Contact sports (football, hockey, soccer)
Golf	Rowing	Rock climbing
Dancing	Cross-country skiing	Jogging / running
Walking	Stationary skiing	Singles tennis
Swimming	Speed walking	Water-skiing
	Doubles tennis	Baseball / softball
	Ice skating	Handball
		Martial arts

* Rehabilitation program needs to be adjusted to each patient (medical history, current health status, individual progress during rehabilitation) based on progress, any problems occurring during the post-operative period.

Suggested* Rehabilitation Program for Control Patients

A. Post-treatment (0 to appr. day 7)

[1] Discontinue compression bandage, if used
[2] Control inflammation and swelling, if applicable
[3] Advance range of motion (active, active-assisted, and passive), if applicable
[4] Full weight bearing without assistive device as tolerated
[5] Continue early quadriceps exercises

B. Post-treatment (appr. from day 7 to day 14)

[1] Stationery bicycle with seat high to encourage extension
[2] Straight leg abduction/adduction exercises
[3] Closed chain exercises

C. Post-treatment (appr. from week 6 onwards)

[1] Open chain exercises if well tolerated

All patients must be instructed about all post-treatment restrictions, particularly those related to occupational and/or excessive loading activities. The following table lists the recommended, recommended with experience, and not recommended activities:

Recommended	Recommended with Experience	NOT recommended
Low-impact aerobics	Cycling	Racquetball / Squash
Bowling	Hiking	Contact sports (football, hockey, soccer)
Golf	Rowing	Rock climbing
Dancing	Cross-country skiing	Jogging / running
Walking	Stationary skiing	Singles tennis
Swimming	Speed walking	Water-skiing
	Doubles tennis	Baseball / softball
	Ice skating	Handball
		Martial arts

* Rehabilitation program needs to be adjusted to each patient (medical history, current health status, individual progress during rehabilitation) based on progress, any problems occurring during the post-treatment period.

Appendix E

Knee MRI Protocol for IDE Study

Pre-Intervention MRI should be performed according to the following MRI protocol provided below. If a baseline MRI - not older than 6 months prior to review - is available upon enrollment, this could be used for initial screening of the study candidate. However, only the baseline study MRI performed according to the present protocol will be used to qualify the candidate against the applicable inclusion/exclusion criteria for participation in the clinical trial.

Post-Intervention MRI's should be performed at 1.5, 12, and 24 months according to the MRI protocol provided below using the same equipment as the baseline MRI.

The MRI should be taken according to the following protocol in order:

- To examine the patient post-intervention for osteophytes formation, synovitis, and bone edema over time relative to baseline
- To provide qualitative information about the cartilage and the subchondral bone of the post-intervention knee over time relative to baseline
- To examine those patients receiving the NUsurface device for device-related adverse events relative to baseline
- The MRI, composed of sequences performed according to this protocol, is designed for a 1.5T MRI, however, when possible, images should be obtained on a 3T MRI. If a higher Tesla equipment is available at the study site, the research staff should refer to the Sponsor to obtain the MRI protocol parameters applicable for the specific equipment
- **NOTA BENE:** Whichever type of MRI is used for the baseline image, whether 1.5 or 3 Tesla (T) (or higher), the same strength MRI should be used at 12 and 24 months with the same settings.
- For each sequence the written values below are for the 1.5T magnet. The values for using a 3T magnet are noted in brackets.
- The study should be obtained utilizing a dedicated knee coil (standard for knee MRI protocol), multi-channel is preferred for a better quality.
- If fat suppression is inhomogeneous, switch T2/PD fat sat with STIR.

SAGITTAL:

Proton Density Weighted FSE without FAT suppression

TR	TE	ETL	FOV	Slice thick./gap	Matrix	NEX	BW	Freq. direction
>2000	25-31	7 for 1.5T (8 for 3T)	14 cm	3.0/0 mm	512 x 256	2	16 for 1.5T (32 for 3T)	A/P

T2 FSE with FAT suppression

TR	TE	ETL	FOV	Slice thick./gap	Matrix	NEX	Freq. direction
>2000	45-50 for 1.5T (40 for 3T)	8 for 1.5T (16 for 3T)	14 cm	3.0/0 mm	512 x 256	2	A/P

CORONAL:

T2-weighted FSE with FAT Saturation

TR*	TE	ETL**	FOV	Slice thick./gap	Matrix	NEX	BW	Freq. direction
>2000	45-50 for 1.5T (40 for 3T)	5-8 for 1.5T (16 for 3T)	14 cm	3.0/0.5 mm (4.0 / 0 mm for 3T)	512 x 256	2	16 for 1.5T (50 for 3T)	S/I

* adjust to no. of slices
** dependent of blur produced by scanner

T1-weighted images

TR	TE	Partitions	FOV	Slice thick./gap	Slab	Matrix	NEX	BW	Freq. direction
400-800	min	64	14 cm	3.0/0 mm	96 cm	512 x 256	1	16 for 1.5T (32 for 3T)	S/I

AXIAL

T2-weighted FSE with FAT Saturation

TR*	TE	ETL**	FOV	Slice thick./gap	Matrix	NEX	BW	Freq. direction
>2000	≤50 eff for 1.5T (40 for 3T)	5-8 for 1.5T (16 for 3T)	14 cm	3.0/0.5 mm (≤4.0 / ≥0 mm for 3T)	512 x 256	2	16 for 1.5T (50 for 3T)	A/P

* adjust to no. of slices
** dependent of blur produced by scanner
NOTE: All sequences are 2D. If high quality T2 3D FSE with fat suppression can be obtained at the site, then it may be added.

References:

[1] Recht MP, Goodwin DW, Winalski CS, White LM. MRI of articular cartilage: revisiting current status and future directions. Am J Roentgenol. 2005 Oct;185(4):899-914.

[2] Kneeland JB, Reddy R. J Magn Reson Imaging. Frontiers in musculoskeletal MRI: articular cartilage 2007 Feb;25(2):339-44.

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

Appendix F

KOOS Disability Level Categories

80 --100 Normal Any observed knee pain does not interfere with activities of daily living. Usually no treatment needed, apart from perhaps analgesic or other drug therapy. KOOS Pain above 86.1 and KOOS Overall values above 86.2 have been determined by Englund et al 2003 Arthritis & Rheumatism to be asymptomatic.

60 -- 80 Mild Knee Disability Knee pain may be coped with for most activities of daily living. The patient's Activities of Daily Living, Sports/Recreational activities, and Quality of Life are mildly affected.

40 -- 60 Moderate Knee Disability Patients experience moderate pain and problems with walking, running, lifting, and standing. Activities of Daily Living and Quality of Life are difficult and moderately affected.

20 -- 40 Severe Knee Disability Patients experience severe pain during walking, running, lifting, and/or standing. Activities of Daily Living and Quality of Life severely affected. Knee brace or cane often necessary.

0 -- 20 Extreme Knee Disability Extreme knee pain during walking, running, lifting, and/or standing that is a crippling, constant problem. Activity of Daily Living and Quality of Life constantly and extremely affected. Knee brace, crutch, and/or canes usually required.

The Knee injury Osteoarthritis Outcome Score (KOOS) has 42 questions broken into 5 categories of 1) Pain, 2) Symptoms, 3) Activities of Daily Living, 4) Sports/Recreation, and 5) Quality of Life—all as to how they relate to the index knee. Each question has 5 possible answers with most questions being answered by 1) none, 2) mild, 3) moderate, 4) severe, or 5) extreme. The results of the questionnaire are converted to a 0 to 100 scale for each of the 5 categories, with a KOOS Overall score being the average of the 5 subpart scores. Having 5 categories with 5 answers each easily allows the 0 to 100 KOOS Overall score (as well as the subscales) to be divided into a 5 Parts of 20 points each that categorize the patient's disability of the knee. Dividing the Disability Divisions of KOOS into 5 Parts of 20 points each is modeled after the validated Oswestry Disability Index (ODI) described in: Fairbank J, Couper J, Davies J, et al. The Oswestry Low Back Pain questionnaire. Physiotherapy 1980;66:271–273.

Dividing the KOOS subscales into 5 parts of 20 points each allows each patient's knee disability to be categorized.