The SUN Clinical Trial:
Safety Utilizing NUsurface® Meniscus Implant

A multi-center, single-arm, prospective, open label, non-randomized, observational clinical study

Clinical Investigation Plan (CIP)

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Sponsor:
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REVISION HISTORY

Revision	Description of changes	Date
A	First Issue	9 Mar 2015
B	Second issue, submitted to FDA as part of an interactive review: • Sec. 10 added: Suspension or Premature termination of Clinical Investigation • Sec 8 updated: risks associated with radiation exposure to x-rays, MRI risks were updated. Risks associated with knee arthroscopy were added.	9 Apr 2015
C	Add Exclusion Criteria # 36 & 37 to clarify Inclusion Criteria #6. Add example to section 10.2 to call out specific reasons for device removal	13 Apr 2015
D	Fourth issue, submitted to FDA as S001 to IDE G150052: • Summary updated to match the protocol contents • Updated definitions 15 & 16 • Par. 3.1 & 3.2 updated with the inclusion of $KOOS_5$ as part of the primary endpoint definition • 6.5.3 modified. Statement added clarifying that an investigational device with a tear will be removed.	3 May 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The information contained in this document, especially unpublished data, is the property of the Sponsor of this clinical investigation, Active Implants LLC.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 Institutional Review Board or Ethics Committee. 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.

I, the undersigned, have read and undersigned the specified protocol, and agree with the contents. The protocol, the Investigator's Agreement and any additional information provided by the Sponsor will serve as a basis for cooperation in the study.

Principal Investigator

*Name:*_____

*Location:*_____

_____ _____
Signature Date

Sponsor Representative

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Signature Date

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APPENDICES

TERMS AND DEFINITIONS

ADE	Adverse Device Event
ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
A/P	Anterior/Posterior
BMI	Body Mass Index
BW	Bandwidth
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CMII	Clinically Meaningful Incremental Improvement
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data and Safety and Monitoring Board
EC	Ethics Committee
Eff	Effective
EQ-5D	EuroQol 5 Dimension health outcome survey
ETL	Echo Train Length
FDA	Food and Drug Administration
FOV	Field of View
FSE	Fast Spin Echo (a type of MRI)
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IKDC	International Knee Documentation Committee
IRB	Institutional Review Board
ISF	Investigator Site File
ISM	Independent Safety Monitor
KOOS	Knee injury and Osteoarthritis Outcome Score
$KOOS_5$	Average score of the 5 KOOS Score subscales (Pain, Symptoms, Activities of Daily Living, Activities in Sports, Quality of Life)
$KOOS_{pain}$	Pain sub-scale of the KOOS Questionnaire
LLC	Limited Liability Corporation
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NEX	Number of Excitations
OR	Operating Room
PD	Proton Density
PI	Principal Investigator
PCU	Polycarbonate-Urethane
PRO	Patient Related Outcome

QA	Quality Assurance
QoL	Quality of Life
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event/Serious Adverse Event
SAP	Statistical Analysis Plan
S/I	Superior/Inferior
SOP	Standard Operating Procedure
STIR	Short Tau Inversion Recover
SUN	Safety Utilizing NUsurface Meniscus Implant
T	Tesla (either T1 or T2)
TE	Echo Time
TKA	Total Knee Arthroplasty
TMF	Trial Master File
TR	Repetition Time
UHMWPE	Ultra High Molecular Weight Polyethylene
UKA	Unicondylar Knee Replacement
VAS	Visual Analog Scale
WOMET	Western Ontario Meniscal Evaluation Tool

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

1. **Adverse Event (AE)** is any untoward medical occurrence or complaint in a patient whether device related or not whether serious or not that occurs during the course of the clinical trial.

2. **Adverse Device Event (ADE)** is any untoward and unintended response to the NUsurface® Meniscus Implant including insufficiencies or inadequacies in instructions for use or deployment of the device.

3. **Automatic Study Failure** occurs if a negative MRI of the device is detected at 1 or 2 years as defined in the protocol or the device is surgically removed for any reason.

4. **Bailout or Screening Failure** is an enrolled study patient that is excluded from the study by the investigator before surgery or a bailout during surgery because the patient did not fulfill all of the inclusion criteria or had one or more of the exclusion criteria (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. **Baseline** is the evaluation of the patient just prior to NUsurface device implantation.

6. **Dislocation** is the displacement (more than 50% of the device length, more than 90 degree rotation, or complete inversion) of the NUsurface device from its implanted position between the medial femoral condyle and the medial tibial plateau.

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

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 <60%) of the meniscus is removed.
   - 8.2. **Subtotal Meniscectomy** is a meniscectomy where 60% 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 surgeries the patient incurs during 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 post-implantation return of the patient to the operating room for a subsequent knee surgery on the index knee receiving the NUsurface device, e.g. infection or lateral meniscus surgery.

     NOTE Re-operation only occurs if Terms 9.4 or 9.5 below do not apply. If the device is removed because of an infection, an investigation will determine whether device-related or not.
   - 9.4. **Revision** is a post-implantation surgery in which the position or the soft tissue around the originally implanted NUsurface device is changed or altered and the NUsurface device is not removed or replaced.
   - 9.5. **Removal** is the physical removal the NUsurface implant from the patient whether or not the device is replaced with another NUsurface implant.

     NOTE Post-implantation surgeries will be categorized in only one of the above categories. Categories 9.1 to 9.5 are mutually exclusive meaning that any post-implantation surgery will not be in more than one category. Removals of the NUsurface Meniscus 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 an Automatic Study Failure.

10. **Safety Success at 1 year** is determined if ≥ 90% of the patients are not device malfunctions, only Class I and II device-related adverse events are detected, and no single device-related adverse event occurs in more than 10% of the patients.

11. **Safety Success at 2 years** is determined if ≥ 90% of the patients are not automatic study failures, only Class I and II device-related adverse events are detected, and no single device-related adverse event occurs in more than 15% of the patients.

12. **Serious adverse event** is any untoward medical occurrence 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.

13. **Serious adverse device event** is any untoward medical occurrence that causes any of the 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.

14. **Subluxation** is an MRI detection of a partial dislocation (< 50%) or misplacement of the NUsurface device relative to the medial femoral condyle and the medial tibial plateau (e.g. in the sagittal MRI view, the posterior aspect of the device is located superior and posterior to the 2-4mm posterior rim of the medial meniscus).

15. **Successful Probable Clinical Benefit at 1 Year** occurs if the patient has ≥ 86.1 Points $KOOS_{pain}$ AND ≥ 86.2 Points $KOOS_5$ OR ≥ 30 Points $KOOS_{pain}$, ≥ 17 Points $KOOS_{pain}$ improvement relative to baseline, ≥ 19.4 Points $KOOS_5$ improvement relative to baseline and a positive MRI of the device, meaning no dislocation, high signal intensity, or fracture of the device is detected in the 1 Year MRI (device malfunction).

16. **Successful Probable Clinical Benefit at 2 Years** occurs if the patient has ≥ 86.1 Points $KOOS_{pain}$ AND ≥ 86.2 Points $KOOS_5$ OR ≥ 40 Points $KOOS_{pain}$, ≥ 19.4 Points $KOOS_{pain}$ improvement relative to baseline, ≥ 19.4 Points $KOOS_5$ improvement relative to baseline and has a positive MRI of the device, meaning no dislocation or fracture of the device is detected in the 2 Year MRI (automatic study failure).

17. **Surgery** is defined as a clinical procedure in an operating room that requires incising the skin of the patient.

18. **Treatment** begins at the time of NUsurface implantation.

Title: The SUN Clinical Trial: Safety Utilizing NUsurface® Meniscus Implant

Type of Study: A multi-centered, single-arm, prospective, open label, non-randomized, observational, study

Size of Study: The study consists of up to 118 subjects treated with the NUsurface® meniscus implant.

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

Number of Sites: Up to 20 sites located in the US, Europe and/or Outside the US (OUS).

Study Duration: After up to 18 months of recruitment at each site, an additional 60 months of follow-up for a total of up to 78 months.

Description of Treatment:

Surgical insertion of the NUsurface® Meniscus Implant into the medial compartment of the knee.

Study Rationale: The rationale for performing this clinical study is to gather safety and probable clinical benefit data to support of a future De Novo regulatory petition in the U.S. and/or provide additional clinical data of the safety and effectiveness of the NUsurface® Meniscus Implant.

Primary Objectives:

Safety

To demonstrate peri- and post-operative safety of the NUsurface® device up to and including 24 months post-implantation, along with an interim analysis of safety at 12 months on a subgroup of NUsurface patients defined in the SAP.

Clinical Benefit

To confirm probable clinical benefit of pain reduction, functional and quality of life improvement relative to baseline at 24 months with an interim analysis at 12 months on a subgroup of NUsurface patients defined in the SAP.

Secondary Objectives:

Safety

To demonstrate the long-term (up to 60 months post implantation) safety of the NUsurface® device as measured by the rate of serious post-operative device related events.

Clinical Performance

To demonstrate probable benefit up to 60 months post implantation by means of Patient Related Outcome (PRO) measurements.

- To evaluate the changes in the patient perceived pain compared to Baseline up to 60 months post-implantation with the $KOOS_{Pain}$ sub-scale.
- To evaluate the changes in the Patient Related Outcomes and all other

measured outcome data relative to baseline at all post-operative evaluation time points.

- To evaluate the changes in the patient Quality of life relative to Baseline at preset time points.

Study endpoints

Primary endpoints:

Safety

- Serious and non-serious, device-related and non-device related adverse events recorded during the implantation, up to 24 months following implantation.

Clinical Performance

- Evaluation of performance defined as NUsurface® Meniscus Implant providing knee pain reduction and improvement in functionality and quality of life up to 24 months post-implantation, as measured by $KOOS_{pain}$ and $KOOS_5$ scores.

Secondary endpoints:

Safety

- Adverse events, both serious and non-serious, both device-related and not, occurring between 24 and 60 months post-implantation.

Clinical Performance

- Evaluation of performance defined as NUsurface® Meniscus Implant providing knee pain reduction and improvement in functionality and quality of life up to 60 months post-implantation, as measured by $KOOS_{pain}$ and $KOOS_5$ scores.

Additional Evaluations:

- Changes in patients' perceived Pain as evaluated by VAS, IKDC and WOMET at 12, 24, 36 and 60 months as compared to Baseline.
- Changes in patients' Functionality as evaluated by IKDC and WOMET at 12, 24, 36 and 60 months as compared to Baseline.
- Changes in patients' Quality of Life as evaluated by $KOOS_{QoL}$, WOMET, and EQ-5D at 12, 24, 36 and 60 months as compared to Baseline.
- Changes in 12 and 24 month MRI's relative to 1.5 months and Baseline.

Surgery and Follow-up Schedule:

Baseline, surgery, 6 weeks, 3 (by phone), 6, 12, 24, 36 and 60 months. Patients will continue to be followed annually until all treated patients reach 60 months.

1 KEY ROLES

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Investigators and investigation sites

A current list of investigators and investigational sites will be provided upon request to the Sponsor.

2 INTRODUCTION

2.1 Background

2.1.1 Meniscal anatomy and function

The knee menisci are two semi-lunar (“crescent moon” shape) fibro-cartilaginous wedges found superior to the tibial surface, The medial meniscus is usually C shaped and covers approximately 64% of the tibial plateau. It is from its shape that the meniscus gets its name since the word itself is Greek for crescent moon. The major meniscal function is to distribute stress across the knee during weight-bearing, provide shock absorption, and serve as secondary joint stabilizers. The medial meniscus bears 40-50% of joint load during extension and up to 85-90% of load in flexion. A normal intact meniscus moves several millimeters in the anterior-posterior direction as it helps transmit the load from the femur to the tibia [1].

The menisci possess highly complex structural, geometric, and mechanical properties that provide for their unique function. The natural meniscus contains collagen fibers, arranged predominantly in the circumferential direction, within a hydrated matrix [2]. This fiber arrangement supports the large hoop stresses that optimize distribution of contact stresses within the knee joint and prevent meniscal extrusion [3]. An undesired extrusion of the meniscus, due to disruption of collagen fibers, may lead to knee pain and dysfunction by altering meniscal mechanics [4]. It has been shown, for example, that resection of 15-34% of a meniscus may increase contact pressure by more than 350%, and that normal knees have 20% better shock-absorbing capacity than meniscectomized knees [1, 5].

2.1.2 Meniscal tears

Tears of the meniscus are a common source of knee pain. Meniscal tears can be classified according to the tear length, depth and location of tear, or according to the tear pattern, as listed in the table below. Longitudinal tears occur parallel to the direction of the circumferential collagen fibers. Bucket-handle tears are a variant of a longitudinal tear in that the circumferential collagen fibers are also disrupted as the tear travels from the innermost aspect of the meniscus toward the periphery. Vertical longitudinal meniscal tears can be repaired in young patients (≤ 30). Bucket-handle tears are harder to repair since stray circumferential fibers may interfere with healing. Flap and radial meniscal tears also disrupt the circumferential collagen fibers and are more often debrided or excised rather than repaired. Complex or degenerative meniscal tears can involve multiple tissue-cleavage planes, delamination, and extrusions and are often associated with calcified cyst formation, osteophytes, and/or articular cartilage damage.

Table 1. Tear patterns and potential to be repaired in young patients [1]

Tear pattern	Repair potential
Horizontal tear	Irreparable
Longitudinal tear	Repairable ~ < 30 yrs
Radial (transverse) tear	Potentially repairable
Bucket handle tear	Repairable
Oblique (flap) tear	Irreparable
Complex (degenerative) tear	Irreparable

2.2 Current treatment options

2.2.1 Conservative treatment of pain related to meniscal tears

Non-operative treatment includes physical therapy, weight loss, bracing, rest, activity modification, analgesics, and inflammatory reduction measures such applying ice, taking non-steroidal anti-inflammatory or other medications, or injecting corticosteroids. Injecting hyaluronic acid into stiff knee joints is also a conservative, non-surgical option [1]. If the patient does not improve with these therapies, then surgery can be considered.

2.2.2 Operative treatment of menisci tears

Repair of torn meniscus is an option in young patients whenever the tear is > 1 cm long and in the vascular region or red zone (peripheral, outer third). However, most meniscal tears are irreparable (Table 1) either because the tear is too small or too big, too difficult to reach, or too avascular to heal or the patient is too old to heal easily. Therefore, rather than repairing the tear another operative treatment option is to remove the torn section of the meniscus – under the assumption that the tear is the source of the pain.

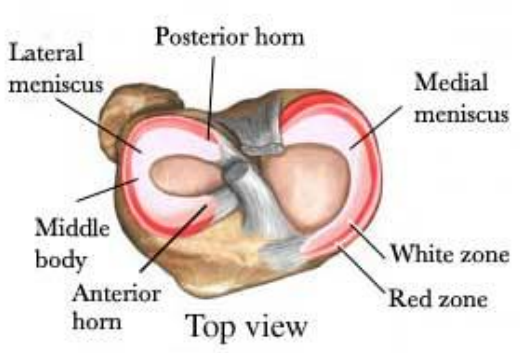

Figure 1 Meniscus Vascular Region (Red Zone)

But why are some meniscal tears painful and others not? One theory as to why some do is because some tears are or become “unstable” during knee activity, creating abnormal meniscal motion that slightly enlarges the tear. Enlarging the tear forms microscopic debris that creates synovitis that in turn causes pain. Another theory is that the tear turns into a flap that becomes entrapped which may in turn cause pressure on the capsule that causes pain. The reason surgical removal of just the tear area often relieves knee pain is that resecting the tear can restore knee motion or meniscal stability while at the same time preserving as much of the meniscus as possible. Such a procedure is called a partial meniscectomy.

2.2.3 Allograft implantation

Meniscal allograft transplantation primarily occurs in symptomatic younger patients (<40) who have undergone previous meniscectomy and who have failed non-operative treatments. Meniscal allograft transplantation has been shown to relieve pain [6]. However, in addition to problems related to availability, size matching, cost and risk of disease transmission, allograft menisci undergo remodeling after implantation, causing shrinkage and reduced mechanical strength [7-9]. These factors may lead to allograft tear, uneven load distribution, instability, and/or degenerative changes to the knee.

2.2.4 Meniscal scaffolds

Using a porous scaffold to rebuild the meniscus has been described in the literature [10-13]. Issues about the durability and ingrowth of the scaffold under knee loading conditions [12, 14], the variability in the body response to the resorbable scaffold, and the quality of the tissue formed have been raised. All of these issues become more pronounced in older patients (>40 years old) [15].

2.2.5 Metal interpositional devices

Self-centering, non-fixed meniscal-shaped metal interpositional spacers have been used to treat patients with a meniscus insufficiency or tear. Early forms of the spacer concept by McKeever (1960) [16] and McIntosh (1958) [17] evolved into the UniSpacer™ (Zimmer, Warsaw, IN) and iForma™ (ConforMIS, Burlington, MA) metal interpositional devices. Early published clinical results for the Unispacer™ device are mixed with some studies citing high rates of revision, dislocation, and post-op pain [18, 19]. Later published results of complication/revision rates report decreased rates with the refinement of the surgical technique and patient indications/contraindications [20,21]. Conformity between the meniscus and articular surfaces is a key factor for successful performance, especially in its ability to distribute load [22]. However, conformity of a metal interpositional device does not occur since metal spacers are rigid and possess a modulus of elasticity orders of magnitude greater than the meniscus [23,24].

2.3 Clinical Study Rationale

The surgical treatment options of repair, allograft, and scaffolds are usually used and have the best results in younger patients and are seldom used in middle-aged patients. Partial meniscectomies have never been shown to be superior to conservative care in middle-aged patients. The main problem with performing surgery on middle-aged patient is their poor capacity for healing and tissue regeneration. Because of these facts, surgeons are hesitant to perform any surgical treatment option on middle-aged patients. For elderly patients or patients with bone-on-bone, more aggressive procedures like Unicompartmental Knee Arthroplasty (UKA) or Total Knee Arthroplasty (TKA) are available. Thus, a “treatment gap” exists for middle-aged patients with mild to moderate osteoarthritis and meniscal insufficiency.

Active Implants LLC (the Sponsor) has developed a polycarbonate-urethane (PCU)/UHMWPE fiber-reinforced artificial meniscus implant that is intended to redistribute the stresses transmitted between the femur and tibia during the gait cycle. Lowering the stress on the cartilage should not only reduce the knee pain but the implant should aid normal knee joint function. The clinical study rationale for performing this investigation is to gather safety and probable clinical benefit data on the NUsurface® Meniscus Implant and confirm whether or not this device is a possible new treatment option for patients having a medial meniscus insufficiency caused by a previous partial meniscectomy.

3 OBJECTIVES OF THE CLINICAL INVESTIGATION

3.1 Objectives

3.1.1 Primary Objective

Safety
To demonstrate peri- and post-operative safety of the NUsurface® device up to and including 24 months, along with an interim analysis of safety at 12 months on a subgroup of NUsurface patients defined in the SAP (doc 00578).

Performance
To demonstrate probable clinical benefit up to 24 months post implantation by means of Patient Reported Outcome (PRO) measurements.

- To evaluate the changes in the patient perceived pain compared to Baseline up to 24 months post-implantation with the $KOOS_{Pain}$ sub-scale.
- To evaluate the changes in the patient perceived pain compared to Baseline up to 24 months post-implantation with the $KOOS_5$ sub-scale.
- To evaluate the changes in the Patient Related Outcomes and all other measured outcome data relative to baseline at all post-operative evaluation time points.
- To evaluate the changes in the patient Quality of life relative to Baseline at preset time points.

3.1.2 Secondary Objective

Safety
To demonstrate peri- and post-operative safety of the NUsurface® device up to and including 60 months as measured by the rate of serious post-operative device-related events.

Performance
To demonstrate clinical performance up to 60 months post implantation by means of Patient Reported Outcome (PRO) measurements.

- To evaluate the changes in the patient perceived pain compared to Baseline up to 60 months post-implantation with the $KOOS_{Pain}$ sub-scale.
- To evaluate the changes in the patient perceived pain compared to Baseline up to 60 months post-implantation with the $KOOS_5$ sub-scale.
- To evaluate the changes in the Patient Related Outcomes and all other measured outcome data relative to baseline at all post-operative evaluation time points.
- To evaluate the changes in the patient Quality of life relative to Baseline at preset time points.

3.2 Endpoints

3.2.1 Primary Endpoints

Safety

- Serious and non-serious, device-related and non-device related adverse events recorded during the implantation, up to 24 months following implantation.

Clinical Benefit

- Evaluation of performance defined as NUsurface® Meniscus Implant providing knee pain reduction and improvement in functionality and quality of life up to 24 months post-implantation, as measured by $KOOS_{pain}$ and $KOOS_5$ scores.

3.2.2 Secondary Endpoints

Safety

- Adverse events, both serious and non-serious, both device-related and not, occurring between 24 and 60 months post-implantation.

Clinical performance

- Evaluation of performance defined as NUsurface® Meniscus Implant providing knee pain reduction and improvement in functionality and quality of life up to 60 months post-implantation, as measured by $KOOS_{pain}$ and $KOOS_5$ scores.

Additional evaluation

- Changes in patients' perceived Pain as evaluated by VAS, IKDC and WOMET at 12, 24, 36, and 60 months as compared to Baseline.
- Changes in patients' Functionality as evaluated by IKDC and WOMET at 12, 24, 36, and 60 months as compared to Baseline.
- Changes in patients' Quality of Life as evaluated by $KOOS_{QoL}$, WOMET, and EQ-5D at 12, 24, 36, and 60 months as compared to Baseline.
- Evaluation of study MRI's relative to 1.5 months and Baseline.

4 DESIGN OF THE CLINICAL INVESTIGATION

The purpose of this clinical investigation is to assess the safety and determine if the NUsurface® Meniscus Implant has a probable clinical benefit in the selected target patient population, which includes U.S. Medicare age subjects.

The design of the clinical investigation is a multi-center, prospective, single-arm, non-randomized, open label study for the treatment of knee pain caused by a previous meniscectomy (post-meniscectomy syndrome).

The study will be conducted in up to 20 clinical centers located in U.S. and/or Outside the US (OUS). No center will enroll more than 35% of the total number of patients.

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. 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 U.S. Medicare population (age 65-75 inclusive) and determine whether U.S. Medicare aged patients may benefit from the treatment.

5 POPULATION AND STUDY INDICATIONS

5.1 Study Population

The planned clinical study will be conducted in up to 118 patients who meet all of the inclusion criteria and have none of the exclusion criteria.

5.2 Inclusion criteria

In the opinion of the investigator, if ALL of the following 8 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
6) Is able to do the study required follow-up visits, questionnaires, X-rays and MRI's
7) Is able to read and understand the English language if treated at a U.S. site or read and understand one of the official country languages if treated at a site Outside the U.S.
8) Is able and willing to understand and sign the Informed Consent Form

5.3 Exclusion criteria

In the opinion of the investigator, if ANY of the following 37 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
36. Certain patient populations that are at high risk for poor healing or outcomes such as patients who have a co-morbidity that reduces life expectancy to less than 36 months
37. Patients who are contraindicated for MRI (i.e., pacemaker, defibrillator, cochlear implants, etc.)

5.4 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, defined as missing two or more follow-up visits

Upon request, the patient can withdraw from the study at any time. The reason for withdrawal will be investigated and 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 and SAP.

5.5 Duration of the clinical investigation

It is anticipated that it could take the participating sites up to 18 months to enroll up to 118 study subjects. Follow-up duration is 60 months resulting in study duration of up to 78 months or more. Although the participation in the trial by the patients is planned to end at 60 months, investigators will be asked to continue to follow all subjects annually until the last patient enrolled has completed 60-month follow-up.

5.5.1 Bailout

If the patient was enrolled 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 section 10.4 of this protocol.

6 PARTICIPANT SELECTION AND ENROLLMENT

6.1 Point of Enrollment

Point of enrollment is defined as the time when a patient signs and dates the study Informed Consent Form.

6.2 Pre-study screening

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 one 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. 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 of this protocol 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.

6.3 Intra-operative procedures

Administration of the NUsurface® meniscus implant is provided through a surgical procedure (see Appendix D). 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.

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

The NUsurface® device is provided in multiple sizes in both right and left dexterities. Radiographic imaging of the index knee taken pre-treatment will be used by the investigators to measure the size of the intra-

operative trial to start the sizing process with. Optimal and final size selection will occur as per the approved surgical training manual (see doc. no. WI-00027) during the open arthrotomy step of the surgical procedure.

6.4 Post-operative procedures

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

6.5 Follow-up procedures

Post-treatment evaluations will be carried out immediately post op, and at 1.5, 3, 6, 12, 24, 36, and 60 months post implantation. The 3-month evaluation will be by phone. Each patient will be seen annually until the last patient has been entered into the study.

Patients who are automatic failures (e.g. dislocation or infection followed by removal) will be followed at their regularly scheduled time until the end of the study. Patients who had the device removed will continue to be studied because those patients would have been exposed to the investigational device. None of the failures will be analyzed for clinical performance after becoming automatic study failures. Instead each will be analyzed for safety through the capture of adverse events.

6.5.1 Validated Questionnaires

6.5.1.1 KOOS

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 [36]. These forms provide a comprehensive evaluation of the patients' pre-treatment and post-treatment 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, 24, 36, and 60 months (Appendix A).

6.5.1.2 IKDC

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, 24, 36, and 60 months (Appendix A) is required per the protocol.

6.5.1.3 Pain VAS

The Visual Analog Scale (VAS) is a validated measurement tool for patient assessment of pain [37]. 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, 24, 36, and 60 months (Appendix A).

6.5.1.4 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 20 cm scale for assessing pain. This instrument is used at baseline and at 1.5, 6, 12, 24, 36, and 60 months (Appendix A).

6.5.1.5 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).

6.5.2 Post-operative MRI of the knee

MRI images will be taken at 1.5, 12, 24 and 60 months post-implantation 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, 24 and 60 month images to the baseline.

Based on clinical judgement of the principal investigator, if a post-operative MRI of the index knee ever detects a tear in the investigational device, the device will be removed.

7 DEVICE DESCRIPTION

7.1 Intended use

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

7.2 Device Design Goals

The following goals were the essential requirements in the design of a meniscal implant to replace the function of a normal meniscus:

a) Mimic load distribution of the natural meniscus

b) Mimic intra-capsular movement of the natural meniscus

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

d) Have the meniscus prepared with a minimally invasive approach

e) Not need bone resection nor suture attachment

f) Require a relatively short rehabilitation

7.2.1 Design Rationale

The design rationale was to create a device (NUsurface® Meniscus Implant) conceptually analogous to the structural characteristics of the natural meniscus. Since the normal meniscus has a highly orientated collagen fiber network to handle hoop stresses and better distribute contact pressures within the knee joint

[3, 33-36], the NUsurface® Meniscus Implant is circumferentially reinforced with high tensile Ultra High Molecular Weight Polyethylene (UHMWPE) fibers.

7.2.2 Device description

The NUsurface device is offered in left and right versions and in 7 sizes. Radiopaque trials of the same sizes are also offered.

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 inserted through a minimal arthrotomy incision and 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

Figure 1 Photograph of NUsurface® Meniscus Implant

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 over 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, The Netherlands). UHMWPE has been used in orthopedics for joint replacement for over 50 years. The UHMWPE fiber version selected has also been tested for biocompatibility according to ISO 10993.

7.2.3 Materials of construction

Bionate® 80A polycarbonate-urethane (PCU) is a tough polymer with a relatively low elastic modulus (10-100 MPa [25]) similar to the natural meniscus. PCU material is one of the most extensively tested plastic biomaterials. This material has biocompatibility and biostability properties equal to or better than other plastic materials used in orthopaedics [26-28]. 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 because it is pliable, yet durable, and offers mechanical and hydrophilic properties comparable to the natural meniscus [25, 29-31]. Specifically, the

natural meniscus is an orthotropic material [24, 29]. By circumferentially reinforcing the PCU with high strength UHMWPE fibers and offering multiple sizes the NUsurface Meniscus Implant mimics the orthotropic properties of the normal meniscus.

7.3 User training requirements

Prior to each study site activation, Active Implants LLC, 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.

7.4 Device Regulatory Status

7.4.1 Regulatory status in the USA

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 future De Novo regulatory petition in the US or other regulatory application.

The study will be conducted 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, laws and regulations of the country in which the study is conducted, and this CIP.

7.4.2 Regulatory status in Europe and Israel

The NUsurface® Meniscus Implant has a CE Mark for Europe and also market approval in Israel. The labeled indications for use are:

1. *Primary or post-meniscectomy patients with acute or chronic medial compartment pain who have or have had a traumatic or degenerative meniscal tear(s) and/or meniscal insufficiency. The device is only indicated for use in patients where the medial femoral and tibial cartilage contacting the implant will be of an Outerbridge Grade 0, I, II, or III.*
2. *Revision of any previous meniscus substitute procedure in patients with the above indication.*

This indication for use covers the inclusion/exclusion criteria described in this study protocol.

The study will be conducted in compliance with the latest version of the Declaration of Helsinki, the requirements on clinical investigations as laid out in annex 7 of directive 90/385/EEC, in annex X of directive 93/42/EEC as amended by directive 2007/47/EC, and in the international standard ISO 14155 (“Clinical Investigation of medical devices for human subjects – Good Clinical Practice”).

7.5 Device Accountability

The NUsurface® meniscus implant 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

7.5.1 Study centers located in the USA

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.

7.5.2 Study centers located outside of the USA

The NUsurface® Meniscus Implant has been classified as a Class IIb device according to Annex IX of MDD 93/42 EEC as amended by Directive 2007/47/EC. INTERTEK/AMTAC (0473) has been selected as Notified Body for the manufacturer of record, Active Implants Israel Ltd. The NUsurface® Meniscus Implant received CE Mark approval in March 2008.

7.6 Receipt of Supplies

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

7.7 Storage

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

7.8 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.

8 RISKS AND BENEFIT OF THE STUDY DEVICE AND CLINICAL INVESTIGATION

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

The risks associated with any knee surgery are also possible for those patients receiving NUsurface® Meniscus Implant. In particular, the following are risks associated with the surgical procedure (occurring in less than 1 in 100 cases):

- Infection inside the joint
- Bleeding, scar, deep vein thrombosis, pulmonary hemorrhage, damage to the nerves, blood vessels or tendons around the knee
- Compartment syndrome
- Muscle athrophy
- Limb edema

The risks associated with x-ray and/or MRI imaging are also possible for those patients receiving the NUsurface® Meniscus Implant:

- Exposure to x-rays carrying a theoretical risk of triggering cancer at a later date (as does exposure to background radiation). An x-ray of the knee is the equivalent of a few months' to a year's worth of background radiation, and has a 1 in 10,000-100,000 chance of causing cancer
- There are no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. However, the following are important safety concerns to consider before performing or undergoing an MRI scan:
    - The magnet may cause pacemakers, artificial limbs, and other implanted medical devices that contain metal to malfunction or heat up during the exam.
    - Any loose metal object may cause damage or injury if it gets pulled toward the magnet.
    - If a contrast agent is used, there is a slight risk of an allergic reaction. MRI contrast agents can cause problems in patients with significant kidney disease.
    - Dyes from tattoos or tattooed eyeliner can cause skin or eye irritation.
    - Medication patches can cause a skin burn.
    - The wire leads used to monitor an electrocardiogram (ECG) trace or respiration during a scan must be placed carefully to avoid causing a skin burn.
    - Prolonged exposure to radio waves during the scan could lead to slight warming of the body.

In addition to these above listed risks, the NUsurface device may have the additional possible risks:

- bending or breakage of the device components or bone
- dislodgement or movement of the implant from out of its original 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)

8.2 Anticipated probable clinical benefit

The study device and surgical procedure may be of probable benefit to the patient by:

- Reducing pre-treatment (baseline) knee pain as measured by the $KOOS_{Pain}$ Sub-scale by a clinically meaningful incremental difference (CMII) and by being > 30 points at 12 months and > 40 points at 24 months.

9 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

9.1 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 unfavorable 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., ECG 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 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.

9.2 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 criteria:

- 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.

9.2.1 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.

9.2.2 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.

9.3 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).

9.4 Relationship to study treatment

For each event, the investigator and the Sponsor independently will assess the causal relationship between the 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.

Possibly 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).
- Cannot 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.

9.5 Reporting procedures

9.5.1 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, 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.

9.5.2 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: age, 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
- Criteria 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 or email within three working days (contact details in section 9.5.3). The Investigator or designee will provide a detailed written report within 7 working days. Whenever appropriate, the Sponsor will discuss these serious adverse events with the Investigator, Medical Advisors, and/or Data and Safety Monitoring Board (DSMB). Any adverse event reporting requirements to the IRB/EC will be followed with the site surgeon making the determination for the IRB/EC of whether the AE is serious. All other adverse events will be recorded at the next scheduled visit.

9.5.3 Emergency contact details

U.S.A:

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10 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 10.1, 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.

10.1 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.

10.2 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 35 (>30% of 118 NUsurface implant patients) NUsurface device removals for any reason such as infection, tears, etc. automatically suspends further enrollment of patients into the study at ≤ 12 or ≤ 24 months if full enrollment is not yet completed.
- Greater than 30 (>25% of 118 NUsurface implant patients) NUsurface dislocations (whether diagnosed clinically, at removal, or by MRI imaging) will automatically suspend further enrollment of patients into the study at ≤ 12 or ≤ 24 months if full enrollment is not yet completed.

10.3 DSMB Suspension of Further Patient Enrollment

The Data and Safety Monitoring Board (DSMB) may suspend further enrollment of study patients 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 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% enrolled subjects into the 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 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.

10.4 FDA Suspension of Further NUsurface Enrollment

During the IDE, the FDA will be provided annual reports on April 16th 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 Jul 16, Oct 16, and Jan 16 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.

11 STATISTICAL CONSIDERATIONS, INTERIM, AND FINAL ANALYSIS

Complete or further details of the statistical considerations and the interim and final analysis are contained in a separate study document called the Statistical Analysis Plan, SAP (doc no 00578). The following is a summary of its contents.

11.1 Sample size

The originally planned sample size of the SUN clinical trial is 118 subjects.

11.2 Statistical Methods

The SUN study is an observational, non-comparative trial. Therefore, the primary statistical analysis will be based on descriptive and frequentist statistical techniques. All statistical analyses will be performed with patients as units of measurement. Further details are provided in the SAP for the study.

11.3 Poolability of Data

At the conclusion of the study, as described in the SAP, the results from the present trial will be compared for poolability with the results from other clinical trials of the identical NUsurface® Meniscus Implant with same inclusion/exclusion criteria. If the results show the data are poolable, the data will be pooled. Further details are in the SAP.

11.4 Replacement of Patients

If one or more patients discontinue prematurely, additional patient(s) may be enrolled to ensure at least 100 evaluable patients will be available at 24 months. If the discontinuation is related to a possible adverse event of the operation, the discontinued patient (as well as the replacement patients) will be included in the statistical evaluation of adverse events, but not in the clinical benefit evaluation. Similarly if a significant change in the device, surgical technique, or study design occur additional patients may be added to replace the patients treated before the change occurred. Further details are in the SAP.

11.5 Interim analysis of the data

The primary goal of the SUN clinical trial is to evaluate Safety Utilizing NUsurface® Meniscus Implant. The clinical data may be used for regulatory, publication, marketing, and/or reimbursement purposes. For the United States the goal of the study is to support a De Novo regulatory petition application. Details can be found in the SAP, doc no 00578. Interim Analysis Success is defined in the SAP. The Terms and Definitions section of this CIP also defines a safety success (definition 10) and successful probable clinical benefit (definition 15) at 1 year.

11.6 Final analysis of the data

A final analysis of the primary endpoint will be performed at the end of the study when all SUN study patients reach 2 years and have a 2 Year MRI. Additional details of the Final Analysis including definitions of success are provided in the SAP, doc no 00578. The Terms and Definitions section of this CIP also defines a safety success (definition 11) and successful probable clinical benefit (definition 16) at 2 years.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 Amendments to the clinical investigation plan

Any study plan amendment is required to be submitted for information/consideration to the reviewing IRB or EC and the appropriate regulatory authority.

IRB or EC 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.

12.2 Protocol violations and deviations

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.

12.3 Serious breach requirements

A serious breach is a breach, which is likely to effect to a significant degree:

a) the safety or physical or mental integrity of the participants of the trial; or
b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsors (clinical@activeimplants.com) must be notified within 24 hours. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

Not every violation from the protocol needs to be reported to the regulatory authority as a serious breach. If the Sponsor deems the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventive actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

12.4 Data management

12.4.1 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.

12.4.2 Case Report Forms (CRFs)

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.

12.4.3 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.

12.4.4 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 notes 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).
- 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.

12.4.5 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.

12.4.6 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.

12.5 End of study

The end of study is defined as the last participant's last visit.

The Investigators and/or the Sponsor have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the IRB/REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the IRB/REC and Regulatory Authority within 1 year of the end of the study.

13 GOOD CLINICAL PRACTICE

13.1 Ethical conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate Institutional Review Board/Research Ethics Committee and local R&D department approval (where applicable) will be obtained prior to commencement of the study.

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.

13.2 Investigator responsibilities

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.2.1 Informed Consent

The Investigator is responsible for ensuring Informed Consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasized that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Sponsor but understand that their name will not be disclosed outside the hospital.

A designated member of the site team and the patient will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The patient will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study is adequately informed about the investigational device, protocol and their trial related duties.

13.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.2.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the Sponsor, including but not limited to:

- A signed Investigator's Agreement (as part of the Clinical Trial Agreement documents);
- Curriculum Vitae (CV), preferably signed and dated by the Investigator.

The Sponsor will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

13.2.5 GCP Training

Members of each study staff must have evidence of appropriate GCP training or it will be provided.

13.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection with regard to the collection, storage, processing and disclosure of personal information. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14 PATIENT COMPENSATION

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

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 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 A

Recruitment is expected to be completed within 18 months from local approval of the study for each site. Study evaluation continues until 60 months of follow up has occurred with the last patient entered into the study. The following table is the study timeline evaluation methods.

Evaluation Method	Baseline	Surgery	1.5 Mo	3 Mo**	6 Mo	12 & 24 Mo	36 Mo	60 Mo
Range	n.a.	n.a.	± 2 w	± 2 w	± 1 mo	± 2 mo	± 3 mo	± 6 mo
Assessments								
Screening	✓							
Treatment		✓						
3 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 +	✓		✓			✓		✓
Fluoroscopy index knee		✓						

*Any pre-surgery measurement of varus/valgus alignment should be performed using a 91-cm (36-inch) or 130-cm (51-inch) Standing Antero-posterior X-ray including the Hip and Ankle. A bilateral X-ray comparing the two leg alignments is also recommended.

** According to potential investigators, partial meniscectomy 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-surgery.

+ MRI Scans are to be performed according to Appendix E.

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

All patients entered into the study will be evaluated annually until the last patient reaches the 24-month time point and then the above schedule for long-term follow-up is followed All follow-up visits occurring outside of the stated windows will be noted in the patient CRFs.

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 clinical performance 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 clinical performance. 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 approximately 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 (approximately 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 (approximately 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 (approximately 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 (Vogel LA, Carotenuto G, Basti JJ, Levine WN. Physical Activity after Total Joint Arthroplasty. Sports Health 2011; 3(5):441-450 Epub 29 July 2011 DOI: 10.1177/1941738111415826):

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.

Appendix E

Index 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 MRI could be used for initial screening of the study candidate. However, only a baseline study MRI performed according to the present protocol will be used to qualify the candidate against the study protocol inclusion/exclusion criteria for participation in the clinical trial. Because it is known that cartilage and knee conditions can change quite rapidly, the shorter the time between taking the study Baseline MRI and the date of surgical implantation of the subject NUsurface device the more accurate the Baseline status of the index knee will be documented. Preferably and whenever not possible to delay surgery, the study Baseline MRI should be taken 3 months or less from the planned date of surgery.

Post-Intervention MRI's should be performed at 1.5, 12, 24, and 60 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 1.5, 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 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)	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	9.6 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 ≤ gap < 0.5 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.