A Clinical Investigation Evaluating Efficacy of a Full-Thickness Placental Allograft (Revita®) in Lumbar Microdiscectomy Outcomes

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STUDY SUMMARY

Title	A Clinical Investigation Evaluating Efficacy of a Full-Thickness Placental Allograft (Revita) in Lumbar Microdiscectomy Outcomes
Methodology	Randomized, controlled trial, blind study
Study Duration	Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study) is approximately 2.5 years
Study Center(s)	Multi-center (Polaris Spine and Neurosurgery Center, Atlanta, GA and Northside Hospital, Atlanta, GA)
Objectives	Primary Objective: To evaluate the efficacy of Revita full thickness placental allograft in improving back and leg pain post-microdiscectomy Secondary Objectives: To evaluate post-microdiscectomy reherniation rate in patients treated with Revita
Number of Subjects	182 randomized patients in two arms; Treatment and Control
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria** - Male and female patients, 18-70 years old, in any distribution. - Symptomatic with radiating low back and leg pain for greater than 6 months prior to surgery with a clinical diagnosis of lumbar protruding disc. - Consent and compliance with all aspects of the study protocol, methods, providing data during follow-up contact - See methods section for full list of inclusion criteria **Exclusion Criteria** - Male and female patients younger than 18 years old or older than 70 years old. - Smoking, additional health risk factors contraindicated with Revita use - Involvement with any other ongoing studies. - See methods section for full list of exclusion criteria
Study Product, Dose, Route, Regimen	- Treatment Group: Will receive Revita allograft (2x2cm) - Control Group: Will receive current standard of care
Statistical Methodology	Primary Endpoint: Low back and leg pain as measured by the Oswestry Disability Index (ODI), 12-Item Short Form Survey (SF12) Secondary Endpoints: Reherniation rate.

Purpose:
The primary objective is to evaluate the efficacy of Revita full thickness placental allograft use in improving back and leg pain, when applied to patients undergoing lumbar microdiscectomy.

Background:
Microdiscectomy is a routine procedure to alleviate herniated vertebral disc material that is compressing the spine or spinal nerves. Scar tissue formation and reherniation can be common following microdiscectomies. Reherniation and formation of scar tissue can lead to symptoms such as radiating back and leg pain that were treated by the initial surgery. As a barrier membrane, Revita is designed to prevent the formation of scar tissue at the surgical site, which is expected to reduce the return of symptoms frequently seen in current standards of microdiscectomy surgeries.

Goals of the study:
1. To evaluate Revita full thickness placental allograft application in improving back and leg pain as measured by the Oswestry Disability Index (ODI) compared to the control group.
2. To evaluate reherniation rate in patients with Revita full thickness placental allograft applied to the annulus of the index lumbar level just prior to closure.
3. To improve ODI/SF12 scores and reduce radiating lower back and leg pain in the treatment group (Revita application).

Duration of the Study:
The study is estimated to complete enrollment within 6 months from study initiation; however, enrollment will remain open until the study goal is met. The duration of this study for each subject will be a maximum of two (2) years.

Product Description:

Revita is donated allograft placental tissue, aseptically processed, and dehydrated to remove moisture while preserving biologic components and the structure of the placental matrix. Following preservation, Revita allografts are terminally sterilized using Electron Beam irradiation, providing additional assurance of safety.

The Revita allograft is an opaque, white to off-white dehydrated material. Revita is donated human tissue regulated by the United States Food and Drug Administration (FDA) as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service (PHS) Act. Revita™ allografts are aseptically processed according to FDA current Good Tissue Practice requirements. StimLabs is registered with the FDA as a Tissue Establishment.

Revita is classified as a 361 HCT/P regulated solely under Section 361 of the Public Health Service Act and 21 CFR 1271. Revita is neither an FDA regulated drug nor device.

Revita is comprised of human amniotic membrane and chorionic membrane obtained from donated human placental tissue. The allograft contains only non-viable cells that

were present at the time the tissue was donated, with no supplementary viable or non-viable cells added during processing.

Revita is uniquely processed using the patent-pending Clearify™ process to preserve the natural orientation of the placental membranes. The Clearify process gently processes unwanted constituents from the placental membrane, yielding a safe, sterile product. The process preserves the naturally occurring extracellular matrix which contains proteins, growth factors, and glycoproteins. The Clearify process is optimized to process the amniotic and chorionic membranes together allowing the retention of the jelly-like intermediate layer which lies between the membranes. The processed full thickness membrane is presented in dehydrated form, cut into various sizes, and terminally sterilized for a variety of clinical applications. The Revita allograft should be maintained in its original packaging and stored at ambient temperature (0ºC to 38ºC) until ready for use. When stored properly in their original packaging, Revita allografts are shelf-stable for up to five (5) years.

Product Intended Use:

Revita is to be used as a wound covering, or barrier membrane, over chronic and acute wounds, including dermal ulcers or defects.

Product Acquisition:

The Revita allografts will be purchased by Northside Hospital from StimLabs at no cost to the patient.

Potential Benefits and Risks to Patients:

Every effort is taken during donor screening and production by the sponsor to prevent the spread communicable diseases. StimLabs performs donor screening, eligibility determination, aseptic processing and terminal sterilization for all donors and tissue products.

The primary goal at StimLabs is to maximize patient safety. To fulfill this goal, StimLabs employs stringent donor screening and laboratory testing to reduce the risk of transmitting communicable disease. Donor screening includes, but may not be limited to, review of relevant medical records including a current donor risk assessment interview, a physical examination of the donor, laboratory test results, as well as other information pertaining to risk factors for relevant communicable diseases.

All communicable disease testing was performed on this allograft by a laboratory registered with FDA to perform donor testing and certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR Part 493); or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services in accordance with those provisions. Donor blood samples taken at the time of tissue recovery were tested for the following:

Human Immunodeficiency Virus (HIV) Type 1 and Type 2 antibody

Human T-Lymphotrophic Virus (HTLV) Type I and Type II antibody

Hepatitis C antibody (HCV)

Hepatitis B surface antigen (HBsAg)

Hepatitis B core total antibody (HBcAb)

Rapid Plasma Reagin (RPR) for Syphilis or Serologic Test for Syphilis (STS)

Human Immunodeficiency Virus Type 1 (HIV-1) Nucleic Acid Test

Hepatitis C Virus (HCV) Nucleic Acid Test

Hepatitis B Virus (HBV) Nucleic Acid Test

Cytomegalovirus Antibody (CMV Total Ab)

West Nile Virus Nucleic Acid-Test (during active mosquito season per FDA Guidance)

The tests for transmissible infectious diseases produced negative results. The names and addresses of the testing laboratories, the listing and interpretation of all required infectious disease tests, and a listing of the documents reviewed as part of the relevant medical records are on file and available upon request.

Due to limitations in testing technology, testing and donor screening cannot totally eliminate the risk that human tissue will transmit disease.

The donor has been evaluated and has been determined to be suitable for transplantation based on the donor suitability criteria current at the time of tissue recovery in accordance with United States Food and Drug Administration (FDA) regulations, local and state regulations, and StimLabs protocols.

Methods:

Study Design.

Blind study involving one hundred and eighty-two (182) subjects undergoing elective lumbar microdiscectomy will be placed in two randomized arms. One control group of ninety-one (91) subjects will undergo a typical lumbar microdiscectomy without the addition of Revita. The other ninety-one (91) will undergo a typical lumbar microdiscectomy with the addition of a 2x2cm Revita full thickness allograft. Once the microdiscectomy has been performed, a 2x2cm Revita allograft will be applied to the annulus of the index lumbar level just prior to closure in a manner according to package directions and instructions for use per the sponsor.
The patients in the Treatment group will not know that they will be receiving a Revita allograft.

Data will be collected via the OBERD system as the primary source of patient response collection. A dedicated hard-copy paper system specific to each patient will serve as secondary data collection. Each patient will be contacted by members of the research staff at each follow up point.

Study population and selection criteria.

All aspects of the study and consent forms will be IRB approved prior to implementation. All participants will require full informed consent, be willing and able to comply with all study requirements and will meet the following criteria; male or female aged 18-70 (inclusive), must be ambulatory with radiating low back and leg pain for greater than 6 months prior to surgery with clinical diagnosis of lumbar protruding disc.

Subjects will be excluded from the study based on the following criteria:

- Severe hypertension (systolic blood pressure greater than or equal to 200 mm Hg or diastolic blood pressure greater than or equal to 182 mm Hg)
- BMI greater than 45 kg/m^2
- Subject has had major surgery at the index level
- Is an active smoker or stopped smoking in the last 6 months
- Any pain that could interfere with the assessment of index level pain (e.g. pain in any other part of the spine)
- Active rheumatoid arthritis
- Active, local or systemic malignancy such as lung cancer or leukemia
- History of vascular disease or sickle cell anemia
- Use of the following medications:
    - No significant anticoagulant therapy (e.g. Heparin or Lovenox) during the study (treatment such as Aspirin and Plavix are allowed)
    - No systemic treatments that may interfere with safety or efficacy assessments during the study
    - No immunosuppressants
    - No use of corticosteroids
- Subject is pregnant or plans to become pregnant within 24 months of treatment
- Subject does not provide full consent
- Subject is involved with a worker's compensation, personal injury, or other legal matters related to their health

Recruitment methods.

Subjects will be identified through existing patients of Polaris Spine & Neurosurgery Center as well as through physician referrals. The Primary Investigator, Dr. Morrison and his partners (co-investigators) will be performing the microdiscectomy procedures for both control and treatment groups.
This study will be listed at www.clinicaltrials.gov.

Data collection and reporting.

Data will be collected at the following points: Immediately prior to the microdiscectomy, 1, 2, 3, 6, 12 and 24 months post-microdiscectomy. Data will be collected using the Oswestry Disability Index (ODI), 12-Item Short Form Survey (SF12) and evaluating reherniation rate. The ODI is a 10-topic questionnaire used to quantify disability due to low back pain. The SF12 is a 1-page, 12-item questionnaire that surveys patients' self-perception of health and any changes in ability to perform daily tasks. Baseline data will be collected in clinic prior to surgery, follow up data will be collected via the OBERD system, email/phone surveys and/or office visits. Responses collected at each time point will include ODI and SF12 data and be compared against the baseline ODI and SF12 scores reported just prior to microdiscectomy.
Data from the study will be maintained for two (2) years after the date the investigation is completed, terminated or until the records are no longer required to support the protocol, whichever date is later. Custody of the records may be transferred. Patient records and data are eligible for inspection and/or copying by applicable regulatory authorities.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. [21 CFR 50.25(c)]

Expected outcomes.

It is the sponsor's expectation that both short and long-term evaluations of the application of Revita will show improved patient outcomes over traditional microdiscectomy plans of care. Improvements in both ODI and SF12 scoring are expected from the treatment group compared to the control group. Data interpretation and the statistical significance of the results will be described later in this protocol.

Adverse reactions.

There is no expectation of any adverse outcomes or reactions due to a patient being treated with Revita. Revita allografts are minimally manipulated during processing and contain no additives or chemicals that would be expected to cause an Adverse Event (AE). All participants will be given access to contact info of the PI or co-investigators performing their microdiscectomy. Any adverse reactions should be reported immediately to the PI or co-investigators.

Reasons for Withdrawal or Termination

A subject may be discontinued from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of *possible* reasons for study treatment discontinuation:

- Screening Failure
- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse Event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study participation

- Protocol violation requiring discontinuation
- Lost to follow-up
- Sponsor request for early termination of study
- Subject death

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and the Case Report Form (CRF). If a subject is withdrawn from treatment due to an AE (adverse Event), the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. The Investigator must make every effort to contact subjects who are lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

Handling of Participant Withdrawals of Termination:
Although subjects may withdraw from the study at any time and for any reason, (or may be withdrawn at the Investigator's discretion), subject withdrawal should be avoided as much as reasonably possible. In any case, appropriate follow-up for endpoints should be continued. Subjects who prematurely discontinue are not to be replaced. For subjects considered lost to follow-up, the CRF must be completed up to the last visit performed.

Premature Termination or Suspension of Study:
This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, the Sponsor and the Institutional Review Board (IRB), as appropriate. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor and/or the IRB.

Methods and Study Schedule:

Subjects eligible for the study will review and undergo informed consent. Once consented, subjects will be randomly assigned on a 1:1 basis to undergo:

- Treatment Group, blind: Microdiscectomy with 2x2cm Revita allograft
- Control Group, blind: Current standard of care following a microdiscectomy (no additional tissue application).

Baseline/Screening Visit (-91 to -1 days from Day 0)

The following procedures will be performed at the Baseline/Screening visit:

- Review the study with the subject and obtain written informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization
- Assign the subject a unique screening/enrollment number
- Review and record medical history, surgical history, and medication history to determine eligibility based on inclusion/exclusion criteria
- Perform urinary pregnancy test for women of childbearing potential
- If patient has a smoking history and indicates he/she quit recently (within last 6 weeks from screening),
- Record demographics (age, race, ethnicity, gender)
- Document vitals
- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination
- Administer ODI and SF12

Treatment Visit (Day 0)

The following procedures will be performed on the day of microdiscectomy treatment **prior** to treatment if they were not completed at screening visit or if treatment occurs more than 2 weeks after the screening visit:

- Administer ODI and SF12

The procedures for microdiscectomy and anesthesia should occur as per standard clinical/hospital protocols.

Randomization of qualified subjects will be incorporated into the OBERD system once patient presents to the clinic for treatment and all the inclusions/exclusions are confirmed.

The following standard of care techniques will be used according to the arm the patient is randomized to:

Control Group (blind):

The ninety-one (91) member control group will undergo typical microdiscectomy treatment.

Treatment Group (blind):
The ninety-one (91) member treatment group will undergo typical microdiscectomy treatment with the addition of a Revita allograft. The graft will be placed dry over the annular defect and wrapped around the exposed dura. Once in place, the graft will be rehydrated with 3-5cc of sterile saline.

The following procedures will be performed the day of treatment, ***post treatment***:

- Assess for adverse events
- Provide subject with post-operative instructions to go home with.

Follow-Up Visits

After hospital discharge, clinical follow-up will occur at the following time points: 1, 2, 3, 6, 12 and 24 months or at any time that the subject or health care provider believes an adverse event has occurred. Patients will have a grace period of 14 days after each time point to complete follow up ODI and SF12 surveys. Surveys not completed in this timeframe will not be included in the final data set to provide a clearer picture of data collected from each timepoint.

The following procedures will be performed at all follow-up visits, unless otherwise noted:

- Assess for adverse events
- Assess for complications following treatments
- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination
- Administer ODI and SF12
- Evaluate for reherniation

Final Study Visit

The following procedures will be performed at the final post treatment visit:

- Assess for adverse events
- Assess for complications following treatments
- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination
- Administer ODI and SF12

Unscheduled Visit

The following procedures will be performed if the subject presents to the clinic at any other time point not specified above:

- Assess for adverse events

- Assess for complications following treatments
- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination

Early Termination

All subjects have the right to withdraw from study participation at any time during the study. If, for whatever reason, a subject withdraws from the study, an Early Termination visit will be performed.

The following procedures will be performed (if agreed upon by the subject) at the *Early Termination visit*:

- Assess for adverse events
- Assess for complications following treatments
- Document all current medications, including medications over-the-counter and herbal medications
- Perform physical examination
- Administer ODI and SF12

RANDOMIZATION

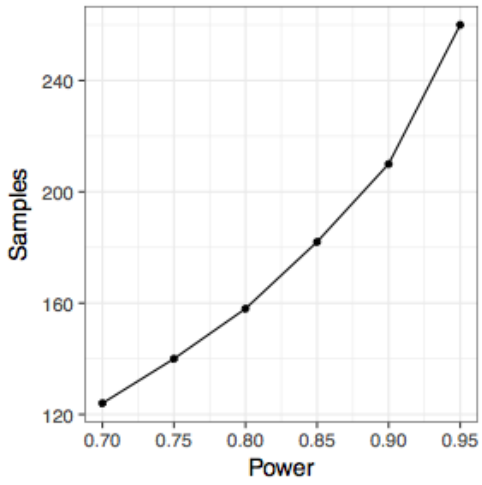
Subjects who meet all inclusion and exclusion criteria will be randomized on Treatment Day in a 1:1 ratio to either the Treatment Group or the Control Group, in accordance with a computer-generated schedule prepared by a biostatistician. The randomization schedule will be incorporated into the OBERD system. Randomization will then be performed by study personnel directly in the OBERD system. Study personnel will be instructed not to randomize until subject has been confirmed to meet all inclusion/exclusion criteria on treatment day.

SAMPLE SIZE JUSTIFICATION

Sample Size Calculations

The following type I error rates and decision boundaries for the study are specified:

- primary outcomes are ODI and SF-12 scores
- null hypothesis: $\mu_{Revita} = \mu_{SOC}$
- type I error rate: α=0.05
- sampling ratio: κ=1
- effect size: 0.45



Power Analysis

	Power, 1-β*					
	0.70	0.75	0.80	0.85	0.91	0.95
Sample Size	124	140	158	182	210	291

*Power, 1-β, is defined as the likelihood of correctly detecting an effect when an effect exists. When power is high, probability of Type II error (i.e. concluding there is no effect when an effect exists) goes down.

Loss to follow-up
Possibility of loss to follow-up at 12 months postoperative is moderate and can be assumed at 15%, adjusting the sample size calculation at 80% power to n=158+24=182.

Recommendation
The sample size was calculated on the basis of the null hypothesis (H_0: $\mu_{Revita} = \mu_{SOC}$). In a previous study [Anderson DG, et al. Cryopreserved amniotic membrane improves clinical outcomes following microdiscectomy. Clin Spine Surg 2017;30(9):413-418], patients treated with a cryopreserved amniotic (cAM) tissues during elective lumbar microdiscectomy surgery experienced a significantly higher improvement in pain, disability, and quality of life compared to those receiving no tissue as standard of care.

For a fixed sample size design, the sample size required to achieve a power of 1-β=0.80 for a two-sided t-test at level α=0.05 under these assumptions amounts to a total of 158 patients, or 79 patients in each treatment group. This calculation also provides adequate power for two-sided equivalency chi-squared tests of secondary outcomes between treatment groups.

As the study outcome for the primary endpoint are available 2 years after treatment, the drop-out rate is expected to be moderate. A potential dilution of the treatment effect due to drop-outs is take into account (e.g. loss to follow-up); it is assumed that this can be compensated by additional 15% of patients to be enrolled, and therefore the total sample size required for a fixed sample size design is n=158+24=182 patients, or 91 patients in each treatment group.

STATISTICAL ANALYSIS PLAN

Primary Endpoint
Low back and leg pain as measured by the Oswestry Disability Index (ODI), 12-Item Short Form Survey (SF12)

Secondary Endpoints
Reherniation rate.

All analyses will be performed using per-protocol population as well as intention-to-treat population (to include subjects who are withdrawn prematurely or randomized but not treated per randomization arm).

ASSESSMENT OF SAFETY

Adverse events (AE) will be monitored and collected by the study team from the point of signed consent until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. For each AE, a detailed explanation will be obtained from the subject and subject's medical record. All AEs will be recorded on the CRFs.

Definition of Adverse Event

An AE is defined as any unanticipated medical occurrence regardless to relationship of the investigative arm of the trial. An AE can be any unintended sign, lab abnormality, symptom, or disease associated with the trial. Any abnormality that presents during a medical test are to be defined as an AE if it produces clinical signs and/or symptoms, requires intervention, or deemed clinically significant by the Investigator.

Definition of Serious Adverse Event

An adverse event is considered serious if it results in any of the following:

1. Death
2. A life-threatening AE
3. Requires inpatient hospitalization or prolongs existing hospitalization
4. Persistent disability/incapacity
5. Medically important event by the Investigator

Definition of Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Severity of Event

The Investigator will be asked to assess the severity of the AE using the following categories:

Mild: Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

Relationship to Study Products

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely: The relationship of the AE and the study device or the study procedure can definitely be established.

Probably: While a clear relationship to the study device or to the study procedure cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.

Possibly: There is no clear relationship between the AE and the study device or study procedure; however, one cannot definitely conclude that there is no relationship.

Unrelated: There is no relationship between the AE and the study device or study procedure. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced.

Expectedness

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study products.

Time Period and Frequency for Event Assessment and Follow-Up

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

SAE Reporting

In the case of a SAE, the Investigator must notify the Sponsor within 1 working day after the Investigator first learns of the event. The IRB must also be notified according to their notification policies.

UADE Reporting

In the case of a UADE, the study Investigator shall notify the Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. The study Sponsor is responsible for conducting an evaluation of an UADE and shall report the results of such evaluation to the reviewing IRB and the Investigator within 10 working days after the Sponsor first receives notice of the effect.

Pregnancy

If a female subject becomes pregnant during the trial, she must be followed up until the outcome of the pregnancy is known. The outcome of the pregnancy must be reported to the Sponsor on the appropriate AE CRF.

Data Safety Monitoring

As the treatments and surgical techniques are currently being used as standard of care, the study team does not anticipate subjects experiencing any adverse events solely due to being in the study. This is simply a proposal to formally randomize and follow subjects undergoing two commonly performed procedures, both of which have been shown to be safe and approved. Therefore, a formal Data Safety Monitoring Board will not be needed for this study.

DATA MONITORING

The Principal Investigator will be responsible to ensure the study is conducted in accordance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and that the data recorded is valid. To achieve this objective, the study will be continuously monitored and reviewed on a monthly basis by the study team.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).
A Clinical Monitoring Plan will be created by the Sponsor and describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

DATA HANDLING AND RECORD KEEPING

The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

Only study personnel will collect data. Hard copy documents will be retained for the duration of the study until data entry. All hard copy documents will be kept in a locked cabinet in the research coordinator's office. Data entry will be completed in the OBERD secure database (which will cover all the created CRFs). OBERD data will be exported into Excel or SAS file format (password protected), which will then be used for data analysis. Only de-identified data will be used for data analysis. All hard copy documents will be shredded within five years after completion of the study upon Sponsor approval.

Collected de-identified data will be sent to a biostatistician for statistical analysis.

INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

CONSENT PROCESS

Subjects will be approached when they come through the clinic being evaluated and considered for microdiscectomy for radiating lower back and leg pain. Each potential subject must provide written consent with full knowledge of the procedures involved. The informed consent, approved by the IRB and in accordance with regulatory guidelines, must be fully explained by the Investigator or member of the study staff including the study aims, methods, benefits and risks, and signed by the subject before enrollment into the study. Potential subjects will be informed that study participation is voluntary and that they may withdraw at any time. The subjects will be told that choosing against participation will not affect the care received for treatment. The subjects will be informed that they will be authorizing access of investigational staff to confidential medical records. The subject will be given sufficient time to read the consent and ask any questions. Once the informed consent is signed, the subject will be given a copy of the document.

PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
All protocol deviations/violations should be documented using the Protocol Deviations/Violations CRF and submitted to the IRB according to their reporting guidelines.

LAWS AND REGULATIONS

This clinical study will be conducted in compliance with all national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines. The trial will be registered on www.clintrials.gov and on other sites, as appropriate.

PUBLICATION AND DATA SHARING POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation

of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

STUDY PERSONNEL AND ROLES

Thomas Morrison III, MD	Principal Investigator	Responsible for all study related issues
Max Steuer, MD, Christopher Tomaras, MD, Raymond Walkup, MD	Co-Investigators	Data collection; screen, consent, and follow up with subjects
Carlie Ivie	Project Manager	Data management and analysis; addresses IRB issues; and communicates with IRB
Lydia Jones, Sarah Gamache, Matt Sartorio	Study Coordinator	Data collection; screen, consent, randomize, and follow up with subjects
Alessandria Struebing	Statistician / Data Manager	Data management and analysis

CONFLICTS OF INTEREST

No conflicts of interest have been reported.

APPENDIX I

The trial will be conducted in accordance with the ICH E6, the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 91, 21 CFR Part 56, and 21 CFR Part 812. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signature of Principal Investigator	**Date (mm/dd/yy)**
Printed Name	
Name of Institution	

APPENDIX II

Schedule of Events

Visit	Screening / Baseline	Treatment / Day 0	Month 1	Month 2	Month 3	Month 6	Month 12	Month 24	Early Termination	Unscheduled Visit
Visit Window	-30 day	-	+ 0-14 days	+ 0-14 days	+ 0-14 days	+ 0-14 days	+ 0-14 days	+ 0-14 days	-	-
Informed Consent										
Assign subject ID										
Medical/Social History (incl. Demographics, Ht, Wt, BMI)										
Inclusion/exclusion criteria										
Concomitant Meds										
Physical Exam (incl. temp, BP, HR)										
Urinary pregnancy test										
Randomization										
AE / surgical complications collection										

1. Only employment status will be collected
2. To be performed for women of childbearing potential, if not performed as standard of care
3. To be performed on subjects with history of diabetes who do not have serum HbA1c test done within 6 weeks prior to screening
4. Questionnaires must be administered PRIOR to surgery on Treatment Day and Physical Examination at Follow-Up/Early Termination Visit

To be performed if Early Termination occurs AFTER 3-month follow-up visit