1.1 CONFIDENTIAL

Viable **A**llograft **S**upplemented Disc Regeneration in the **T**reatment of Patients with Low Back Pain with or without Intervertebral Disc Herniation – **VAST** Trial

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Product: VIA Disc

Trial Number: VAST-001-017

PROTOCOL APPROVAL FORM

Protocol No: VAST-001-017

Study Title:

Viable **A**llograft **S**upplemented Disc Regeneration in the **T**reatment of Patients with Low Back Pain with or without Intervertebral Disc Herniation – **VAST** Trial

This study protocol was subjected to critical review. The information it contains is consistent with Vivex's current knowledge of the risks and benefits of the, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2000 and clarified in 2004[1], and the guidelines on Good Clinical Practice.

The study protocol has been reviewed and approved by the following:

Douglas Beall, MD_____ _____

Name Date
Principal Investigator

Timothy Ganey, PhD_____ _____

Name Date
Protocol Author

Shab Namin, PhD_____ _____

Name Date
Study Manager

H. Thomas Temple, MD_____ _____

Chief Medical Officer Date

Investigator's Statement: *"I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment. I agree to await IRB approval for the protocol and informed consent before initiating the study to obtain consent from potential subjects prior to their enrollment into the study, to collect and record data as required by this protocol and case report forms, to prepare annual, final and adverse event reports as required by this protocol, and to maintain study documentation for the period of time required."*

Principal Investigator Signature	Date of Signature

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PROTOCOL SYNOPSIS

Title	**Viable Allograft Supplemented Disc Regeneration in the Treatment of Patients with Low Back Pain with or without Intervertebral Disc Herniation – VAST Trial**
Objective	To evaluate the safety and efficacy of viable allograft transplantation for the treatment of patients with symptomatic disc degeneration and tissue loss
Study Design	Multi-center, prospective, parallel, triple arm study to assess patients who participated in the VAST trial and receiving either viable allograft, saline, or allograft after cross-over. These patients will be evaluated at baseline, injection, 6 months, and 12 months. Subjects will then have an option for a 24 months and 36 months extension after their index procedures. Patients who received saline or active allograft in the VAST study, will be allowed to receive viable allograft and followed for an additional 12 and 24 months after that election. These subjects will need to meet initial inclusion/exclusion criteria again before another injection.
Endpoints	Primary: • Improvement in Oswestry Disability Index (ODI) at 6 and 12 months after treatment. • Durability of Oswestry Disability Index (ODI) at 24 and 36 months after initial inclusion compared with 12 month improvement. • Improvement in Visual Analogue Scale of Pain Intensity (VASPI) at 6, and 12 months after treatment. • Durability of Improvement in Visual Analogue Scale of Pain Intensity (VASPI) 24 months and and 36 months after initial inclusion compared with 12 month improvement. Secondary

	• Improvement in ODI, SF-36, and VASPI at 6 and 12 months after treatment • Improvement in ODI, SF-36, and VASPI scores for optional 24 month and 36 month follow up subjects • X-ray and MRI measurements at 6 and 12 months after treatment • AE/SAE rates after treatment • Hospitalization rate at 12, 24, or 36 months after treatment • Re-operation rate at 12, 24, or 36 months after treatment • Resource utilization following treatment and at 6 and 12 months (and optional 24 & 36 month) follow up visits
Study Population	Patients evaluated for degenerative intervertebral disc disease demonstrating Pfirrmann Grade [3-6] by MRI
Clinical Sites	Up to twenty (20) sites in the United States
Sample size and **randomization**	Approximately 220 subjects randomized to viable allograft or placebo or control in 3.5:1:1 ratio: n_{active} = 140 $n_{placebo}$ = 40 $n_{control}$ = 40 For study extension: The original randomized population will be pooled and reconsented for an optional follow up for 24 and 36 months.
Study Design	The study is composed of three separate phases. There will be the Screening Phase followed by the Active Phase equaling 12 months then followed by the optional long term follow up at 24 months and 36 months. Patients need to meet entry criteria for all phases.

	During the Screening Phase, subjects will be assessed for study eligibility, X-ray and MRI within the previous 6 months, SF-36, ODI, and VASPI to establish a baseline for participation. If meeting eligibility, they will be scheduled for allograft treatment, placebo (saline) treatment, or conservative care treatment. Those who meet the Active Phase entry criteria will be randomized at Day 0 to either receive the viable allograft, placebo as saline, or be assigned to continue conservative treatment. Specified subjects, as noted below, will return to the clinic for a safety assessment 1 month after the transplant, and subsequently at 6, and 12 months for safety and efficacy assessments. Patients who continue conservative care will be evaluated at 3 months, as well as 6 and 12 months. Physicians at their discretion can bring subjects back for follow-up to assure safety at any time point throughout the duration of the study. The first 24 patients to be randomized (at least 4 from each treatment group) will have an additional study visit 1 month after treatment. All data from the 1-month study visit will be collected and reviewed by the Steering Committee to confirm that enrollment can continue. Subjects will have the option to continue with a long-term follow up at time points of 24 and 36 months. Questionnaires will be completed over the phone with the study coordinator's prompting or during an in-office visit. All randomized subjects will also have the option to receive an allograft injection during the 24 month office visit after meeting inclusion/exclusion criteria.
Inclusion Criteria	• Able to provide an English written Informed Consent • Age 18 to 60 years inclusive • Male or female • Body mass index <35 • Pfirrmann Grade [3-6]

	• Radiographic confirmation by MRI/X-ray of: (1) translational instability defined as ≤5 mm, or (2) angular instability defined as ≤5° • Back pain (with or without radicular leg pain) measured by: (1) ODI of at least 40%, and (2) VASPI of at least 40mm • Pathologic level between L1 and S1 • 1 or 2 vertebral level involvement that has been evaluated for at least 6 months and treated with conservative care • Symptomatic back pain attributable to intervertebral disc for a minimum of 6 months • No previous surgical treatment at the disc level(s) being considered • Psychosocially, mentally and physically able to fully comply with this protocol, and follow-up schedule • Ability to undergo allograft transplantation • Life expectancy >2 years • No contraindications to MRI • No history of malignancy (basal cell carcinoma) or chronic infectious disease (e.g. HIV, Hepatitis) • Agree to use appropriate contraception; not planning on becoming pregnant for 24 months after treatment • Patient disc for transplant confirmed by inter-discal pressure measurement, or disc-imaging study. • No signs or symptoms of infection • No chronic use (>7 consecutive days) of anticoagulants (such as aspirin) or NSAIDs prior to treatment
Exclusion Criteria	• Seropositive or seronegative spondyloarthropathy • Type III Modic changes • Prior surgeries of segments between L1 and S1 • Chemonucleolysis or percutaneous laserectomy of the affected disc prior to the study • Chronic facet syndrome

	• Stenosis of the spinal canal that is moderate to severe or more in degree • Spondylodiscitis • Spondylolisthesis (lysis and degenerative) • Severe motor deficit or cauda equina disorder based on investigator determination • Congenital abnormalities of the spinal nerves • Pelvic and inguinal angiopathy • Neurogenic inguinal syndrome • Syringomyelia • Diastenomatomyelia • Traumatic neurological disorders • Diseases of the kidney (nephritis, pyelonephritis) • Other severe diseases of any other major body system as judged by the investigator • Regular intake of systemic steroids • Malignant diseases of any solid organ or any hematologic malignancy during the previous 5 years • Patients who have participated in a clinical trial within the last month prior to inclusion • Moderate to severe or greater lumbar stenosis of both transplantation endplates and adjacent levels
Treatment Strategy	Single, or two-level intervertebral disc treatment with viable allograft, placebo, or conservative care treatment for Pfirrmann grade III - VI disc imaging assessment
Statistical Analysis	Primary analysis: The primary efficacy analysis will be performed on the modified intent-to-treat (MITT) population. The MITT population is defined as all subjects who underwent the viable allograft treatment or placebo treatment, and at least one valid post-transplant assessment of ODI and VASPI. The null hypothesis is that there is no difference in ODI at 12 months following viable allograft implantation between the three treatment groups 1.) Allogeneic Cells with supplemental

	micronized nucleus pulposus, 2.) saline, or 3.) conservative, non-surgical, care. For all Screening and Active Phase baseline data, descriptive statistics will be presented. A hierarchical test procedure will be applied. In the first step the distributions of the pre-post difference of the groups will be compared using Wilcoxon rank-sum-test. In case of a significant result, a responder analysis will be done using Fisher's exact test. All secondary variables will be analyzed in an exploratory way using adequate statistical procedures

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IRB	Institutional Review Board
ITT	Intention To Treat
LOCF	Last Operation Carried Forward
MEC	Medical Ethics Committee
MITT	Modified Intent-To-Treat
MRI	Magnetic Resonance Imaging
n	Number
NaCl	Sodium chloride
NP	Nucleus pulposus
OPDQ	Oswestry Low Back Pain Disability Questionnaire
ODI	Oswestry Disability Index
PP	Per Protocol
PTT	Partial thromboplastin time
SAE	Serious Adverse Event
SAS	Statistical analysis system
SF-36	Short Form 36
SOP	Standard Operating Procedure
SUADE	Serious Unanticipated Adverse Device Event
UADE	Unanticipated Adverse Device Event
V	Visit
VASPI	Visual Analogue Scale of Pain Intensity

3 OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of viable allograft transplantation for the treatment of patients with symptomatic disc degeneration and tissue loss.

The primary criterion is the outcome of the Oswestry Low Back Pain Disability Questionnaire (OPDQ) modified according to Hudson-Cook and calculated as the Oswestry Disability Index (ODI) at 6 and 12 months after transplant, and the Visual Analogue Scale of Pain Intensity (VASPI) at 6, and 12 months following allograft supplementation. Secondary parameters of efficacy will include SF-36. Structural outcomes will be assessed using X-ray and Magnetic Resonance Image (MRI) measurements at 12 months. Safety will be assessed by the incidence and severity of adverse events (AEs) and clinically important changes in laboratory tests. All subjects (excluding conservative care crossover subjects) will be randomized to include MRI at 6-month follow-up (MRI or no MRI, ratio 1:1) in addition to all other assessments. Subjects randomized to conservative care will be assessed at 3 months. If at 3 months these subjects demonstrate a significant decline in condition, they will be offered the option to receive allograft treatment and will be followed for the subsequent 6 and 12 months. The conservative care subjects that crossover to the allograft treatment group will all receive an MRI at 6-month and 12-month follow-up after allograft treatment.

A correlation of the clinical results (scores) and the morphological results (X-ray, MRI) will be evaluated. All additional efficacy and safety data will be analyzed descriptively.

The optional long-term follow up will allow for additional objectives to be analyzed. At 24 and 36 months, subjects will have the opportunity to fill out VASPI, ODI, SF-36, and Resource Utilization forms which will be analyzed and compared to the original 12-month data. The active allograft and placebo cross over to allograft treatment at 24 months will also be asked to fill out the same questionnaires. This data will be compared to the first 12 months of data in the placebo group.

4 BACKGROUND

Degenerative changes of the lumbar segments are an inevitable consequence of the aging and are often a reason for chronic back pain and neurological complications. It has been estimated that nearly 80% of the population suffer from lower back pain at least once during their lifetime[2,3] and during recent years degenerative changes of the lumbar segments have become an outstanding medical problem in the industrialized nations.[4,5] Progress in clinical medicine has acknowledged several patho-mechanisms of intradiscal mass change(s) with respect to disc herniation as well as degeneration. In general, the main reason for disc herniation is attributed to trauma, and the degree of degeneration of the disc and the trauma causing herniation vary widely but are correlated. Making the connection important but perhaps more challenging is information regarding degenerative changes linked to genetic, metabolic, and mechanical imbalance.[6,7,8,9,10]

The development of chronic back pain after lumbar disc herniation in conjunction with degenerative changes results in a medical condition often treated surgically. Besides conservative non-surgical methods such as rest, physical therapy, and bracing, often times surgical processes such as discectomy, total intervertebral disc prosthesis as well as replacement of the nucleus are now used for treatment of chronic back pain after disc herniation.[11,12,13,14,15,16,17] So far, no clinically established procedure is available that slows down the progression of degeneration. In this context, the question about the ability of the intervertebral disc to regenerate intervertebral disc cellular matrix subsequent to discectomy has been raised.

Repair of mild degeneration of the disc at the time of herniation, and regeneration of disc matrix following discectomy and transplantation of a variety of *in vitro* derived cell lineages has been proven in animal models.[18,19,20] It has similarly been shown that transplantation of similar cells into traumatic lesions of the knee, results in possible regeneration of cartilage.[21,22]

In the present study, regeneration of vertebral disc matrix will be assessed as an allograft transplant. Based on a proprietary technology developed at UMTB (Vivex, Inc.; Marietta, GA, USA) that retains active cells shown to offer regenerative potential and pairs them with donor-derived nucleus pulposus, a formulation has been aligned to supplement degenerative disc changes with the potential for better mechanical performance and presumably physiologic as well. The cells supporting this product are capable of differentiating into multiple lineages including disc chondrocytes given appropriate conditions and stimulating factors.[23,24,25]

4.1 In-vitro studies

In vitro cultivation of intervertebral disc cells as a monolayer has been performed by several investigating groups[18,26,27] using different media. It was reported, that intervertebral disc cells were able to proliferate *in vitro* and regained their chondrocyte-specific properties after contact with collagenous media. [28,29] This led to the assumption, that *in vitro* expanded intervertebral disc cells could be transplanted into the disc and perhaps integrated into pre-existing collagenous structures.

4.2 Pre-clinical studies

An early (circa 1999) pre-clinical study in a rodent model showed that transplantation of autologous nucleus pulposus cells that had been activated by co-culture with annulus fibrosus cells into degenerated discs in rabbits, delayed the formation of clusters of chondrocyte-like cells, the destruction of disc architecture, and the elaboration of type-II collagen. [30] This early study has led to many more recent attempts, using improved techniques, different models, and both autologous and allogeneic cell lines, to prevent further disc degeneration subsequent to discectomy. Clearly the advantage of exposing naïve cells with full differentiation capacity to appropriate guidance towards a specific phenotype is the direction and dimension intended.

Ganey and Meisel [31] in cooperation with the Emory Spine-Center in Decatur, Georgia (USA) removed intervertebral disc material (segment L1/L2, L3/L4) from 18 dogs while leaving segment L2/L3 unchanged. Subsequently, transplantation of cultured autologous disc-derived chondrocytes (ADCT) into the intervertebral disc (segment L3/L4) was performed to investigate the hypothesis that autologous disc chondrocytes could be used to repair damaged intervertebral disc. Comparisons between the untreated degenerated disc (L1/L2), the normal intervertebral disc (L2/L3), and the disc level that had received the ADCT transplantation (L3/L4) were conducted over a 12-month period. The transplanted cells were integrated into newly developed extracellular matrix, produced an extracellular matrix that displayed composition similar to normal intervertebral matrix, and when the disc heights were analyzed for variance according to treatment, a statistically significant correlation between transplanting cells and retention of disc height was achieved. A good correlation was found between the macropathological results and the x-ray and MRI results.

These results led to the conclusion that progression of degeneration of the lumbar disc after operation can be prevented by transplantation of *in vitro* cultivated disc-derived cells into the intervertebral space and that the MRI is a suitable non-invasive method for evaluation of the changes.

Further work elaborated the use of non-cultured cell lines, or adipose-derived regenerative cells, in repairing the intervertebral disc following partial discectomy in dogs.[32] This study was designed to evaluate the safety and performance of adipose-derived regenerative cells (ADRCs) injected into the canine spine six weeks post discectomy to engraft in the vertebral discs, to stimulate disc matrix deposition, and to enhance recovery by delaying further disc degeneration as measured by imaging, macroscopic and microscopic techniques as well as molecular biology assessments of proteins. The study concluded that the treatment of intervertebral discs with ADRCs in hyaluronic acid is safe and effective in this canine model of intervertebral disc injury that mimics clinical patients undergoing discectomy after herniation. ADRC treated discs in this study closely resembled healthy control discs at 6 and 12 months based on pathology as well as based on measurement of matrix protein amounts. ADRCs remained viable over the 12-month study period and stimulated significant increases in aggrecan and type-II collagen, two critical components comprising a normal disc matrix.

4.3 Clinical studies

In the first clinical approach in man, 8 patients suffering from traumatically caused disc herniation were chosen for an individual treatment (unpublished data, Meisel, Ganey, et al.). All patients underwent a sequestrectomy. Protruded disc material or cells that were removed during discectomy were used for *in vitro* proliferation. Five of the 8 patients received an autologous transplantation of the proliferated disc derived cells 3 months after discectomy.

One aim of this pilot study was to prove that the disc that underwent discectomy was healed after 3 months therefore ensuring that the transplanted ADCTs would not pass out of the disc. This was confirmed by utilizing a standardized volume pressure measurement that is commonly used during chemonucleolysis.[33]

As no statistical analysis was planned for these individual attempts, individual case control observations were performed in order to investigate the methodological and medical questions. After a mean duration of follow-up of 8.2 months (1 - 18 months), the 5 patients who received an ADCT transplant were completely free of complaints, working fulltime and had resumed sports activities. First analyses of the MRI data showed no decrease in intervertebral height, no disc desiccation and no degenerative changes of the adjacent vertebral endplates. These results correlate well with the results of the pre-clinical rodent model.

The promising results of this pilot study led to *EuroDISC*, a prospective, randomized, multicenter clinical trial designed to assess the long-term efficacy of ADCT in a broader population that was initiated in 2002. From that study, 109 patients were followed and an interim of the results summarized as follows:

1. The annulus had healed sufficiently 12 weeks after discectomy to allow for a successful transplant.
2. The transplant was achieved by a minimally invasive percutaneous injection.
3. Patients receiving cells had greater pain reduction.
4. Discs in patients receiving cells had a significant difference in fluid content.
5. Adjacent discs also demonstrated a difference in fluid content.

The results of the pre-clinical and clinical studies described above, provide the confidence that the transplant of ADCTs post-discectomy could be a viable treatment with long term effect and improvement over the standard of care.

5 RATIONALE

Since 1991, several investigating groups have shown using *in vitro* and *in vivo* analyses, that degenerative changes of the intervertebral disc can be retarded, or positively influenced within the meaning of repair of the annulus fibrosus and the nucleus pulposus. [34,35] The clinical relevance of these investigations is still under discussion.

The aim of the VAST trial is to investigate the clinical relevance of the repair of intervertebral disc tissue by a supplementary transplantation of cellularized allograft disc matrix in a controlled clinical study, or continued treatment with conservative, non-surgical intervention. The clinical differences between the three groups will be compared by analyzing pain, functional restrictions and efficiencies of the lumbar spinal column, and neurological deficits using different scores that were especially developed for the assessment of degenerative back complaints.[5,36,37,38,39] Additionally, X-ray and MRI will be performed in order to compare the morphologic changes between the active allograft treatment, placebo treatment and conservative care treatment groups. Evaluations of X-ray and MRI will include changes in the height of the intervertebral disc, modic changes of the adjacent endplates and the fluid content of the operated intervertebral disc.[40,41]

The main target of this new method is to slow down the complex degeneration process of the intervertebral disc that often increases after operation of the disc and to offer prescriptive option to therapeutic intervention that is clinically relevant and economically efficient.[42]

All previous and current human studies of transplanted cells, have involved the use of autologous or allogeneic cells that required *ex vivo* expansion of the cells, which is costly, time-consuming and strictly regulated, making it an intricate procedure. By utilizing allograft preparation technology refined by UMTB through minimal manipulation of the tissue and cells, strict regulatory issues are circumvented. Clinical costs may also be reduced, as the number and duration of hospital admissions may be diminished, and the need for expensive stem cell culture facilities is eliminated.

A variety of autologous ADRCs have been tested and are being utilized in a variety of indications in the clinic including breast reconstruction surgery subsequent to mastectomy,[43,44,45] cosmetic surgery of the face[46,47] and breast,[48] and both acute[49] and chronic[50] cardiovascular disease. While the mechanism of action remains to be fully elucidated, pre-clinical studies indicate that a variety of cells transplanted into the disc are capable of generating extracellular matrix and providing the necessary cellular components required to prevent further disc degeneration following discectomy. Cells aligned to this study and supplementary allograft material offer confidence in

differentiation towards a nucleus pulposus phenotype, therefore, it is warranted to conduct this study and to confirm this technology in a controlled, safe, and regulated environment.

To minimize patient risk, the first 24 patients (at least 4 from each group) will have an additional clinic visit one month after transplantation and will undergo a full safety assessment; including X-ray and MRI (see Appendix A). All data collected up to and including this point in the study will be collected and reviewed by the Steering Committee, who will determine if patient recruitment can continue. The parameters used by the Safety Committee to determine whether recruitment can continue, will be pre-defined in a separate document but will include the following:

1. A comparison of the adverse event (AE) profile between the three groups including rate, relationship, and severity.
2. A comparison of the clinical laboratory parameters between the three groups.
3. A comparison of vital signs and physical examination findings between the three groups.
4. A comparison of X-ray and MRI findings between the three groups.

6 STUDY DESIGN

This is a, prospective, randomized, parallel-arm, multicenter study that will enroll up to 220 evaluable patients at up to 20 clinical sites. The outcomes of this trial will be based on assessment of primary and secondary endpoints at 6 and 12 months after treatment of supplementary allograft compared to conservative care in subjects who have pain attributable to disc degeneration as judged by MRI scoring (Pfirrmann), physical examination, and patient reported pain. Optional long term follow up at 24 and 36 months for all randomized subjects will allow for additional secondary endpoints to analyze pain.

The study is composed of three phases – the Screening Phase (enrollment), Active Phase (12 months) and the optional follow up period (additional 24 months). As outlined in Figure 1, there is an indeterminate overlap of up to 14 days between the end of the Screening Phase and the start of the Active Phase for individual subjects in order to evaluate the protocol, and consent to their participation. After completing the Informed Consent procedure, screening and study specific procedures can be performed. Only patients that meet the entry criteria for both phases are eligible and can participate in this study.

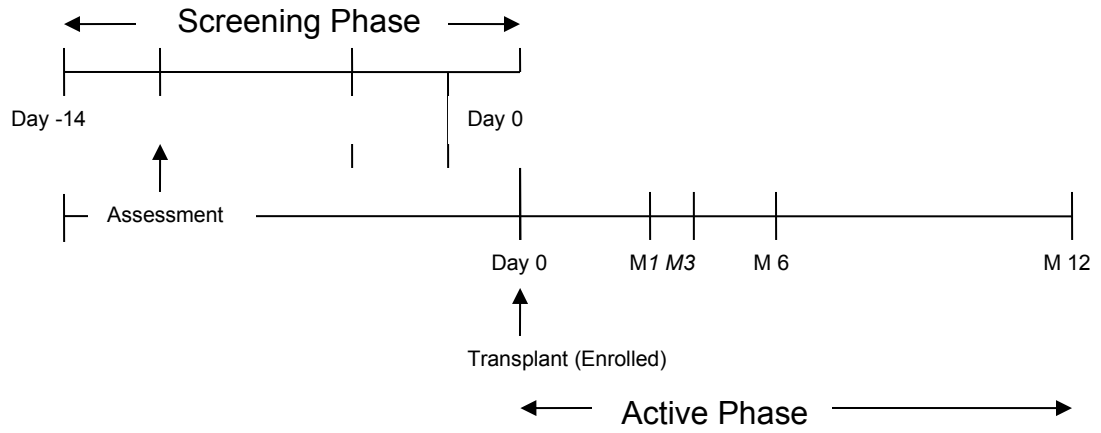
During the 14 days of the Screening Phase (Day -14 to Day 0), patients will be assessed for study eligibility to establish their baseline condition, and will be randomized to either conservative care (maintaining current level of care), or be provided with supplementary allograft transplantation (Day 0 of the Screening Phase), or receive placebo treatment (saline). All patients who are randomized to conservative care in the Screening Phase (Day -14 to Day 0), will be evaluated as per standard of care and will be assessed along with those who are selected for eligibility to enter the Active Phase of allograft transplantation.

The first 24 subjects randomized (at least 4 subjects from each group) will return to the clinic for a safety assessment 1 month after treatment. Subsequent clinic visits will occur at 6 and 12 months following treatment for safety and efficacy assessments. Subjects randomized to conservative care will additionally receive a clinical follow-up at 3 months to assess pain, change, or loss of function since their initial visit.

Optional long term follow up at 24 and 36 months for all randomized subjects will allow for additional secondary endpoints to analyze pain. Subjects who wish to participate in the long term follow up will reconsent with the informed consent addendum 2 during an office visit. Subjects then will be reassessed for inclusion/exclusion criteria and fill out VASPI, ODI, SF-36, and Resource Utilization questionnaires. If eligible for an allograft injection, the PI will perform a neurological exam, physical exam, labs, and give the subject applicable questionnaires. An MRI and x-ray will be performed on subjects receiving another injection for safety purposes.

The 36-month visit can be performed over the telephone by the study coordinator if the subject wishes.

Figure 1 – Study Design



6.1 Study Population

The study population will consist of approximately 220 male or female patients of any ethnicity from 18 to 60 years of age who demonstrate clinical disc degeneration at one or two vertebral level from L1 to S1 that would be considered candidates for conservative care, or surgery. Patients must be classified with moderate to severe disability (ODI ≥40%) and chronic pain (VASPI ≥40 mm). Eligible patients must have no contraindications to allograft transplantation, have a life expectancy of >2 years, and be willing to return to the clinic for multiple safety and efficacy assessments for up to 12 months following enrollment.

6.2 Patient Identification and Randomization

The Informed Consent Form (ICF), signed prior to any study specific screening procedures being completed, will provide details on both the Screening Phase and the Active Phase of the study. Each patient that signs Informed Consent will be randomized to the active allograft, placebo, or conservative care treatment group. The randomization will occur through a secured envelope system, during which the subject will be provided with a unique subject identification number (XX-XXX, site number-subject number). During the Screening Phase, all subjects randomized to active allograft or placebo treatment will be scheduled for a transplantation procedure, while the conservative care treatment subjects will be followed as per the routine standard of care.

On or before Day 0 of the Active Phase, the patency of the affected disc will be confirmed, and subjects determined eligible from the screening phase who have consented to participation and are randomized to allograft treatment will receive the study material. Patients are considered enrolled in the study when they undergo successful treatment in the Active Phase and receive either allograft treatment, placebo (saline) treatment, or conservative care treatment.

6.3 Blinding

The assignment to treatment (active allograft, or placebo, or conservative care) is open label at Day 0 of the Active Phase to the extent that subjects receiving allograft or placebo will not be aware of what they have received, while those assigned to conservative care will be aware. All site study staff will be aware of the group to which each subject is randomized. Sites will be trained to ensure that subjects receiving the allograft or placebo treatment will remain blinded to their treatment throughout the study duration. Subjects will be unblinded during the study exit or upon signing of the new informed consent for the study extension.

6.4 Treatments administered

Subjects screened and eligible for the Active Phase of the study will have diagnosis of the affected disc to normal standard procedures for all treatment groups. At the baseline visit (Day 0) of the Active Phase, eligible subjects who are randomized into allograft or placebo treatment will undergo a transplantation procedure. This procedure will consist of the following:

1. Transplant supplemental viable allograft into the affected disc
2. Transplant placebo saline treatment as alternative arm of study.

These procedures are outlined in detail in Appendices B and C respectively.

At 24-months, placebo saline subjects and active allograft subjects are eligible to receive the allograft injection.

6.5 Identity of investigational product(s)

The product is generated from human allograft nucleus pulposus containing viable cells. Each product is individually prepared but is not specific for the patient being treated. The details for the preparation of cells and supplemental allograft are described in Appendix C.

6.6 Selection of the study dose

A minimum of $6*10^6$ cells will be suspended in 2 ml of matrix (NP). The investigator will ensure delivery of the dose available to reach highest possible benefit for the subject, i.e., volume

available degenerative disc being patient specific, and subsequent to Pfirrmann scoring, desiccation, and volume that can be delivered.

The volume of material has been derived from previous studies that have shown volume, cell density, and deliverability to be important criteria that demonstrate clinical differences. Subjects enrolled and randomized to receive the viable allograft will receive one injection of approximately $6*10^6$ cells mixed in a 1:1:0.75 by-volume ratio of cells:saline:matrix (NP) injected into the center of the affected disc(s) in the location of the nucleus pulposus. No more than 2.0 ml will be available for injection at each level into the nucleus pulposus of the symptomatic disc, or discs.

6.7 Prior and concomitant therapy

Prior complaints, surgeries, diagnostics and therapies will be documented concerning the affected intervertebral disc and other related diseases and medication. All significant medical history (as determined by investigator) must be documented regardless of when it occurred. All concomitant medication taken within 30 days prior to obtaining informed consent, and taken at any time during the study during both Screening and Active Phases will be documented on the case report forms (CRFs).

6.8 Treatment compliance

A lack of compliance during the Screening Phase will result in an exclusion from the Active Phase of the study. Once treatment occurs, a subject can only be excluded from the study due to the following:

1. Withdrawal of consent
2. Lost- to follow-up
3. Death
4. Subject undergoes subsequent surgery on the treated disc
5. Investigator withdrawal due to subject's study compliance

6.9 Study Duration

The study duration for all enrolled subjects in this trial is approximately 12.5 months, including a 2-week Screening Phase for enrollment following initiation of consent documentation, 12 months of follow-up after treatment in the Active Phase, and an optional long term follow up period of an additional 24 months. Study enrollment is anticipated to require approximately 3-6 months. Therefore, the total study duration will be approximately 39.5 – 42.5 months. Subjects who have unremitting pain, or worsening conditions and who had been randomized to

the conservative group will be evaluated clinically and be given the option to crossover into the allograft supplement group. All randomized subjects will have the option to receive the allograft treatment during the optional long term follow up at 24 months. These subjects will fill out questionnaires at 36 months and have the opportunity to do so over the phone.

This study may be terminated by the sponsor if deemed necessary and documented by an amendment to this protocol. If the study is terminated, the sponsor will support follow-up of those subjects who entered the study as though the study had not been terminated.

6.10 Subject Withdrawal and Replacement

Subjects may withdraw from the study at any time without penalty and for any reason without prejudice to their future medical care. In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the appropriate case report form (CRF). If a subject is prematurely withdrawn from the study after randomization (Day 0 of the Active Phase), the investigator must document the reason(s) and make every effort to perform a final Termination Visit. The procedures to be followed for the Termination Visit are the same as those defined for the Month 12 Visit.

Subjects that are consented, screened and randomized, but do not undergo a successful transplantation (Day 0 of the Active Phase) will be considered screen failures. These randomization assignments will be re-used. The randomization and the replacement of subjects will be orchestrated through a 3rd party designated independent of the data collection or analysis.

7 EFFICACY AND SAFETY MEASUREMENTS

7.1 Study Procedure

In the scope of routine procedures of the investigating centers, each patient with the given indication will undergo treatment as defined in the study. Besides the investigator's standard of care procedure, after being informed about and giving consent to the screening for potential participation in the study, the following evaluations will be performed for each patient.

7.1.1 Screening Phase Day -14 to Day 0 or VS1:

Potential subjects will be identified and will provide written informed consent for the entire study before undergoing screening and study specific procedures. The investigator or designee will check the inclusion and exclusion criteria and collect the patient data and medical history. A physical examination will be performed and all concomitant diseases and medication will be documented. The scores/scales defined as ODI, VASPI, and SF-36 will be completed by the subject, and assisted by the physician or physician designate (as needed), and a "baseline" MRI, X-ray, and laboratory evaluation will be performed. All required assessments are outlined in Appendix A. VS1 may require multiple clinic visits during this 14-day eligibility screening period. Patients will have had disc pain for a minimum of 6 months to be included. Ineligible subjects should be identified early in the process and prior to completing an MRI and X-ray. MRI and X-ray images up to 6 months prior to treatment are acceptable.

7.1.2 Active Phase Day 0 or VA1:

The Baseline Visit (Day 0) of the Active Phase will occur for subjects that are consented and meet eligibility criteria. MRI/X-ray images performed up to 6 months prior to Day 0 are acceptable to be used for eligibility criteria assessment. Subjects who continue to meet all inclusion and exclusion criteria will need to have all baseline questionnaires, scores/scales, and additional assessments completed, including concomitant diseases, medication information and resource utilization as outlined in Appendix A. All subjects randomized to the allograft or placebo treatment groups will have the patency of the affected disc confirmed. Hereafter, these subjects will undergo preparation for receiving the supplemental allograft treatment or randomized to placebo treatment (saline), or randomized to conservative care treatment.

7.1.3 Active Phase 1 Month (± 3 days), or VA2

The first 24 subjects randomized will return to the clinic at 1 Month (± 3 days) for a complete safety assessment including a physical examination, a review of concomitant medication and diseases, AEs, and clinical labs. Efficacy scales/scores will also be completed by the subject, and assisted by physician (as needed), and at least 4 patients from each group will be represented. All required assessments at 1-month follow-up are outlined in Appendix A.

7.1.4 Conservative Treatment Group 3 Months (± 14 days), or VA3

Patients randomized to the conservative arm will be evaluated with VASPI, ODI, SF-36 questionnaires as well as complete all required additional assessments as outlined in Appendix A during the 3 months visit. Patients will be evaluated for deteriorating or improving conditions relative to enrollment. Subjects who have experienced a significant decline in condition defined as a 10% increase in pain by VASPI, or a 9-point increase in ODI will be offered the allograft treatment as a crossover. If the subject does not meet the aforementioned changes in ODI or VASPI, or is considering withdrawal, they may also be offered the allograft treatment by physician discretion if condition has significantly declined. Subjects that crossover do not have to re-consent. The crossover allograft treatment can occur at any time period after the 3-month follow-up visit. To administer the crossover allograft treatment, a new visit will be scheduled and this visit will be considered as the new Active Phase Day 0. In addition to the 3 months follow-up visit assessments, these crossover subjects will receive a MRI and X-ray prior to the allograft treatment. All assessments done at this 3 months follow-up visit will be considered as the new baseline assessments. These crossover subjects will receive follow-up visits at 6 months and 12 months after allograft treatment. Crossover subjects will not be replaced by enrolling new patients in the conservative care treatment group.

7.1.5 Active Phase Month 6 (± 30 days) or VA4:

All randomized subjects will return to the clinic 6 months (± 30 days) subsequent to treatment for all safety and efficacy assessments as outlined in Appendix A. ODI, VASPI, and SF-36 questionnaires will be completed by the subject, and assisted by physician or physician designee. All subjects (excluding conservative care crossover subjects) will be randomized to include MRI at 6-month (MRI or no MRI, ratio 1:1) follow-up in addition to all other assessments. This randomization is performed to assess whether predictability at 6 months indicates performance at 12 months. The conservative care subjects that crossover to the allograft treatment group will all receive an MRI at 6-month follow-up after allograft treatment. All subjects will receive an X-ray at the 6-month follow-up visit. Additionally, a review of resource utilization since the Day 0 visit will be completed.

7.1.6 Active Phase Month 12 (+ 30 days) or VA5:

All randomized subjects will return to the clinic 12 months (+ 30 days) subsequent to transplantation for safety and efficacy assessments as outlined in Appendix A. ODI, VASPI, and SF-36 questionnaires will be completed by the subject, with assistance from physician or physician designee. All subjects will receive an MRI and X-ray at the 12-month follow-up visit. A review of resource utilization through the 12 Month visit will be completed.

7.1.7 Optional Long-Term Follow Up Month 24 & Month 36 (+ 3 Months) or VA6 & VA7:

All randomized subjects will have an option to continue to be monitored for long-term follow up. Before study procedures begin, the informed consent addendum 2 for study extension will need to be signed. At the 24-month in-office visit, subjects will first be reevaluated for inclusion/exclusion and fill out VASPI, ODI, SF-36, and Resource Utilization. If eligible for allograft treatment, the PI will perform a neurological exam, physical exam, labs, and give the subject applicable questionnaires. All randomized subjects will have the option to receive allograft treatment at 24 months in accordance with the inclusion/exclusion re-evaluation. An MRI and x-ray will be performed on subjects receiving another injection for safety purposes. If needed, a second office visit may be scheduled within 14 days of the original evaluation to allow appropriate time for the laboratory investigation and MRI. All follow up subjects will complete VASPI, ODI, SF-36, and Resource Utilization questionnaires at both follow up visits. The 36-month will consist of questionnaires and can be performed over the phone if the subject chooses.

7.2 Appropriateness of measurements

The Oswestry low back pain disability questionnaire (according to Hudson-Cook) or OPDQ, a self-rating scale, will be used to calculate the Oswestry Disability Index (ODI), the primary efficacy criterion. The use of this scale in clinical trials is recommended for its acceptable test quality and satisfactory test-retest reliability.

A composite primary endpoint with the ODI as well as a pain score (VASPI) will be used to increase the efficiency of this small trial.

Additionally, the SF-36, an often-used scale to assess patients' general condition and quality of life, and the visual analogue scale of pain intensity (VASPI), a standard to measure general pain are used as secondary criteria.

Therefore, a number of measurements are used to assess the clinically relevant symptoms in intervertebral disc pain as well as functional disability. Additionally, morphological changes will be observed by MRI and X-ray.

7.2.1 Primary efficacy variable

The reduction of back pain attributable to lumbar disc degeneration, assessed by the outcomes of the ODI and VASPI questionnaires, that will be determined for the primary efficacy variable at 6 and 12 months after treatment .

7.2.2 Secondary efficacy variables

Analogous to the primary parameter, the rates concerning the other recorded scores, and the ODI at other time points, with different definitions of healing will be analyzed as well.

MRI will be evaluated with respect to intervertebral height, disc desiccation, adjacent vertebral endplate morphology and Pfirrmann grading score.

An assessment of the tissue repair by X-ray and MRI will be performed by a panel of physicians blinded to treatment.

8 INCLUSION / EXCLUSION CRITERIA

8.1 Inclusion Criteria

Patients will be entered into this study only if they meet ALL of the following criteria:

- Able to provide an English written Informed Consent
- Age 18 to 60 years inclusive
- Male or female
- Body mass index <35
- Pfirrmann Grade [3-6]
- Radiographic confirmation by MRI/X-ray of:
  (1) translational instability defined as ≤5 mm, or
  (2) angular instability defined as ≤5°
- Back pain (with or without radicular leg pain) measured by:
  (3) ODI of at least 40%, and
  (4) VASPI of at least 40mm
- Pathologic level between L1 and S1
- 1 or 2 vertebral level involvement that has been evaluated for at least 6 months and treated with conservative care
- Symptomatic back pain attributable to intervertebral disc for a minimum of 6 months
- No previous surgical treatment at the disc level(s) being considered
- Psychosocially, mentally and physically able to fully comply with this protocol, and follow-up schedule
- Ability to undergo allograft transplantation
- Life expectancy >2 years
- No contraindications to MRI
- No history of malignancy (basal cell carcinoma) or chronic infectious disease (e.g. HIV, Hepatitis)
- Agree to use appropriate contraception; not planning on becoming pregnant for 24 months after treatment
- Patient disc for transplant confirmed by inter-discal pressure measurement, or disc-imaging study.
- No signs or symptoms of infection
- No chronic use (>7 consecutive days) of anticoagulants (such as aspirin) or NSAIDs prior to treatment

8.2 Exclusion criteria:

- Seropositive or seronegative spondyloarthropathy
- Type III Modic changes
- Prior surgeries of segments between L1 and S1
- Chemonucleolysis or percutaneous laserectomy of the affected disc prior to the study
- Chronic facet syndrome
- Stenosis of the spinal canal that is moderate to severe or more in degree
- Spondylodiscitis
- Spondylolisthesis (lysis and degenerative)
- Severe motor deficit or cauda equina disorder based on investigator determination
- Congenital abnormalities of the spinal nerves
- Pelvic and inguinal angiopathy
- Neurogenic inguinal syndrome
- Syringomyelia
- Diastenomatomyelia
- Traumatic neurological disorders
- Diseases of the kidney (nephritis, pyelonephritis)
- Other severe diseases of any other major body system as judged by the investigator
- Regular intake of systemic steroids
- Malignant diseases of any solid organ or any hematologic malignancy during the previous 5 years
- Patients who have participated in a clinical trial within the last month prior to inclusion
- Moderate to severe or greater lumbar stenosis of both transplantation endplates and adjacent levels

MATERIALS AND METHODS

8.3 Test Material

The material used for this study will be a proprietary supplemental cellular allograft nucleus pulposus obtained from donors at UMTB. The tissue will be processed using UMTB SOP and provided to participating clinical sites for transplantation.

8.4 Study Procedure

On Day 0 of the Active Phase, eligible subjects will undergo transplantation of supplemental allograft, or saline (placebo), or continue active standard of conservative care. This conservative care procedure will not be defined by this protocol however standard practice is to be followed by each physician. All subjects who undergo successful treatment will continue in the study and be followed as per the standard of care. Subjects randomized to continuing conservative care will be assessed at 3 months, and clinical indices will be assessed. These conservative care subjects who have experienced a significant decline in condition defined as a 10% increase in pain by VASPI, or a 9-point increase in ODI will be offered the allograft as a crossover. If the subject does not meet the aforementioned changes in ODI or VASPI, or is considering withdrawal, they may be offered the allograft treatment by physician discretion if condition has significantly declined.

8.4.1 Transplant of supplemental allograft into the affected disc

All subjects randomized to active allograft will undergo an intervertebral lumbar injection into the target disc. The procedure of injecting the intervertebral disc will involve placing a 22-gauge needle into the center of the affected intervertebral disc. No contrast will be used prior to the injection of the supplemental allograft and 1mL of cells (approximately $6*10^6$ cells) mixed in a 1:1:0.75 by-volume ratio (Cells in cryoprotectant: Saline: NP) will be injected into the center of the affected disc(s) in the location of the nucleus pulposus. At least 1.5-2 milliliters of the resulting mixture will be available for injection into the nucleus pulposus of the symptomatic disc. Volume injected will be recorded.

Vital signs will be recorded prior to injection. The treatment injection should be carefully controlled. The injection procedure MUST be stopped if any of the following occur:

- The investigator cannot accurately place the needle tip in the nucleus pulposus
- The subject becomes hemo-dynamically unstable during the injection procedure.

The following information regarding the treatment procedure must be documented:

- Procedure start and stop time
- Treatment administration stop time
- Treatment interruption information, if applicable
- Total volume of treatment injected
- Pain on implantation
- Anesthesia type(s)

The information collected above will also be collected during the placebo cross over visit.

8.5 Assessments

- Informed Consent will be obtained between Screening Day -14 and Active Day 0, prior to any study procedures being performed. The addendum for optional long term follow up will be collected before procedure and questionnaires are performed.
- An assessment of eligibility using the inclusion and exclusion criteria will be conducted starting at Day -14 of the Screening Phase. Prior to randomization at Day 0 of the Screening Phase, eligible subjects must meet all inclusion criteria and no exclusion criteria for the Active Phase. This will also be assessed after the ICF addendum for long term follow up is collected to determine if the subject is still eligible.
- Medical History and Patient Demographics will be recorded during the Screening Phase.
- An abbreviated Physical Examination will be done in the Screening Phase within the 2 weeks prior to transplant, as well as at Month 6, and 12, and at 3 months for the subjects randomized to continue conservative care. This will be done for subjects completing the placebo crossover injection as well.
- Resource utilization data (lost time from work, number and kind of previous surgeries, duration of complaints (preoperatively), duration of rehabilitation, complications, additional physician visits, etc.), will be obtained during the Screening Phase as a baseline to similar data obtained during the Active Phase at Months 6, and 12. This will also be collected during the long term follow up visits of 24 and 36 months.
- Physicians clinical assessments will be collected in the Screening and in the 2 weeks prior to transplant, and in the Active Phase at Months 6, and 12, and in the conservative

care patients at 3, 6, and 12 months. A neurological exam will be completed before placebo crossover additionally.

- Patient self-assessments including VASPI, ODI, and SF-36 will be collected at every scheduled clinic visit. VASPI, ODI, and SF-36 will be collected in person at 24 months and at the 36 month interval, these questionnaires can be performed over the phone during optional long term follow up.

- MRI evaluating the intervertebral height, adjacent endplates, deprivation of fluid and Pfirrmann score will be obtained during the Screening Phase and in the 2 weeks prior to transplant, and in the Active Phase at 12 months. Subjects will be randomized, yes or no (1:1 ratio), to receive an MRI at 6 months. Conservative care subjects that crossover to the allograft treatment group will all receive an MRI at 6-month follow-up after allograft treatment.
- X-rays will be performed static (standing), anterior-posterior and lateral in the Screening Phase prior to transplant. After transplantation, during the Active Phase (Months 6, and 12) a static and an additional dynamic (flexion/extension) X-rays will be performed.
- Adverse Events (AEs) and Serious Adverse Events (SAEs) will be recorded once the patient is enrolled (Day 0 of the Active Phase). A detailed discussion of AEs and SAEs is located in Section 14. Optional checkup evaluations will be performed in the case of complications. Failure of treatment defined as the necessity of a follow-up operation will be documented separately.
- Laboratory investigation will be conducted according to the routine procedures of each investigational center. The valid normal ranges including the methods for all parameters will be provided to the sponsor prior to the start of the study. Only laboratory values outside the normal range will be evaluated and commented upon by the investigator. The following parameters will be determined:

  Hematology:

  - hemoglobin
  - hematocrit
  - erythrocytes
  - leukocytes
  - thrombocytes
  - erythrocyte sedimentation rate

  Clinical Chemistry:

  - creatinine
  - alkaline phosphatase
  - AST/SGOT
  - ALT/GPT
  - γ-GT
  - glucose

  Coagulation:

  - PTT

8.6 Study Schedule

The Study Schedule with all required assessments is listed in Appendix A.

9 STUDY OBJECTIVES AND ENDPOINTS

9.1 Objective

The primary objective of this study is to evaluate the safety and efficacy of viable allograft transplantation for the treatment of patients with symptomatic disc degeneration and tissue loss. There will be three treatment groups: (1) supplemental viable allograft treatment, (2) placebo (saline) treatment, and (3) conservative care treatment.

9.2 Primary Endpoint

The primary efficacy endpoint of the study is improvement in the ODI at 6 and 12 months after treatment, and improvement in Visual Analogue Scale of Pain Intensity (VASPI) at 6 and 12 months after treatment.

9.3 Secondary Endpoints

Secondary parameters of efficacy will include the ODI, the SF-36, and the VASPI following treatment. Structural outcomes will be assessed using X-ray and MRI measurements at the same time points. Safety will be assessed by the incidence and severity of AEs and clinically important changes in laboratory tests.

A correlation of the clinical results (scores and scales) and the morphological results (X-ray, MRI) will be evaluated. All additional efficacy and safety data will be analyzed descriptively.

The effect supplemental allograft transplant on resource utilization, i.e., days off work, subsequent surgeries, other clinic visits will also be measured and compared

10 RISKS

10.1 Transplantation Risk Management

There are certain known risks associated with lumbar disc injection, expected risks with products that are used in the production of the viable allograft. These risks include the administration of viable cells may elicit immunogenic and/or inflammatory responses resulting from exposure to the donor cells and/or manufacturing content. To date no clinical signs or symptoms have been associated with the development of antibodies to HLA, NP matrix, or cryopreservative material. To this procedure, there are no xenogenic components included in the production of the viable allograft product.

10.2 Overall Study Risk Management

- The following measures implemented by the investigator will minimize the risks associated with subjects' participation in this study:

  PI is careful in selection of personnel (including clinical investigators at the sites) with extensive experience in conducting clinical studies and in procedures such as provocative disc evaluation, and percutaneous delivery.

- PI and study staff follow the study protocol, and the PI ensures that all study staff are trained and have a strong knowledge and understanding of the clinical protocol, including patient selection criteria and procedure requirements
- PI ensures that the investigators are trained on the procedure requirements in the protocol.
- PI and study staff carefully follows patient eligibility criteria for the investigation to ensure that only properly selected patients are being enrolled and treated.
- The protocol is designed such as patient treatment and follow-up procedures will be consistent with those of the established treatment options for the selected patient population; all subjects will receive standard of care treatment

With these risk minimization procedures in place, associated risks of interventional procedures in all subjects are expected to be minimal and acceptable.

11 BENEFITS

While benefits from participation in this study cannot be guaranteed, it is expected that supplemental transplantation will improve the long-term outcome in subjects who have disc disease by providing mechanical stabilization, biochemical subsidization, and cellular components to sustain matrix viability.

12 RISK / BENEFIT ANALYSIS

Both pre-clinical and early clinical results of *in vitro* generated disc-derived cells transplanted into the intervertebral disc space in lieu of, or subsequent to discectomy are promising, thus raising the need for a standardized, well designed clinical trial. Based on prior results for individual patients treated with the surgical standard of care plus *in vitro* generated disc-derived cells, a reduced rate of degeneration after herniation would be expected with the inclusion of an autologous stem cell transplant. Statistical differences have also been defined for levels adjacent to those treated that were correlated with Oswestry disability and quality of life indices.

No clinical data exist in this patient population receiving a transplant of allogeneic donor-derived viable matrix. Therefore, the documented risks are those associated with the procedures.

The risks for this procedure include hematoma, epidural bleedings, infections (from local infections up to spondylodiscitis and/or meningitis), neurological deterioration as serious as lesions of the cauda equina (paraplegia secondary to ascending bleeding or infection), paresis, sensory disturbances, disorder of potency or disorder of sexual sensibility, cerebrospinal fluid fistula, retroperitoneal lesions (large vessels, ureter, intestine), instability of the vertebral column, relapsing herniation, incomplete improvement (paresis, sensory disturbances), bladder or bowel dysfunction and recurrence of complaints, in particular pain.

So far, no additional risks due to the application of autologous *in vitro* generated chondrocyte suspension, or matrix carrier itself have been documented. In more than 700 documented cases of autologous stem cell transplants (mainly applied to the knee) similar to the procedure to be followed in this trial, no immunoreaction to the transplant was registered. Furthermore, no infectious reactions to autologous cell transplants have been reported in the literature so far.

The volume supplement of the intervertebral disc space performed in the application of the cell-suspension, comprises no additional risks as no additional intervention will be done to the patient.

In summary, on the basis of today's knowledge of either autologous cell or expanded allogeneic cell transplantation, the risks associated with the therapeutic approach to be utilized for each individual patient is acceptable in the scope of the expected, but yet to be proven clinical benefit.

13 DATA ANALYSIS

13.1 Data Management

13.1.1 Data collection

The outcome of all data collected during each follow-up visit according to Appendix A for the three treatment groups will be documented on the study-specific Case Report Forms (CRFs). For all visits and for each patient, CRFs will be completed and all results will be forwarded to Vivex Biologics, Inc. or designated representative for data management and analysis after source data verification by the responsible monitor has been completed.

13.1.2 Database management and quality control

Logical and statistical plausibility checks will be performed on all data entered into the database. All data which are used for the analysis will be documented in individual data listings.

13.1.3 Interim analysis

For safety and efficacy reasons, interim analyses are planned to be performed after the first 24 subjects have completed the Month 1 assessment of the Active Phase. This analysis will be performed in a descriptive manner only and no un-blinding will occur unless a safety signal is evident. A Steering Committee will be convened to review the results of the interim analysis. A similar review will occur when they complete the Month 6 assessment of the Active Phase, where primary endpoints of pain and ODI, and randomized MRI will be available for analysis.

13.2 Statistical Methods and Determination of Sample Size

13.2.1 Populations for analysis

Statistical analysis will be done for the ITT and PP population should be last observation carried forward (LOCF).

13.2.2 Statistical and analytical plans

The statistical evaluation will be done using appropriate statistical software packages.

For all baseline data, descriptive statistics will be presented. In the case of continuous parameters, statistical parameters for location and dispersion (e.g. n, mean, standard deviation, range) will be calculated. For discrete data, appropriate frequency tables will be produced.

Primary criteria:

The primary criteria will be analyzed in a confirmatory way using a two-sided approach on an α-level of 0.05 based on the total score. A hierarchical test procedure will be applied. In the first step the pre-post difference of the groups will be compared using Wilcoxon rank-sum-test.

In case of a significant result a responder analysis will be done in the following way:

For each number r = 1, ..., 10 the subjects will be categorized as responders, if the pre-post-difference is greater or equal r. The corresponding contingence table will be tested using Fisher's exact test resulting in a p-value p_r.

The p_r will be sorted and the Bonferoni-Holm procedure on a 5 % level will be applied.

Secondary criteria:

All secondary variables will be analyzed in an exploratory way using adequate statistical procedures. The subscales of ODI may be analyzed separately using the same procedure as for the total score of OPDQ. To support the validity of OPDQ the correction of OPDQ with QUE will be done.

13.3 Sample Size Considerations

The primary criteria will be analyzed using Wilcoxon rank-sum-test. Based on Fairbanks, 2000[51], Hudson-Cook, 1989[36] and Fritz, 2001[52] a common standard deviation σ = 15.5 score points can be assumed.

Fritz, 2001, calculated a Minimum Clinically Important Difference of 6 score points. Reliability is reported in the literature in the range of 0.75 - 0.91. Worst case using the standard deviation above results in a measure error of 7.75 score points. Thus, we assume a clinically relevant difference of 9 score points. Under this assumption the probability p (x < y) = 0.341 (x, y observations in the groups, respectively). A sample size of 40 in each group will have 80 % power to detect a probability of 0.341 that an observation in one group is less than an observation in the other group using Wilcoxon rank-sum-test with a 0.05 two sided significance level (calculations are done using nquery 4.0).

14 ADVERSE EVENTS / SERIOUS ADVERSE EVENTS

14.1 Adverse Event

According to GCP, an adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject who was treated with an investigational device, and does not necessarily have a causal relationship with the treatment or device. An adverse event (AE) can therefore be any unfavorable and unintended sign, symptom, or disease, whether or not related to the investigational device.

For this study, all AEs (including expected and unexpected AEs) and SAEs will be captured in the CRF. Adverse events (AEs) occurring during the Screening Phase will not be collected. Expected AEs are those that are listed below as known risks, including those described in this protocol, the study Informed Consent, the allograft instructions for use, and any procedural (surgery and anesthesia) informed consent signed by the patient for the diagnosis, and/or transplant:

- Immunological response
- Transmission of disease of unknown etiology
- Transmission of infectious agents (including but not limited to: HIV, hepatitis, syphilis, or microbial contaminants.
- Inflammatory response
- Development of tumor
- Hematoma,
- Epidural bleedings,
- Infections (from local infections up to spondylodiscitis and/or meningitis),
- neurological deterioration as serious as lesions of the cauda equina (paraplegia secondary to ascending bleeding or infection),
- Paresis,
- Sensory disturbances,
- Disorder of potency or disorder of sexual sensibility,
- Cerebrospinal fluid fistula,
- Retroperitoneal lesions (large vessels, ureter, intestine),
- Instability of the vertebral column,
- Relapsing herniation,
- Incomplete improvement (paresis, sensory disturbances),
- Bladder or bowel dysfunction
- Recurrence of complaints, in particular pain.

14.2 Serious Adverse Event

Serious Adverse Events (SAEs) are defined as any untoward medical occurrence that:

- Results in death, or
- is life-threatening, or
- requires inpatient hospitalization or prolongation of existing hospitalization, or
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect (in an offspring), or
- is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate. All SAEs will be captured in the CRF.

14.3 Serious Unanticipated Adverse Device Effect

A serious unanticipated adverse device effect (SUADE) is defined as any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

14.4 Procedures for AE Reporting

All AEswill be recorded by the investigator or designee on the appropriate CRF. The investigator will evaluate the relationship of the AE to the transplant, the device, and study procedures as related, not related, or unknown, and will record the findings, including all pertinent details of the event on the AE CRF. Adverse events (AEs) occurring during the Screening Phase will not be collected.

The investigator will report any SAE (including SUADEs) occurring during this study to the sponsor designated representative within 24 hours of first identifying the SAE. The designate will notify the sponsor Medical Monitor immediately (within 24 hours) and the committee that approved the protocol within 10 calendar days or in accordance with the conditions of the MEC approval. The investigator will take appropriate measures to ensure the patient's optimal care and will document these measures on the appropriate CRF.

All UADEs will be reported to the sponsor and the reviewing EC within 10 working days of the study site becoming aware of the events

All AEs experienced by a patient will be monitored until the event has resolved, or has established a new chronic baseline, or until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

15 REGULATORY OBLIGATIONS

15.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Before the beginning of the trial, the protocol will be submitted to the appropriate Ethics or other authoritative Committees of the principal investigator. The study will only be performed when a full approval of this protocol has been obtained from the appropriate committee(s). Additionally, the protocol will be submitted to the Ethics Committees of the test centers involved. Any amendments to the protocol will be submitted to the Ethics or other authoritative Committees.

Documentation of the date of the meeting, constitution of the committee and voting members present at the meeting will be requested by the sponsor/CRO.

The approval will be submitted to the appropriate competent federal higher authority together with a copy of the study protocol, blank CRFs and informed consent. In case of a positive approval the study can be started immediately.

Ethics Review Committees (ERC) must be constituted according to the law and guidelines and Authority Approval.

This protocol will be submitted to the appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study.

15.2 Informed Consent Process

Prior to the administration of any tests or procedures required in this protocol for either the Screening or Active Phase, the investigator or designee will obtain informed consent in writing from all potential subjects considered for entry into this trial. Each patient must sign and personally date the informed consent. Copies of the informed consent will be retained in the medical record and the subject's study binder. A copy of the signed informed consent will be given to the subject to take home.

The consent form and as necessitated by local law, an additional patient information leaflet for study participation, will explain the nature of the study, its objectives and potential risks. Furthermore, it will detail the requirement of the participant, the trial treatment and the probability for random assignment to each treatment group, all trial procedures, alternative procedures and the fact that he is free to withdraw his consent at any time without reason. Details of indemnity and insurance are also attended with assurance.

As required by ICH-GCP the subject will give in writing his authorization that the study data may be given for review to the responsible authorities, and that the monitor will be granted direct access to the subject's original medical records for verification of clinical data.

Notification to Authorities

The study protocol together with the investigators' names, the investigation sites and the votes of the Ethic Committees will be presented to the responsible health authorities and retained by the sponsor.

15.3 Steering Committee

A Steering Committee will be established for the conduct of the study with the purpose to observe the course of the study and to ensure the highest possible safety for each participating patient. The data to be reviewed, and the timing of the review/s, will be defined in the Steering Committee mission and guidance documents.

In particular, the Steering Committee will receive the 1-Month data for the first 24 randomized patients and will determine based upon this information if the recruitment of the remaining 196 subjects can continue. Participants in the steering committee will include Dr. Randolph Bishop, MD, a neurosurgeon, and Dr Chris Hancock, MD, an interventional radiologist, and be chaired by H Thomas Temple, MD, Chief Medical Officer for Vivex Biologics, Inc.

15.4 Site Selection and Qualification

A qualification and selection visit will be performed to evaluate site facilities, investigator qualifications, adequacy of staffing, and understanding of clinical and regulatory requirements.

15.5 Site Initiation

All investigators and appropriate study staff will be required to participate in an investigator meeting which will provide training to all sites at one time or if applicable onsite training in order to provide orientation and training regarding the device operation and applicable procedures, protocol and CRFs. Physicians and office staff necessary to execute the trial will be trained to the composition of the test article, to the history of the implant in intervertebral disc therapy, and then provided a laboratory course in preparation of the allograft which will include mixing, placement in syringe, and delivery into the center of the disc. Injected discs will be imaged, planed with a band saw (if at UMTB facility), and distribution confirmed to depict the intended distribution of the material in a clinical setting.

15.6 Monitoring

During the course of the study, the sponsor or designee may make site visits to review protocol compliance, perform source data verification, assess test article accountability, and ensure compliance with pertinent regulatory requirements. All review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Satisfactory verification of CRF completion, source document verification and query resolution may be required to monitor the progress of the study. Moreover, regulatory authorities may wish to carry out such source data checks and/or on-site audit inspections with reasonable notification to the study site. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

15.7 Required Reports

The following reports are required of the investigator:

- Reports to Pharmacovigilance (appointed by Sponsor) of any SAEs immediately or at least within 24 hours of the study site becoming aware of such events
- Reports to the sponsor and the reviewing EC of any UADEs within 10 working days of the study site becoming aware of events (unless the UADE is a serious event, in which case it must be reported to the sponsor immediately or at least within 24 hours of the study site becoming aware of such events)
- Report to the sponsor, within 5 working days, of withdrawal of approval by the reviewing EC or regulatory authority
- Progress reports to the sponsor, monitor, and the reviewing EC at regular intervals (at least yearly)
- Report to the sponsor and the reviewing EC of any deviation from the protocol to protect the life or physical well being of a patient in an emergency situation. Such notice will be given as soon as possible, but in no event later than 5 working days after the emergency occurred
- Reports of any study procedure(s) being performed without prior written informed consent being obtained. Such notice will be given to the sponsor and the reviewing EC within 5 working days of the study procedure(s) being performed

- Final report submitted to the sponsor and the reviewing EC as soon as possible, but no later than 3 months, after the conclusion of the study or the conclusion of the investigator's participation in the study
- Other reports to the reviewing EC as may be required

16 STUDY REQUIREMENTS

To protect the rights and welfare of subjects, the study will be conducted in conformance with the Declaration of Helsinki, the ICH E6 guidelines on Good Clinical Practice (GCP), and/or the laws and regulations of the participating country, whichever affords the greater protection to the human patient.

All investigators, sub-investigators and study personnel are required to read and follow the protocol, as well as any literature that accompanies the products prior to conducting the study procedure for the first time. All investigators participating in this study will be required to be trained in the proper use of the study procedures and in the components of this protocol by the sponsor.

The PI is ultimately responsible for the conduct of this study; however, he/she may designate a member or members of his/her staff to assist with the collection of data and completion of CRFs. The designee(s) will be documented on an authorization form that is signed by the PI and kept in the Regulatory Binder, to be updated as necessary.

Obtaining informed consent in accordance with national policy is mandatory for patient participation. All patient data is kept confidential and procedures will be implemented to ensure that patient confidentiality is not compromised.

If alternative consent materials are used, they must be approved by Vivex Biologics, Inc. at the clinical site prior to use. Documentation of the approved informed consent must be provided to Vivex Biologics, Inc. prior to study commencement at the clinical site.

After Informed Consent has been obtained, all screening procedures have been performed, and eligibility for the study has been confirmed, the subject will be considered enrolled in the study. After this point, the reason(s) must be documented on the CRF for any patient who has dropped, withdraws, or for any reason cannot complete this study.

16.1 Quality Assurance

All data concerning the study will be documented on the patient's medical record and on CRFs designed especially for this study, or on data clarification forms (DCFs) if necessary. Each CRF and DCF will consist of an original plus two copies.

In line with ICH-GCP guidelines, clinical monitors will arrange regular visits to the trial center(s) to check progress with the study and to collect completed CRFs. One copy will remain in the study center, the original will be passed to Vivex Biologics, Inc. or designated representative for data management. The original will be send to the sponsor at the end of the study. Until then,

the originals will remain at Vivex Biologics, Inc. or designated representative for data management. The CRFs will be checked for completeness and plausibility by the clinical investigator and the monitor (manually) as well as by Vivex Biologics, Inc. or designated representative for data management.

In addition, the representatives of the Clinical Quality Assurance department at the sponsor, of the CRO, and of regulatory authorities, are permitted to inspect the study documents (Study Protocol, Case Report Forms, study medication, original medical records/files). All patient data shall be treated confidentially.

In order to guarantee that the performance of the study is in accordance with the ICH-GCP stipulations, in-house and on-site Audits may be carried out. Study protocol and final report will be additionally examined by the Quality Assurance Unit of the sponsor and/or Vivex Biologics, Inc. or designated representative for data management.

The investigator agrees to give the auditor access to all relevant documents for review. The same applies in case of an inspection the authorities.

After every on-site audit the investigator will receive an audit confirmation by the auditor. This has to be filed together with the study documentation and be made available to the authorities in case of supervision. At the end of the study, audit certificates will be included in the final report.

16.2 Monitoring

It is the responsibility of the investigator to assure that the study is conducted in accordance with the protocol and that valid data are entered into the CRF.

The investigator will permit a representative of Vivex Biologics, Inc. or designated representative for data management to monitor the study as frequently as necessary to determine that data recording, and transplant handling and protocol adherence are satisfactory. The CRFs and related documents will be reviewed in detail in accordance with the SOPs of Vivex Biologics, Inc. or designated representative for data management and Good Clinical Practice regulations (ICH-GCP).

In fulfillment of their obligation to the sponsor to verify compliance with this protocol, Vivex Biologics, Inc. or designated representative for data management will require that the investigator permits the monitor and/or the sponsor's monitor to review that portion of the patient's primary medical records which directly concern this study.

It is the investigator's obligation to ensure that documentation of all relevant data such as medical history/concomitant diseases, date of study enrollment, visit dates, results of examinations, administrations of medication and adverse events is correctly entered in the patient's file.

Vivex Biologics, Inc. or designated representative for data management will affirm and uphold the principle of the subject's right to protection against the invasion of privacy. Throughout the study, all data will only be identified by patient number, patient initials and date of birth. Anonymity of the data will be maintained in all data analyses.

All obtained data will be checked for plausibility and completeness by the monitor and in-house by Vivex Biologics, Inc. or designated representative for data management.

17 PROCEDURES AND INSTRUCTIONS

17.1 Special safety-related procedures

No special safety-related procedures, other than those attending the risks of surgery, need to be defined. In the case of complications/emergency, physicians will use their clinical judgment on the best course of action. All complications related to supplemental allograft transplantation will be documented by the physician and will be forwarded to Vivex Biologics, Inc.

17.2 Administrative procedures

Vivex Biologicsl, Inc. will be responsible for the supply of Vivex Biologics, Inc. equipment and will provide training on the use for the mixture of the supplemental transplant allograft. A Vivex Biologics, Inc. representative will be present for the initial 2 implantations at each site to ensure proper procedure is followed. Once the site has experience in randomization, data collection, and allograft delivery as determined by Vivex Biologics, Inc., on-site support will be available on request and through a 24-hour phone system. The interventional procedures will be performed by experienced centers and physicians named by Vivex Biologics, Inc. to ensure the highest quality of the implantation.

17.3 Ethics and Good Clinical Practice

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice and the appropriate regulations of relevant national regulations and the Declaration of Helsinki (revised version of Edinburgh, Scotland, October 2000).

APPENDIX A - STUDY SCHEDULE

Visit	VS1 [a]	VA1 [a]	VA2 [b]	VA3 [c]	VA4	VA5	VA6	VA7
Visit Window	Screening (Day -14 to 0)	Day 0	1 month (±3 Days)	3 months (±14 Days)	6 months (± 30 Days)	12 months (+ 30 Days)	24 months (± 3 Months)	36 months (± 3 Months)
Informed Consent	**X**						**X**	
Eligibility Criteria	**X**							
Eligibility Criteria Check		**X**					**X**	
Randomization		**X**						
Injection Treatment (Allograft or Saline)		**X**					**X**[f]	
Demographic Data	**X**							
Medical History	**X**							
Physical Examination		**X**	**X**	**X**	**X**	**X**	**X**[f]	
Neurological Examination		**X**	**X**	**X**	**X**	**X**	**X**[f]	
MRI and X-ray Evaluations	**X**		**X**	**X**[d]	**X**[e]	**X**	**X**[f]	
Laboratory Investigation	**X**		**X**	**X**	**X**	**X**	**X**[f]	
Urine/Pregnancy Test, if applicable		**X**						
VASPI Questionnaire	**X**		**X**	**X**	**X**	**X**	**X**	**X**
SF-36 Questionnaire	**X**		**X**	**X**	**X**	**X**	**X**	**X**
ODI Questionnaire	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Resource Utilization	**X**				**X**	**X**	**X**	**X**
Concomitant Medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**

[a] VS1 and VA1 may both occur on Day 0.

[b] Month 1 Visit (VA2*) to be performed for the first 24 subjects randomized only.

[c] Subjects randomized to conservative care will be evaluated at 3 months to assure they are not experiencing further debilitating changes. During this visit, subjects may be offered crossover to allograft treatment. To administer the crossover allograft treatment, a new visit will be scheduled and this visit will be considered as the new Active Phase Day 0 (VA1).

[d] MRI and X-ray to be done in the event a subject crosses over from conservative care to the Allograft treatment.

[e] At the 6-month follow-up visit, subjects will be randomized to receive a MRI, (1:1 ratio). Crossover subjects to allograft treatment will all receive an MRI at the 6 month visit after allograft treatment. All subjects will receive an X-ray at the 6 month follow up visit.

[f] At the 24-month in-office visit, subjects will first be reevaluated for inclusion/exclusion and fill out VASPI, ODI, SF-36, and Resource Utilization. If eligible for allograft treatment, the PI will perform a neurological exam, physical exam, laboratory investigation, and MRI/X-ray.

APPENDIX B– Supplemental TRANSPLANTATION /OTHER APPENDICES

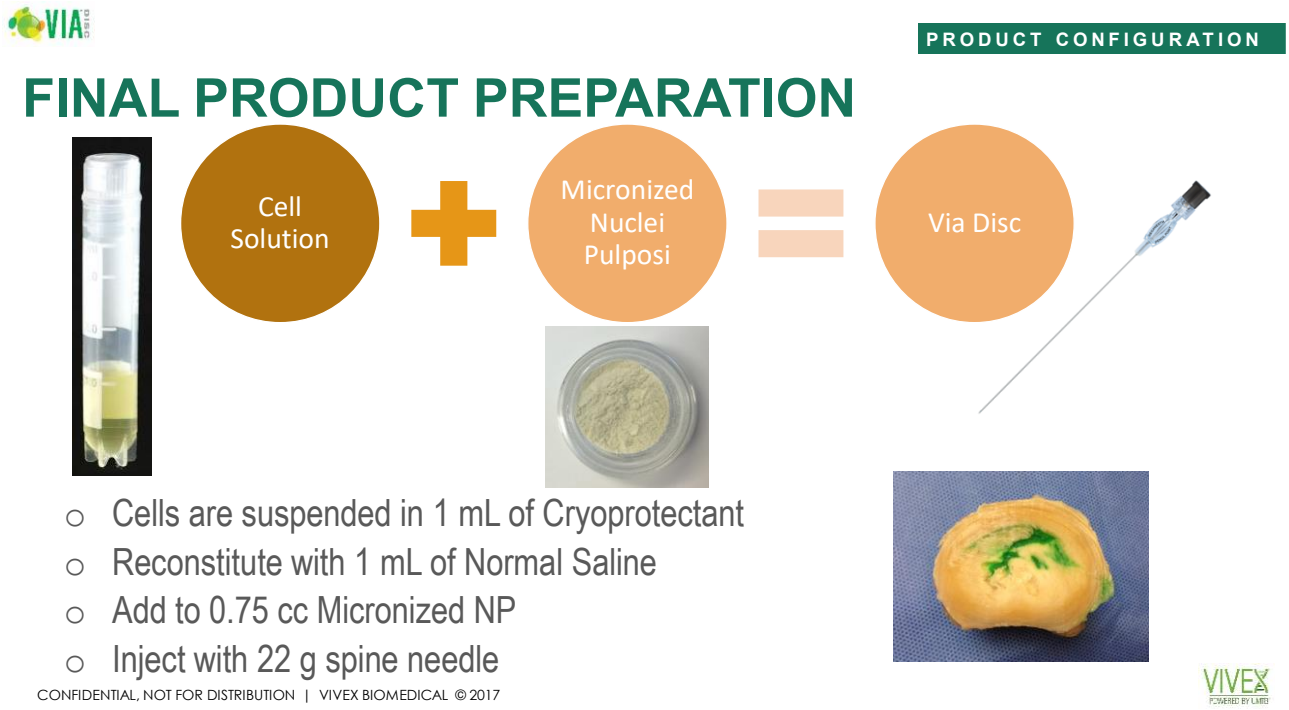
12.3 Used Scores and Scales

12.3.1 Oswestry Low Back Pain Disability Questionnaire modified according to Hudson-Cook (OPDQ) and calculated as the Oswestry Disability Index (ODI)

12.3.2 VAS (pain)

12.3.3 SF-36, (United States) version

APPENDIX C – Supplemental TRANSPLANTATION



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