Clinical Investigation Plan

(ReActiv8-B)

A Clinical Trial under an Investigational Device Exemption (IDE)

ReActiv8 Implantable Neurostimulation System for Chronic Low Back Pain

Sponsor

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Revision History

Rev	Change Description	Effective Date
A	Initial Release to production	27-Aug-2015
B	Exclusion Criteria: • Minor clarification to the wording for financial gain exclusion • Removed the compliance exclusion for the pain diary Updated Product modifications and product additions Updated Statistically section to match updated SAP which includes details on the interim analysis as requested from the FDA Modified the medication collection of rescue medications for other pain conditions as recommended by the FDA Table 5 Study Completion plan updated on availability of product use after study Clarification that the telephone call prior to visits could also be done electronically Clarification that the trainers for the PIT will follow a plan for training and PIT training materials will be developed by the qualified trainers and used consistently at each site Minor typographical errors and inconsistencies corrected throughout document	10-Dec-2015
C	Exclusion Criteria: • Minor clarification to the wording for pathology seen on MRI (see Eligibility Criteria in Table 1 and sections 5.2 and 10.1.3). • Minor clarification to the wording for prior diagnosis of lumbar vertebral compression (see Eligibility Criteria in Table 1 and section 5.2). Timing of implant visit from baseline revised from 30 days to 45 days to allow sufficient time for diagnostic tests and independent MRI assessment to be completed and surgery scheduled (see Study Schedule in Table 1 and section 6.2). Clarified that the Percent Pain Relief (PPR) metric is obtained by a question asked to the Subject by the Investigator or Coordinator (and not via a questionnaire). See section 4.6.4.	05-Sep-2016

	Sponsor address change and overall study principal investigator address change (see section 11). Minor typographical errors and inconsistencies corrected throughout document.	
D	Removed the Upper Limit for age of subjects in the Trial. Revised to reflect the requirement for a Psychological Assessment for every subject prior to inclusion in the Trial. Revised to clarify that an Informed consent may be signed by an Investigator OR the investigator's delegate. Added a statement that the Study PI conducts a final review for all subjects to ensure inclusion/exclusion requirements are satisfied. Added the ReActiv8 Lead Models 8145/8165 to the ReActiv8 Product Family.	31-JAN-2017
E	Updated age limit for subjects in the Trial to ≤ 75 years old.	25-MAR-2017

Investigator Signature Page

Investigator Acknowledgement Signature:

I have received and reviewed this Clinical Investigational Plan. I will conduct the Trial as described.

_____	_____
Investigator's Name (print)	Site Number
_____	_____
Investigator's Signature	Date

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1. Study Purpose

To evaluate the safety and efficacy of ReActiv8 for the treatment of adults with Chronic Low Back Pain and no prior surgery when used in conjunction with medical management.

2. Overview

MML US Inc. (the Sponsor) is a wholly owned subsidiary of Mainstay Medical Limited (based in Ireland ("Mainstay"). Mainstay has developed an implantable medical device designed as therapy for people with chronic low back pain (CLBP). The device, called ReActiv8®, consists of two implantable leads with four electrodes each, configured to deliver bilateral electrical stimulation to the medial branch of the dorsal ramus nerves as they cross the transverse process at L3 to elicit bilateral contraction of the lumbar multifidus muscles (LM). The leads are coupled to a battery powered implantable pulse generator (IPG) which is activated by an external Activator, and is programmed via a programmer. Several accessories are included as part of the system, for example to facilitate the surgical procedure.

The therapy delivered by the ReActiv8 was explored with a European Feasibility Study in 2011 to 2013 using "off the shelf" general purpose neurostimulation devices from other manufacturers, and results have been published.[1] A report of that Study is included in the Report of Prior Investigations.

ReActiv8 is being investigated under an ongoing clinical trial to generate data for a submission for CE Mark approval in Europe. Subjects are enrolled at several sites in Australia and Europe. Details of this trial can be found at http://clinicaltrials.gov/show/NCT01985230 and the interim results of the ReActiv8-A clinical investigation are included in the Report of Prior Investigations and the Investigators Brochure.

2.1. Chronic Low Back Pain

This section is a summary of the scientific background of the ReActiv8.

Low back pain is usually defined as pain and discomfort, localized below the costal margin and above the inferior gluteal fold, with or without referred leg pain.[2,3] Chronic Low Back Pain (CLBP) is usually defined as back pain for at least 3 months. The NIH Task Force on Research Standards for Chronic Low Back Pain recommended[4] that Chronic Low Back Pain be defined as a back pain problem that has persisted for at least 3 months and has resulted in pain on at least half the days in the past 6 months.

Chronic low back pain is a major health problem, and the World Health Organization reports that "Low back pain is the most prevalent of musculoskeletal conditions; it affects nearly everyone at some point in time and about 4–33% of the population at any given point"[5] and back pain is the number one cause of years lived with disability worldwide in 2013.[6] There are many publications on the epidemiology[7] of back pain including prevalence,[8,9,10] natural history, demographics, and country by country variability.

People with acute low back pain and associated disability usually improve rapidly within weeks, but pain and disability typically continue, and recurrences are common.[11] Although most episodes of acute back pain resolve within 3 months, "recovery after 12 weeks is slow and uncertain. Fewer than half of those individuals disabled for longer than 6 months return to work and, after 2 years of absence from work, the return-to-work rate is close to zero."[12] Like many chronic conditions, the costs are driven by the small proportion of the population who have been

sick for the longest period – for back pain, patients with disability >1 year account for 5% of cases, but 65% of costs.[13,14]

Although there has been a lot of attention and investment applied to surgical treatments for low back pain, only approximately 20% of patients are suitable surgical candidates.[15] The remaining patients are sometimes referred to as having "non-specific low back pain" (NSLBP) or "axial low back pain" (ALBP). There are European clinical practice guidelines for chronic NSLBP[2] and UK guidelines for management of patients with persistent CLBP (published by the National Institute for Clinical Excellence - NICE).[16] US guidelines for acute and chronic low back pain are similar to the European guidelines.[17]

Exercise therapy is frequently prescribed for NSLBP, but the effectiveness of exercise therapy for *acute* back pain is negligible.[18] Systematic reviews of the literature[19,20] concerning therapies for *chronic* low back pain show that exercise is generally ineffective, other than certain types of exercise therapy which can be effective in a small subset of patients.

Many non-invasive conservative therapies have been tried with modest or no success, and several reviews are available.[21] Therapies include lumbar extensor strengthening exercises;[22] watchful waiting (i.e., no therapy),[23] traction therapy,[24] the McKenzie Method of exercise therapy,[25] various types of energy application including ultrasound, TENS,[26] osteopathic therapy,[27] and thermotherapy,[28] and lumbar stabilization exercises.[29]

Following failure of conservative therapy for CLBP, "usual care" or "conventional medical management" for CLBP usually consists of coping mechanisms for pain, and pain medications (often opioids), which are often increased during the episodic flare-ups of pain.

2.2. ReActiv8

Arthrogenic muscle inhibition (AMI)[30] is the physiological mechanism by which pain in a skeletal joint disrupts the motor control to the muscles that stabilize the joint – often observed in the quadriceps post knee surgery. A similar mechanism underlies some types of chronic low back pain, with disruption to the motor control of the key stabilizing muscles – the lumbar multifidus. Evidence includes diminished EMG activity in back pain patients[31] and delayed reflex response of the LM to perturbations.[32] Pain alters the magnitude of activation of deep LM during certain types of activity.[33] Ultrasound imaging evidence of reduced neural drive in back pain patients includes diminished cross sectional area with contraction,[34] reduced ability to cause a muscle thickness change on command,[35] and altered contraction patterns with changes in posture.[36]

Published studies show that subject initiated contraction of the lumbar multifidus with ultrasound guided biofeedback motor control physical therapy exercises can lead to improvements in back pain, but this approach has not been adopted due to practical challenges, economic difficulties, and patient compliance issues. The mechanism of action is believed to be restoration of motor control of the lumbar multifidus, thereby leading to rehabilitation of the muscle, improved spine stability and reduction in back pain.

Electrical stimulation to restore motor control has been successfully used with other skeletal muscles. In particular, stimulation via superficial (skin) electrodes over the motor point of the quadriceps can restore neural drive and allow rehabilitation of the muscle in patients following total knee arthroplasty[37] or other surgical procedures.[38,39] Painful knee osteoarthritis can be treated without surgery but may also lead to pain mediated inhibition of neural drive to the quadriceps, which can be treated effectively with electrical stimulation.[40]

The ReActiv8 has been designed to incorporate the principles of these prior approaches. Bilateral electrical stimulation of the medial branch of the dorsal ramus nerve that innervates the

lumbar multifidus is delivered episodically (10 seconds “on” followed by 20 seconds “off”, for 30 minutes, during two sessions per day). Previous experience with the therapy in the European Feasibility Study showed that many subjects can perceive the muscle contractions, and report the muscle contractions as “soothing” or “pleasurable.”

The intent to implant leads bilaterally and give bilateral stimulation is based on published research that indicates that multifidus dysfunction (atrophy) is likely to be bilateral even if the patient reports unilateral pain.

Beneck showed[41] that in people with chronic unilateral low back pain (<1 year) multifidus atrophy is bilateral with no difference in multifidus volume between the painful and non-painful sides.

D’Hooge explored changes in muscle fiber type of the multifidus erector spinae, quadratus lumborum and psoas using MRI imaging[42] and showed a conversion of (only) multifidus muscle fiber type towards the glycolytic (anaerobic) muscle spectrum bilaterally in patients with unilateral low back pain, and the changes persist after resolution of the pain.

Dickx showed[43] in an experimental human model that using hypertonic saline to induce unilateral pain at one segmental level resulted in bilateral dysfunction of the multifidus muscle and at multiple segmental levels.

Furthermore, the incremental risk of bilateral stimulation over unilateral stimulation is judged to be low – as the primary risk is associated with the surgical procedure itself and the incremental time for placement of the second lead is approximately 15 minutes. Conversely, implantation of one lead only (unilateral stimulation) exposes the subject to the risk of an additional surgical procedure if it is found that a second lead is needed for bilateral stimulation. Therefore, bilateral treatment is preferred over unilateral treatment.

2.3. Discussion on Outcome Measures

Since the primary indication for ReActiv8 is to provide pain relief, the primary endpoint is based on a valid outcome measure for pain.

Many outcome measures have been used in clinical trials for pain, and specifically for low back pain, and more specifically for chronic low back pain. There are multiple recommendations from the IMMPACT group (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)[44,45,46] which are generalizable to many trials for treatment of pain. The Visual Analog Scale (VAS) or the Numerical Rating Scale (NRS) are well accepted measures of pain. VAS is a widely used outcome measure in assessing pain due to the documented reliability, ease in administration and the minimal training requirements to administer the VAS tool.[47]

For this Trial, the primary endpoint is a comparison of responder rates between Treatment and Control groups, where a “responder” is a subject with ≥30% reduction from baseline in average low back pain VAS recalled for the previous 7 days, without any increase from baseline in pain medication and/or muscle relaxants (pain medications) prescribed and taken in the two weeks prior to the Primary Endpoint Assessment Visit.

Oswestry Disability Index (ODI) is a disease specific assessment of the disabling effects of back pain.[48] The ODI covers 1 item on pain and 9 items on activities of daily living (personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling). ODI is reported as a score from 0 to 100%. Recent CLBP studies use a disability index as the primary outcome measure rather than pain.[49,50] In this Trial ODI is an important secondary endpoint.

2.4. Overall Synopsis of the Clinical Investigation

The Clinical Investigation is an international, multi-center, prospective, randomized, sham controlled, blinded Trial with an adaptive statistical design. The Trial is powered for statistical significance and the Statistical Analysis Plan is provided in a separate document and summarized herein. A synopsis in tabular form is shown in Table 1.

All Subjects[a] who satisfy the baseline criteria are implanted with the ReActiv8, and then at the Randomization Visit are instructed to deliver stimulation during two 30-minute sessions (morning and evening) per day. Subjects are randomized (1:1) to the Treatment or Control Arm at the Randomization Visit.

Subjects randomized to the Treatment Arm of the study will have ReActiv8 programmed to deliver stimulation at a Subject-appropriate level (the Treatment group). Determination of the Subject appropriate level is described in the Implant and Programming Manual. Subjects in the Treatment group may or may not feel sensations during stimulation.

Subjects randomized to the Control Arm will have ReActiv8 programmed to deliver minimal stimulation (the Control group). Subjects in the Control group may or may not feel sensations during stimulation.

All subjects will have automatic electrical impedance measurement of electrodes performed immediately prior to each stimulation session.

Thus, with this design, all subjects receive some electrical stimulation. The Informed Consent will advise subjects that electrical stimulation will be delivered, and subjects may or may not feel something associated with the stimulation. Subjects will also be advised in the Informed Consent that they will be randomized to one of two different treatment regimes.

Subjects will be eligible for enrollment if they have chronic low back pain that has persisted >90 days that has resulted in pain in at least half of the days in the 12 months prior to the Baseline Visit, despite medical management including at least pain medications and one attempt of a prescribed physical therapy program for low back pain, and satisfy the other eligibility criteria. It is likely that subjects will have tried and failed other conservative treatment options including one or more of chiropractic, massage, cognitive behavioral therapy, medial branch rhizotomy, nerve blocks, steroid injections, acupuncture or lumbar supports. All treatments that have been tried will be recorded.

All endpoints are assessed at 120 days post randomization (at the Primary Endpoint Assessment Visit).

Compliance with instructions for stimulation delivery will be assessed from data stored in the ReActiv8 IPG, which records the start and stop time of each stimulation session.

The Primary Efficacy Endpoint is a comparison of responder rates of pain where a “responder” is a Subject with ≥30% reduction from baseline in average low back pain VAS, without any increase in pain medication and/or muscle relaxants prescribed and taken in the two weeks prior to the Primary Endpoint Assessment Visit.

Several secondary endpoints will be assessed, including change in ODI, change in EQ-5D Quality of Life, change in Percent Pain Relief, and Subject Global Impression of Change, all assessed as a difference between baseline and the Primary Endpoint Assessment Visit.

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a In this Clinical Investigation Plan, the term used is “subject” instead of “patient” in line with the suggestions of ISO 14155. The terms should be considered as synonymous.

Subgroups will be also analyzed based on Subject characteristics (e.g.: BMI) and by site. Several other endpoints will be analyzed on an exploratory basis.

Safety will be assessed by collecting data on the rate of all serious device and/or procedure related adverse events in all enrolled Subjects. Adverse event data will be collected at each visit beginning with the Baseline Visit. The Safety Cohort consists of all enrolled Subjects in whom implant was attempted or successful. A separate analysis will be conducted of the Safety Cohort without Subjects included in the Surgical Roll In Cohort.

Table 1: Synopsis of Clinical Investigation

Study Purpose	To evaluate the safety and efficacy of ReActiv8 for the treatment of adults with Chronic Low Back Pain and no prior spine surgery when used in conjunction with medical management.
Indication For Use	ReActiv8 is an adjunct to medical management in adults with Chronic Low Back Pain for relief of pain in subjects who have failed at least medical management and physical therapy.
Study Device	Mainstay ReActiv8
Study Design	International, multi-center, prospective, randomized, sham controlled, blinded Trial with an adaptive statistical design. Subjects are blinded, investigators are blinded, and the assessment of primary endpoint data is blinded.
Treatment Arm	ReActiv8 implanted and configured to deliver stimulation at a Subject-appropriate level and Subjects instructed to deliver stimulation in two 30-minute sessions per day (the Treatment group).
Control Arm	ReActiv8 implanted and configured to deliver minimal stimulation, and Subjects instructed to deliver stimulation in two 30-minute sessions per day (the Control group).
Randomization	Subjects meeting all eligibility criteria who have been implanted with ReActiv8 will be randomized post-implant to either the Treatment group or the Control group. Randomization will be performed according to a random permuted block design stratified by clinical site with a 1:1 allocation ratio for Treatment vs. Control.
Anticipated Sample Size	Initial estimate: 128 randomized Subjects implanted with ReActiv8 in the intent to Treat cohort of the study, plus up to 80 Subjects implanted in the Surgical Roll In group. An adaptive statistical design using a single interim look will be used for sample size re-estimation when at least 50% of the implanted Subjects have completed the Primary Endpoint Assessment Visit. Up to 800 Subjects will be enrolled to account for screen failures prior to implant, Surgical Roll In, drop outs, and possible increase in numbers for the intent to treat analyses after the interim look.
Anticipated Number of Sites	There will be up to 40 Investigational sites performing implants. Each site will have a Site Principal Investigator who may or may not be the implanting physician. One or more Sub-investigators per site (or affiliated site if the affiliated site has a different Ethics Committee or IRB) may be used for example for device implantation and Subject recruitment.

Surgical Training and Surgical Roll In	All physicians who will implant any portion of the system will be trained as outlined in the Training Strategy. Following training, up to the first two Subjects implanted by the same physician may be prospectively included in a Surgical Roll In group. Subjects included in the Surgical Roll In group will be randomized to Treatment or Control with a single group randomization, and be analyzed as a separate cohort (the Surgical Roll In Cohort).
Crossover and Open Label Phase	Following endpoint assessment at the Primary Endpoint Assessment Visit: • Subjects randomized to the Control Arm will have ReActiv8 configured to deliver stimulation at a Subject-appropriate level, and Subjects will be instructed to deliver stimulation in two 30-minute sessions per day. Once the Control group has crossed over, it will be referred to as the Crossover group. • All Subjects in the Treatment group will be advised to continue to use their devices for two 30-minute sessions per day. • All Subjects will be permitted to change their medications
Primary Efficacy Endpoint	The Primary Efficacy Endpoint is a comparison of responder rates between Treatment and Control groups, where a “responder” is a Subject with ≥30% reduction from baseline in average low back pain VAS without any increase in pain medication and/or muscle relaxants prescribed and taken in the two weeks prior to the Primary Endpoint Assessment Visit.
Secondary Efficacy Endpoints	The hypotheses will be tested utilizing an overall Type I error of 5%. The overall Type I error will be maintained by utilizing Hochberg’s method to test the collection of the first five secondary objectives. These will be tested only if the primary efficacy endpoint is met. 1. Comparison of change from baseline in ODI between Treatment and Control groups at the Primary Endpoint Assessment Visit 2. Comparison of change from baseline in EQ-5D between Treatment and Control groups at the Primary Endpoint Assessment Visit 3. Comparison of Percent Pain Relief between Treatment and Control groups reported by the Subject at the Primary Endpoint Assessment Visit 4. Comparison of Subject Global Impression of Change at the Primary Endpoint Assessment Visit 5. Comparison of number of Subjects with Resolution of Low Back Pain (remitters or cure, defined as a VAS score ≤ 2.5cm) at the Primary Endpoint Assessment Visit 6. Evaluation of changes in primary and secondary efficacy metrics in Crossover Group following the Outcome Post Crossover Visit.

Supporting Analyses	The Supporting Analyses will include: • Once data are complete, all primary and secondary outcome measures will be assessed at 12 months and compared to baseline within the Treatment group. The analysis will also explore correlation of outcomes to amount of stimulation delivered. • In the Crossover Group, outcome measures will be assessed at the Outcome Post Crossover Visit for all Subjects who met the inclusion criteria for low back pain at the Primary Endpoint Assessment Visit (i.e.: prior to Crossover) (Average Low Back Pain VAS of ≥6.0cm and ≤9.0cm on a VAS scale (0-10cm)) and inclusion criterion for ODI (Oswestry Disability Index score ≥21% and ≤60%). The analysis will also explore correlation of outcomes to amount of stimulation delivered. • Comparison of daily average VAS averaged over the prior 7 days of Journal entry with the single point VAS of recollection of prior 7 days of daily average pain. • Comparison of EQ-5D VAS between Treatment and Control groups at each visit at which EQ-5D is recorded through 12 months. • For both the Treatment and Control groups, a cumulative proportion of responder analysis[51] for both ODI and reduction in back pain (VAS) so that the entire distribution of treatment response is depicted in a graph of the proportion of responders for all percentages from 0% to 100%. • Subject Global Impression of Change at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered. • Treatment Satisfaction Questionnaire at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered. • Clinical Global Impression – Global Improvement (clinician assessment) at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered. • Change in opioids used for treatment of low back pain from baseline to 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered. Additionally, ad hoc exploratory analyses may also be conducted. Note: Supporting analyses may be incomplete at the time of PMA submission.
Primary Safety Assessment	The primary safety assessment is serious device and/or procedure related adverse events in all Subjects in the Intent to Treat Cohort at the Primary Endpoint Assessment visit.
Supporting Safety Analysis	The PMA Submission will include 12 month safety data on all Subjects implanted with ReActiv8 including all Subjects implanted in the ReActiv8-B Trial for whom 12 month safety data are available, and other persons implanted with ReActiv8 in other clinical trials (including the ReActiv8-A PMCF Study) and all post-marketing registries that are registered on www.clinicaltrials.gov. A separate safety assessment will be performed on the Surgical Roll In group, including a poolability analysis.

Health Economics	Cost-effectiveness of ReActiv8 therapy, extrapolated to the lifetime of the device, will be assessed. Key economic outcome measures to be recorded will include: • Change in work status at all visits. • Change in consumption of medications taken for low back pain at all visits compared to Baseline. • Assessment of health care utilization (office visits, hospital visits, emergency room visits, and other therapies such as physical therapy) at all visits. Note that the Health Economics assessment is likely to be incomplete at the time of PMA submission for ReActiv8, since not all Subjects will have reached the 12 month point at that time.
Efficacy Follow Up	All Subjects will be followed for efficacy until PMA approval unless the study is closed prior to PMA approval for any reason.
Safety Follow Up	All Subjects will be followed for safety until PMA approval or 7 years from the Baseline Visit, whichever is longer, unless the study is closed prior to PMA approval for any reason.
Device Data	At each follow up visit during which the ReActiv8 IPG will be interrogated, electrical parameters stored in the IPG such as lead impedance will be recorded. Results of threshold testing (if performed) and any reprograming will be recorded.
Study Duration	Anticipated to be ≤60 months from first Subject Baseline Visit to PMA submission. Informed consent for all Subjects will allow for continuing collection of safety and efficacy data for a total period of 7 years from the Baseline Visit.
Study Schedule	• Informed consent, baseline criteria verification, • ReActiv8 implant (1-45 days post inclusion) • Post-Implant Follow-up: 7 days -0/+10 days post-implant. • Randomization and Activation Visit: 14±3 days post-implant • 14 day visit: 14 ± 7 days post-randomization • 1.5 month visit: 45 ± 7 days post-randomization • 2.5 month visit: 75 ± 10 days post-randomization • 4 month visit: 120 -0/+20 days post-randomization - Primary Endpoint Assessment Visit • 6 month visit: 180 ± 30 days post-randomization • 8 month visit: 240 ± 30 days post-randomization • 12 month visit: 360 -30/+ 60 days post-randomization • Annual follow up every 360 ± 60 days post-randomization until Study Closure For Subjects in the Control group, after the Subject completes the endpoint assessment at the Primary Endpoint Assessment Visit, the ReActiv8 will be programmed to deliver stimulation at a Subject-appropriate level, and other activities will be performed.

	The study will be considered complete with regard to the primary endpoint after the required numbers of randomized Subjects have completed the Primary Endpoint Assessment Visit.
Adjunctive Therapies	• All medications for treatment of low back pain will be stabilized 30 days prior to the Baseline Visit and remain stabilized through the Primary Endpoint Assessment Visit. • All other treatments for low back pain (e.g. interventional pain treatments, chiropractic) will be prohibited until after the Primary Endpoint Assessment Visit.
Eligibility Criteria	***Primary Inclusion Criteria*** 1. Age ≥22 years, ≤75 years 2. 7 day recall of average Low Back Pain VAS of ≥6.0cm and ≤9.0cm (on a 10cm scale) at the Baseline Visit. 3. Oswestry Disability Index score ≥21% and ≤60% at the Baseline Visit 4. Chronic Low Back Pain defined as pain and discomfort localized below the costal margin and above the inferior gluteal fold (with or without referred leg pain) that has persisted >90 days prior to the Baseline Visit, which has resulted in pain in at least half of the days in the 12 months prior to the Baseline Visit, as reported by the Subject. 5. Evidence of lumbar multifidus muscle dysfunction by the Prone Instability Test (PIT). 6. Continuing low back pain despite >90 days of medical management including: a. At least one attempt of physical therapy treatment for low back pain, which may optionally be accomplished over multiple episodes or flare-ups of low back pain. NOTE 1: Subjects who start a physical therapy program but are unable to complete it are still eligible with regards to this inclusion criterion. NOTE 2: Subjects who participated in a physical therapy program in the past since the onset of low back pain but are unwilling or unable to participate in a new physical therapy program are still eligible with regards to this inclusion criterion; b. For Subjects with medications prescribed and used for chronic low back pain, usage shall be at a stable dose in the 30 days prior to the Baseline Visit as reported by the Subject. NOTE 3: A stable dose means the Subject reports no significant change in regular use of medications, which may include PRN use, in the 30 days prior to the Baseline Visit. 7. Be willing and capable of giving Informed Consent. 8. Ability to comply with the instructions for use and to operate ReActiv8, and to comply with this Clinical Investigation Plan. 9. Suitable for ReActiv8 surgery as determined by the implanting physician prior to inclusion. ***Primary Exclusion Criteria*** 1. BMI > 35

	2. Back Pain characteristics: a. Any surgical correction procedure for scoliosis at any time, or a current clinical diagnosis of moderate to severe scoliosis (Cobb angle ≥25°).[52] b. Lumbar spine stenosis, as defined by an anterior-posterior diameter of the spinal canal <10mm in Subjects with lower extremity pain. c. Neurological deficit possibly associated with the back pain (e.g. foot drop). d. Back pain due to pelvic or visceral reasons (e.g.: endometriosis or fibroids) or infection (e.g.: post herpetic neuralgia). e. Back pain due to inflammation or damage to the spinal cord or adjacent structures (e.g. arachnoiditis or syringomyelia). f. Pathology seen on MRI that is clearly identified and is likely the cause of the CLBP that is amenable to surgery. g. Back pain due to vascular causes such as aortic aneurysm and dissection. 3. An independent assessment of any current indication for back surgery according to appropriate guidelines, or has indications for back surgery but cannot undergo surgery for other reasons. 4. Leg pain described as being worse than back pain, or radiculopathy (neuropathic pain) below the knee. 5. Source of pain is the sacroiliac joint as determined by the Investigator. 6. Drug use per Subject report as follows: a. Current baseline use of >120mg oral morphine equivalent per day of opioids. b. Current use of breakthrough dose of >60mg oral morphine equivalent per day. c. Current requirement of opioids for treatment of a condition other than low back pain. d. History of any substance abuse at any time in the five years prior to the Baseline Visit. e. Currently taking >15mg Diazepam per day or equivalent. 7. Surgical or other procedures exclusions: a. Any previous rhizotomy or rhizolysis procedure, including cryoablation, RF ablation or pulsed RF on the dorsal root ganglion (DRG) or the medial branch of the dorsal ramus nerve that crosses or lies below the T8 vertebra, within one year prior to the Baseline Visit. b. Anesthetic block of the DRG or medial branch of dorsal ramus nerve that crosses or lies below the T8 vertebra or injection of epidural steroids for back pain in the 30 days prior to the Baseline Visit. c. Any previous back surgery including laminectomy or discectomy at or below segmental level T8, or spinal fusion at any level. d. Any previous thoracic or lumbar sympathectomy. 8. Any prior diagnosis of lumbar vertebral compression fracture, lumbar pars fracture, pars defect, or lumbar annular tear with disc protrusion that is amenable to surgery.

	9. Planned surgery: a. Any major surgery (including elective surgery) planned in the twelve months following the Baseline Visit (does not include minor surgeries not expected to impact the lumbar spine (e.g. colonoscopy)). b. Any elective surgery of any kind (including, for example, tooth extraction, gynecological surgery or cosmetic surgery) in the time between the Baseline Visit and the Primary Endpoint Assessment Visit. 10. Any co-morbid chronic pain conditions. 11. Other clinical conditions: a. Pregnant or planning to be pregnant in the next 12 months, at the time of inclusion. b. Pregnancy at any time in the 6 months, or lactating at any time in the 3 months, prior to the Baseline Visit. c. Any condition unrelated to the CLBP such as muscle wasting, muscle atrophy, other disability (e.g.: paraplegic, amputee, cerebral palsy) or muscular or skeletal disease (e.g.: arthritis in trunk or limbs, multiple sclerosis, rheumatoid arthritis) which, in the opinion of the Investigator, could limit physical movement or compliance with the protocol, or interfere with the assessment of efficacy of the investigational procedure. d. Poorly controlled diabetes (Type I or Type II) determined by HbA1c >8. e. Past or current neurological disorders (e.g.: known multiple sclerosis, motor neuron disease, Guillain-Barré syndrome, Parkinson's, Huntington's Disease, Alzheimer's, epilepsy, stroke, brain cancer, traumatic brain injury). f. Cancer requiring treatment during the study. g. Any drugs (e.g.: immunosuppressive drugs) or co-morbidity that might inhibit wound healing or electrode scarring, or drugs associated with reduced effectiveness of neuromodulation for other applications. h. Any medical condition requiring anticoagulation (other than aspirin) that, in the opinion of the physician prescribing the anticoagulant, cannot be safely suspended for 5 days prior to device implantation surgery and an appropriate period after implantation surgery. i. Any active infection in the vicinity of the implant site or any systemic infection. 12. Psycho-social exclusions a. Be involved in an injury claim under current litigation. b. Have a pending or approved financial compensation claim (e.g., worker's compensation claim, long term disability claims) or any financial compensation (including social welfare payments) related to the Subject's CLBP. c. Current incarceration (prison or jail) d. Have an assessment of current active depression significant enough (DASS depression score >9[53,54]) to impact perception of pain,

	compliance with intervention and/or ability to evaluate treatment outcome. e. Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome (e.g.: active depression, bipolar disease, Alzheimer's disease) as determined by a psychologist or psychiatrist. 13. Protocol Compliance Exclusions a. Inability or unwillingness to comply with all protocol requirements. b. Inability to maintain the prone or side lying position in a relaxed manner for the duration of each stimulation session. c. Inability to operate the Activator, such as arthritis that limits arm or shoulder movement, or inability to learn how to operate. d. Inability to assess changes in pain intensity or perform wound care. e. Inability or unwillingness to complete the Journal. 14. General exclusions a. Any other active implantable device including an implantable device for back pain (such as an implantable drug pump or Spinal Cord Stimulator), pacemaker, implantable defibrillator, cochlear implant, deep brain stimulator, or other implanted neurostimulation device. b. Prior exposure to an implantable neurostimulator for treatment of pain, including spinal cord stimulation (including trial implant of SCS leads), occipital nerve stimulation or peripheral nerve stimulation. c. A condition currently requiring or likely to require use of MRI or diathermy while implanted with the ReActiv8. d. Therapy with any other investigational intervention (drugs, devices, or procedures) for the treatment of back pain at the time of the Baseline Visit, or at any time in the past if the past investigational intervention did not subsequently gain regulatory approval. e. Current or planned participation in any other clinical trial during participation in this Trial. f. Life expectancy <1 year.

3. The ReActiv8 Therapy

3.1. Summary of ReActiv8

The Mainstay ReActiv8 is an implantable electrical stimulation system that consists of an implantable pulse generator, leads, programmer, activator and magnet. Refer to the Investigator Brochure (IB) or the Implant and Programming Manual for more detail on device specifications and operation.

Implantable Components of ReActiv8

The ReActiv8 IPG, and the ReActiv8 leads (available in either 45 cm or 65 cm lengths), plus suture sleeves, are designed for permanent implant. The implantable components of ReActiv8 are supplied sterile, and are intended for single use only.

- Model 5100 ReActiv8 Implantable Pulse Generator (“IPG”)
- Model 8000-45 ReActiv8 Percutaneous Stimulation Lead, 45 cm length (“lead”)
- Model 8000-65 ReActiv8 Percutaneous Stimulation Lead, 65 cm length (“lead”)
- Model 8145 ReActiv8 Percutaneous Stimulation Lead, 45 cm length (“lead”)
- Model 8165 ReActiv8 Percutaneous Stimulation Lead, 65 cm length (“lead”)

Note: The Model 8000-XX and Model 81XX leads are functionally equivalent. The Model 81XX leads incorporate a change to eliminate unused wires within the lead.

Non-Implantable Components of ReActiv8

The Torque Wrench and Stylet are provided to facilitate implantation of the IPG and leads. The Programmer is used to communicate with the IPG in order to program the IPG operational mode and settings, read history data from the IPG, and obtain IPG and lead status information. The Activator is used to initiate and/or suspend stimulation. The Magnet is used to enter Magnet Mode (with Magnet Mode operation determined by the programmed parameters of the IPG).

- Model 6500/65X0 ReActiv8 Programmer System (“Programmer”) – All Model 65X0 Programmers contain a Lenovo E420 Laptop computer. Model 6500 contains a “universal” set of power cords (for the UK, US, Belgium and Australia), while Model 65X0 contains one power cord that varies by the intended geography for use (e.g., Model 6530 contains a US power cord only). Mainstay provides the following components of the Model 6500/65X0) Programmer in case replacements are needed:
    - Model 6600 Lenovo E420 Laptop (“E420 Laptop”)
    - Model 6700 Medical Grade AC Adapter for the Model 6500/65X0 Programmer
    - Model 6800 Battery for the Model 6600 Lenovo E420 Laptop
    - Model 6000 ReActiv8 Programmer Wand (“Wand”)
    - Model PP00 Universal Replacement Power Cord Package with AUS, UK, USA and Belgian Power Cord
    - Model PP30 USA Replacement Power Cord Package
- Model 7500/75X0 ReActiv8 Programmer System (“Programmer”) – All Model 75X0 Programmers contain a Lenovo E440 laptop computer. Model 7500 contains a “universal” set of power cords (for the UK, US, Belgium and Australia), while Model 75X0 contains one power cord that varies by the intended geography for use (e.g., Model 7530 contains a US power cord only). Additionally, the Model 7500/75X0 Programmer contains the Model 6750 Medical Grade AC Adapter and the Model 6000

Programmer Wand (unchanged from the Model 6500/65X0). Mainstay provides the following components of the Model 7500/75X0) Programmer in case replacements are needed:
  - Model 7600 Lenovo E440 Laptop ("E440 Laptop")
  - Model 6750 Medical Grade AC Adapter for the Model 7500/75X0 Programmer
  - Model 7800 Battery for the Model 7600 Lenovo E420 Laptop
  - Model 6000 ReActiv8 Programmer Wand ("Wand")
  - Model PP00 Universal Replacement Power Cord Package with AUS, UK, USA and Belgian Power Cord
  - Model PP30 USA Replacement Power Cord Package
- Model 7000 ReActiv8 Activator ("Activator")
- Model 4000 ReActiv8 Magnet ("Magnet")
- Model 5500 ReActiv8 Torque Wrench – single use - ("Torque Wrench")

Accessories Included with the ReActiv8

Mainstay supplied accessories included with the ReActiv8 are:

- Torque Wrench (supplied in the IPG package and also available as a standalone accessory)
- Suture sleeve (optional - supplied in the Lead package)
- Lead Stylet (supplied in the Lead package)
- Model TUN1 Mainstay Tunneler

Other Accessories

The Lead is designed to be placed using a commercially available 7 Fr Introducer Kit (not included with ReActiv8) and the Mainstay Model TUN1 Tunneler (included with ReActiv8) or commercially available equivalent.

The ReActiv8 delivers stimulation via electrodes placed adjacent to the medial branch of the dorsal ramus nerve at the preferred location as it crosses the L3 transverse process. The electrodes are located at the distal end of a Stimulation Lead that is connected to an implantable pulse generator (IPG) placed in a surgical pocket typically above the buttocks (in a place similar to that used in Spinal Cord Stimulation implants). Two leads are placed (one each left and right side) and connected to the IPG. The IPG is externally programmable with a Programmer. Stimulation is manually initiated by an external device (Activator) and can be stopped with the Activator or Magnet.

The leads incorporate a fixation mechanism that consists of two sets of 3 point tines – one facing forward and one facing backwards. The tines are positioned to lie on either side of the intertransversarii lateralis, thus reducing the risk of lead dislodgement by either advancement or retraction. The lead body is a polyurethane tube containing spiral wound multi-filar wires and incorporates a lumen to allow passage of a stylet.

3.2. Surgical Implantation and Device Activation

Surgical implantation is adapted from familiar techniques used for medial branch rhizotomy and spinal cord stimulation. Details of the recommended surgical procedure, device programming and use by the Subject are to be found in the Implant and Programming Manual and the User Manual.

In normal use, following implantation and a suitable recovery period, the IPG is programmed to deliver stimulation that elicits smooth contraction of the lumbar multifidus. Typical parameters

are 0.5 mA, 200 µs, 20 Hz, with 10 seconds of stimulation followed by 20 seconds of no stimulation, delivered for a Session of 30 minutes. Refer to the Implant and Programming Manual for device programming.

To start a Session, the Subject is positioned comfortably prone or lying on the side. The Subject initiates delivery of electrical stimulation with the Activator, which can also be used to stop stimulation (e.g.: in case of interruption). Two sessions of stimulation, each of 30 minutes, are delivered each day (e.g. morning and evening).

3.3. Physician Training

All physicians who will implant any portion of the ReActiv8 in the clinical Trial will participate in product training as outlined in the Training Strategy. A “Certificate of Completion” will be issued to each implanting physician who completes the training to the satisfaction of the trainer.

All physicians and other health care personnel who will interact with the programmer (e.g.: non-implanting physicians) will receive training from the Sponsor, which includes lectures and use of a programmer with a simulator (e.g.: a ReActiv8 IPG connected to a dummy load). This training will also include interaction with the external components handled by the Subject, including the Activator and Magnet.

4. Study Design

International, multi-center, prospective, randomized, sham controlled, blinded Trial with an adaptive statistical design.

4.1. Hypothesis

In Subjects with chronic low back pain and no prior surgery and with unsatisfactory pain relief despite medical management (including at least physical therapy and medications), episodic electrical stimulation of the medial branch of the dorsal ramus nerves to cause contraction of the lumbar multifidus muscles can lead to relief of low back pain and the disabling effects of back pain.

4.2. Proposed Indications for Use for ReActiv8

ReActiv8 is an adjunct to medical management in adults with Chronic Low Back Pain for relief of pain in subjects who have failed at least medical management and physical therapy.

4.3. Study Population

Subjects with chronic low back pain that impacts their daily living, who satisfy the following general criteria:

1. Chronic low back pain and disability despite medical management, including at least one attempt of physical therapy treatment for low back pain (which may optionally be accomplished over multiple episodes or flare-ups of low back pain), and may be using prescribed pain relieving drugs (including muscle relaxants) which have been at a stable appropriate dose for a minimum of 30 days.
2. No contraindications for enrollment.

Detailed Inclusion and Exclusion criteria are listed in Section 5.

4.4. Study Size and Duration

A minimum of 116 evaluable Subjects is required to sufficiently power the primary endpoint. To allow for attrition, 128 Subjects will be randomized as part of the Intent to Treat Cohort. Up to 80 additional Subjects will be randomized as part of the Surgical Roll In phase as described below (assuming one implanting surgeon per site). Therefore, the total number of implanted and randomized Subjects will be up to 208. In order to account for screen failures prior to implant up to 800 Subjects will be enrolled. An adaptive statistical design using a single interim look will be used for sample size re-estimation.

4.4.1. Investigational Sites

Investigators may include a number of different specialties including Physical Medicine and Rehabilitation (PM&R), Interventional Pain, Neurosurgery, Neurology and Spine Surgeons. The key investigational activities include Subject recruitment, device implant, and Subject follow up (including device management and Trial data collection). Some investigators will perform all of these activities, and some may not. For example, some PM&R physicians will not perform

surgery, and the surgery will be performed by a Sub-investigator (e.g.: a neurosurgeon) who may be at a different site. The Trial design accommodates this situation.

There will be up to 40 investigational sites with a Principal Investigator who may or may not be the implanting physician. One or more Sub-investigators per site (or affiliated site if the affiliated site has a different Ethics Committee or IRB) may be used for example for device implantation and Subject recruitment.

4.4.2. Surgical Roll In Phase

Following training, up to the first two Subjects implanted by the same implanting physician may be prospectively included in a Surgical Roll In group and not included in the Intention To Treat Cohort. The Surgical Roll In phase for each implanting physician will be deemed complete upon consultation with the implanting physician and the Sponsor. In some cases, there will be no Surgical Roll In phase, for example if the implanting physician participated in the ReActiv8-A Trial. Note that Subjects included in the Surgical Roll In Phase who are not successfully implanted are not included in the Surgical Roll In group.

All Subjects implanted in the Surgical Roll In group will be randomized to either Treatment or Control, and follow the identical visit schedule as Subjects included after the Surgical Roll In phase. With approximately 40 implanting physicians and up to 2 Subjects in the Surgical Roll In phase per implanting physician, up to 80 Subjects may be included in the Surgical Roll In group.

4.4.3. Study Duration

Total study duration is anticipated to be ≤60 months from first Subject Baseline Visit through PMA submission.

Informed consent for all Subjects will allow for continuing data collection for a total period of 7 years from Baseline Visit.

4.5. Assessment of Lumbar Multifidus Dysfunction

The Prone Instability Test (PIT) has been utilized in variety of studies[55] and is used in this Trial to identify Subjects likely to have multifidus dysfunction. The PIT was designed to identify Subjects who would likely respond to a lumbar stabilization exercise program, and in many of these Subjects spine instability is thought to be due to LM dysfunction consequent to compromised neural drive to the LM. It has established reliability (K = 0.87).[56] It was one of 4 variables shown to be predictive of success with a stabilization exercise program for Subjects with low back pain that included exercises designed to reactivate the LM.[57] Additionally, the same study demonstrated that those Subjects who had a positive PIT also had reduced LM thickness change when compared to Subjects who had a negative PIT. The PIT may be the only predictive test that has demonstrated reasonable inter-tester reliability.[58]

The PIT will be performed by appropriately qualified individuals (e.g.: physical therapist, Physical Medicine and Rehabilitation Physician, Orthopedic Surgeon). Each person performing the PIT shall undergo training as follows:

- The training materials shall be standardized across sites.
- The person conducting the training shall be a reputable and appropriately qualified individual with experience in training on the PIT (e.g.: a physical therapist or physical medicine physician who regularly conducts training of other specialists).

- A formal training plan shall be developed in conjunction with the trainer(s), including "hands on" conduct of the PIT.
- Each trainee will be assessed by the trainer, including a "hands-on" demonstration of competence in performing the PIT to validate the training.
- Upon successful completion of the training and assessment, the trainer shall sign a "Certificate of Training" for the trainee to document that the trainee is qualified to conduct the PIT for this Trial.

In summary, to conduct the PIT, the Subject is positioned prone on an examination table. The test is conducted in two stages:

Stage 1: Tester performs Posterior-Anterior (P-A) glides over each lumbar segment for pain provocation and identifies the painful segments.

Stage 2: Repeat P-A with hips extended (Feet just off of the floor) as shown in Figure 1.

A Positive Test is when any previously painful segments become pain-free. The level of instability will be documented.

Figure 1: Conducting the Prone Instability Test

4.6. Outcome Measures

Several outcome measures are used to assess the primary and secondary endpoints of the Trial.

4.6.1. Low Back Pain Visual Analog Scale (VAS)

The primary outcome measure is pain, a Patient Reported Outcome (PRO). The instrument used for evaluating pain is the continuous Visual Analog Scale comprised of a horizontal line 10cm in length, anchored by 2 verbal descriptors, one for each symptom extreme for Low Back Pain, as recommended by IMMPACT.[44]

Subjects will be advised to place a line on the VAS that represents their average low back pain for the last 7 days. The scale is anchored with “no pain” on the left side of the scale to “worst imaginable pain” on the right side of the scale.

Note: This is a study on *low back pain.* Thus the Subject will be presented a VAS that is specific to the low back pain that led to being enrolled in this study. This allows separation of the low back pain symptoms from other pain causing events (e.g.: toothache) which could confuse interpretation of the results. People with low back pain often also report leg pain, which should be distinguished from the low back pain that led to enrollment in the Trial.

The VAS for low back pain is recorded by the Subject at each of the visits and is used for the primary outcome.

A daily Journal will also be collected for 7 days prior to each visit through the 120 day follow-up, completed preferably at the same time of day (e.g.: between 5PM and 8PM).

4.6.2. ODI

Oswestry Disability Index (ODI) is a disease specific assessment of the disabling effects of back pain.[48] The ODI covers 1 item on pain and 9 items on activities of daily living (personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling). ODI is reported as a score from 0 to 100%.

The relevance of changes in ODI has been explored by many authors, and discussions abound on Minimal Clinical Important Difference (MCID), Minimally Important Change (MIC) and the like. It is important to distinguish between significance of change scores for studies on *acute* low back pain where the natural history of improvement would suggest reversion to the mean, and studies on chronic low back pain where the likelihood of improvement is low. Hägg et al[59] suggested that an absolute change of 10 (in the 100 point ODI scale) is the MCID and Ostelo[60] concurs that a Minimally Important Change is 10.

4.6.3. EQ-5D

EQ-5D is the acronym for the European Quality of Life Score on Five Dimensions. There are many instruments used for assessment of Quality of Life,[61] and EQ-5D appears to be the most commonly used in studies of therapies for back pain, and is often used for cost utility assessment.[62] The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The original EQ-5D used a 3 level reporting system (no problems, some problems, extreme problems), and more recently a five level reporting system has been developed and validated (no problems, slight problems, moderate problems, severe problems, and extreme problems), referred to as the EQ-5D-5L, which has been tested and validated.[63,64] This Clinical Investigation uses the EQ-5D-5L, referred to in its short form as EQ-5D.

The EQ-5D is designed for use primarily as a self-reported measure (i.e.: the questionnaire is completed by the Subject alone), and therefore lends itself to clinical trials in which the outcome assessment is to be blinded. Population norms for EQ-5D for various populations have been reported, and categorized by age, gender and social class. EQ-5D is reported as an index up to 1.00 (note: EQ-5D index scores of <0 are possible in some circumstances).

4.6.4. Percent Pain Relief (PPR)

Percent Pain Relief (PPR) is a question asked to the Subject by the Investigator or Coordinator in which the Subject is asked to report the percent pain relief at the time of the current visit compared to the pain at baseline.

4.6.5. SGIC

Subject Global Impression of Change (SGIC) is based on the "Patient Global Impression of Change" as described by Farrar.[65] The Subject is presented with a questionnaire with 7 choices, as shown in Figure 2.

Since I enrolled in the study, my overall status is

1. ☐ Very much improved
2. ☐ Much improved
3. ☐ Minimally improved
4. ☐ No change
5. ☐ Minimally worse
6. ☐ Much worse
7. ☐ Very much worse

Figure 2: Subject Global Impression of Change (SGIC) Questionnaire

4.6.6. Clinical Global Impression

Clinical Global Impression – Global Improvement consists of the questions that are to be completed by the Investigator as shown in Figure 3.

In your opinion as a clinician, compared to the Subject's situation at baseline, would you say the Subject is:

☐ Much better
☐ Slightly better
☐ About the same
☐ Slightly worse
☐ Much Worse

Figure 3: Clinical Global Impression Questionnaire

4.6.7. Resolution of Back Pain

Resolution of back pain (cure) is defined as a Subject with 7 day average low back pain VAS ≤2.5cm on the 10cm VAS.

4.7. Clinical Trial Endpoints

A single primary endpoint will be analyzed. Multiple secondary endpoints and exploratory endpoints will be analyzed.

4.7.1. Primary Endpoint – Low Back Pain VAS

The Primary Efficacy Endpoint is a comparison of responder rates between Treatment and Control groups, where a "responder" is a Subject with ≥30% reduction from baseline in average low back pain VAS without any increase from baseline in pain medication and/or muscle relaxants prescribed and taken in the two weeks prior to the Primary Endpoint Assessment Visit.

Note: The primary outcome measure is intended to assess the efficacy of 120 days of stimulation. Thus the visit for assessment of the primary outcome must occur no sooner than 120 days post randomization.

Records of pain medications will be collected along with all other medications used for treatment of low back pain, which are also being collected for analysis of secondary and cost-effectiveness endpoints. The Subject will report medications taken at each scheduled follow-up visit. Rescue medications taken on an exceptional basis for acute pain conditions other than back pain will also be documented and their possible effect examined as part of sensitivity analyses.

After the Primary Endpoint Assessment Visit, Subjects will be permitted to adjust their drug use as appropriate, based on consultation with their physicians, and data on drugs prescribed and taken will continue to be collected.

4.7.1.1. Hypotheses

The primary efficacy objective will be assessed by the following hypotheses:

H0: $\Pi VAS_T = \Pi VAS_C$

HA: $\Pi VAS_T \neq \Pi VAS_C$,

where ΠVAS_T is the proportion of Subjects meeting primary success criteria in the Treatment group and ΠVAS_C is the proportion of subjects meeting success criteria in the Control group. The hypotheses will be tested using a two-sided binomial test for a difference in proportions. The objective will be met if a statistically significant difference favoring the Treatment group is found.

The study will be considered a success if the primary efficacy objective is met.

4.7.1.2. Sample Size Rationale

The sample size for the study is determined under the following assumptions for the primary efficacy endpoint:

- Minimum power of 80%
- Type I error of 5%
- Assumed primary efficacy success in Treatment group: 50%
- Assumed primary efficacy success in Control group: 25%

Under the above assumptions, a minimum of 116 evaluable Subjects is required in order to demonstrate superiority of the ReActiv8 treatment. The total sample size is increased by 10% to 128 to allow for attrition.

An adaptive statistical design using a single interim look will be used for sample size re-estimation when at least 50% of the implanted Subjects have completed the Primary Endpoint Assessment Visit. Details of the interim analysis are provided in the Statistical Analysis Plan.

4.7.2. Secondary Efficacy Endpoints

All tests of significance will be tested utilizing an overall Type I error of 5%. The overall Type I error will be maintained by utilizing Hochberg's method to test the collection of the first five secondary objectives. These will be tested only if the primary efficacy endpoint is met.

1. Comparison of change from baseline in Oswestry Disability Index (ODI) between Treatment and Control groups at the Primary Endpoint Assessment Visit.
2. Comparison of change from baseline in EQ-5D between Treatment and Control groups at the Primary Endpoint Assessment Visit
3. Comparison of Percent Pain Relief between Treatment and Control groups reported by the Subject at the Primary Endpoint Assessment Visit
4. Comparison of Subject Global Impression of Change at the Primary Endpoint Assessment Visit
5. Comparison of number of Subjects with Resolution of Low Back Pain (remitters or cure, defined as a VAS score ≤ 2.5cm) at the Primary Endpoint Assessment Visit
6. Evaluation of changes in primary and secondary efficacy metrics in the Crossover Group (as defined in Section 4.10) following the Outcome Post Crossover Visit.

4.7.2.1. Hypotheses

ODI

The ODI efficacy objective will be tested under the following hypotheses:

H0: $\mu ODI_T = \mu ODI_C$

HA: $\mu ODI_T \neq \mu ODI_C$

Where μODI_T is the mean change in ODI in the Treatment group and μODI_C is the mean change in ODI in the Control group at the Primary Endpoint Assessment Visit. The hypotheses will be tested using a two-sided two-sample t-test for a difference in mean changes.

In addition, a cumulative proportion of responder analysis of ODI will be performed.[51]

EQ-5D

The EQ-5D efficacy objective will be tested under the following hypotheses:

H0: $\mu EQ5D_T = \mu EQ5D_C$

HA: $\mu EQ5D_T \neq \mu EQ5D_C$

Where $\mu EQ5D_T$ is the mean change in EQ-5D (index score) in the Treatment group and $\mu EQ5D_C$ is the mean change in EQ-5D in the Control group from baseline to the Primary Endpoint Assessment Visit. The hypotheses will be tested using a two-sided two-sample t-test for a difference in mean changes.

Percent Pain Relief

The secondary Percent Pain Relief efficacy objective will be tested under the following hypotheses

H_0: $\mu PPR_T = \mu PPR_C$

H_A: $\mu PPR_T \neq \mu PPR_C$

Where μPPR_T is the mean percent pain relief in the Treatment group and μPPR_C is the mean percent pain relief in the Control group at the Primary Endpoint Assessment Visit. The hypotheses will be tested using a two-sided two-sample t-test for a difference in mean changes.

Subject Global Impression of Change

The secondary Subject Global Impression of Change efficacy objective will be tested under the following hypotheses

H_0: $_{DISTRIBUTION}SGIC_T = {}_{DISTRIBUTION}SGIC_C$

H_A: $_{DISTRIBUTION}SGIC_T \neq {}_{DISTRIBUTION}SGIC_C$

Where $_{DISTRIBUTION}SGIC_T$ is the distribution of the Global Impression of Change in the Treatment group and $_{DISTRIBUTION}SGIC_C$ is the distribution of Global Impression of Change in the Control group at the Primary Endpoint Assessment Visit. The hypotheses will be tested using a two-sided Mann-Whitney test.

Resolution of Low Back Pain

The secondary Resolution efficacy objective will be tested under the following hypotheses:

H0: $\Pi RLBP_T = \Pi RLBP_C$

HA: $\Pi RLBP_T \neq \Pi RLBP_C$

Where $\Pi RLBP_T$ is the proportion of Subjects with a VAS back pain assessment for the previous 7 day of VAS ≤2.5cm (on a 10cm scale) in the Treatment group and $\Pi RLBP_C$ is the proportion of Subjects with a VAS back pain assessment for the previous 7 day average VAS ≤2.5cm in the Control group at the Primary Endpoint Assessment Visit. The hypotheses will be tested using a two-sided binomial test for a difference in proportions.

4.7.3. Primary Safety Assessment

The primary safety assessment is of serious device and/or procedure related adverse events in all Subjects in the Intent to Treat Cohort at the Primary Endpoint Assessment Visit. All reported adverse events will be documented and reported with summary statistics presented for observed rates. There are no formal, statistical hypotheses being tested in the safety assessment.

4.7.4. Supporting Safety Analysis

The PMA Submission will include 12 month safety data on all Subjects implanted with ReActiv8 including all Subjects implanted in the ReActiv8-B Trial for whom 12 month safety data are available, and other persons implanted with ReActiv8 in other clinical trials (including the ReActiv8-A PMCF Study) and all post-marketing registries that are registered on www.clinicaltrials.gov. This data will be provided as a separate analysis of the safety on all implanted persons as an appendix to the ReActiv8-B Trial results.

A separate safety assessment will be performed on the Surgical Roll In Cohort, including a poolability analysis.

4.7.5. Supporting Analyses

The supporting efficacy analyses will include:

- Once data are complete, all primary and secondary outcome measures will be assessed at 12 months and compared to baseline within the Treatment group. The analysis will also explore correlation of outcomes to amount of stimulation delivered.

Note: For all supporting analyses, amount of stimulation delivered will be defined as the number of minutes stimulation was delivered divided by the number of minutes that stimulation could have been delivered.

- In the Crossover Group, outcome measures will be assessed at the Outcome Post Crossover Visit for all Subjects who met the inclusion criteria for low back pain at the Primary Endpoint Assessment Visit (i.e.: prior to Crossover) (Prior week average Low Back Pain, VAS of ≥6.0 cm and ≤9.0 cm on a 10 cm VAS scale) and inclusion criterion for ODI (Oswestry Disability Index score ≥21% and ≤60%). The analysis will also explore correlation of outcomes to amount of stimulation delivered.
- Comparison of daily average VAS averaged over the prior 7 days of Journal entry with the single point VAS of recollection of prior 7 days of average pain.
- Comparison of EQ-5D VAS between Treatment and Control groups at each visit at which EQ-5D is recorded through 12 months.
- For both the Treatment and Control groups, a cumulative proportion of responder analysis, so that the entire distribution of treatment response is depicted in a graph of the proportion of responders for all percentages of low back pain VAS reduction from 0% to 100%. In this manner, the number of Subjects with ≥50% low back pain VAS improvement can be determined, for example.
- Subject Global Impression of Change at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered.
- Treatment Satisfaction Questionnaire at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered.
- Clinical Global Impression – Global Improvement (clinician assessment) at 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered.
- Change in opioids used for treatment of low back pain from baseline to 12 months. The analysis will also explore correlation of outcomes to amount of stimulation delivered.

Additional, ad hoc exploratory analyses may also be conducted.

Note that the supporting analyses may be incomplete at the time of PMA submission since not all Subjects may have reached 12 months post-randomization.

4.7.6. Health Economics

Cost-effectiveness of ReActiv8 therapy, extrapolated to the lifetime of the device, will be measured. Key economic outcome measures to be recorded will be:

- Change in work status at all visits.
- Change in consumption of medications taken for low back pain at all visits compared to Baseline. Note that an analysis may be performed of different categories of medications including for example opioids, muscle relaxants and anti-depressants.
- Assessment of health care utilization (office visits, hospital visits, emergency room visits, and other therapies such as physical therapy) at all visits past the endpoint visit.

Note that both the Treatment and Control group Subjects are required to keep medications constant from randomization until the Primary Endpoint Assessment Visit, and other health care utilization will be as per the protocol (e.g.: no additional therapies, see Section 5.3). Experience in the ReActiv8-A Clinical Trial has shown that some subjects who experience relief from low back pain may reduce their pain medications (despite instructions to keep medications constant), and some subjects may increase medications (thereby classifying them as non-responders). All changes in medications will be recorded.

Following the Primary Endpoint Assessment Visit, all Subjects will be permitted to adjust medications and to use other health care resources. For the Crossover Group, this may yield some information on how Subjects will adjust medications during the treatment phase.

Note that completion of the Health Economics assessments is likely to be incomplete at the time of PMA submission for ReActiv8, since not all Subjects will have reached the 12 month point at that time.

4.8. Control Arm

The intent of eliciting multifidus contraction is to retrain the motor control system and reactivate the multifidus for improved spine stability. Based on data from the Feasibility Study and the data available to date in the ReActiv8-A Trial, there is no straightforward dose response (i.e.: there is a spectrum of responses to the same dose), and the time to measurable response is different between Subjects. Furthermore, there is no known "sub-threshold" stimulation which is indistinguishable to the Subject from "therapeutic stimulation", and therefore a perfect sham is not possible.

The Control Arm for this Trial is Subjects implanted with ReActiv8, and the output programmed to deliver a minimum level of electrical stimulation. This is a sham in the sense that all Subjects receive some level of electrical stimulation, and Subjects in the Control Arm may experience sensations as a result of the stimulation.

In particular, Control Arm Subjects will be subject to the following stimulation:

- Three stimulation pulses of 0.1mA and 31µs duration delivered between the IPG can (-ve) and the most proximal electrode (+ve) on the lead ipsilateral to the location of the IPG delivered every two minutes during a stimulation session.
- Electrical pulses (4 pulses of 31µs, 0.4mA) to assess electrode impedance of the programmed electrode at the start of every stimulation session.

The risk of bias is addressed by the following:

- All randomized Subjects will have implant surgery. Thus any possible placebo effect due to surgical intervention will be the same in both arms.
- All Subjects with have the same follow up schedule until the endpoint assessment. Thus any response due to the Hawthorne effect[66] will be the same in both arms.
- All Subjects will be instructed to have the same device interactions (lie down, press "start" and get up after 40 minutes – 30 minutes stimulation and ten minutes' rest). Thus any placebo response due to the device interactions or simply lying down and relaxing for 80 minutes per day will be the same in both arms.
- All Subjects will experience interactions with the programmer at the follow up visits. In particular, all Subjects will have battery state, lead impedance and compliance data read out from the IPG.
- Subjects in both arms may or may not experience sensations associated with the stimulation. It is likely that Subjects in the Treatment group will perceive muscle contraction. It is possible that Subjects in the Control group will experience a brief muscle twitch every two minutes, and possibly one or more muscle twitches at the start of each session in response to the electrical impedance testing pulses.
- The proposed primary endpoint is binary (e.g., success or failure), and thus the Subject needs to reach a substantial level of pain reduction in order to be counted as a success. This makes it less likely that a placebo effect will bias the study results.

4.9. Blinding and Blinding Assessment

The following persons will be blinded to Subject allocation to Treatment or Control Arm:

1. Subjects
2. Investigators (but may become unblinded as a result of managing any AEs)
3. Other healthcare providers (e.g.: primary care physicians)
4. Members of the Adjudication Committees

Subjects will not be informed of allocation to Treatment or Control at any time prior to the Primary Endpoint Assessment Visit. Subjects in the Crossover Group will feel LM contractions with stimulation, and are likely become unblinded following crossover. There will not be a Blinding Assessment at any time after the Primary Endpoint Assessment Visit.

Measures taken to improve the likelihood of maintaining blinding of Subjects include:

- Careful wording in the Informed Consent – e.g.: "you may or may not feel a sensation during participation in this Trial. The effect of the treatment may not be achieved until sometime after initiation of treatment as every person reacts differently to treatment. Nevertheless, the treatment may be providing an effect, and therefore it is important that you continue to follow instructions at every daily treatment session."
- Subjects will be advised to not tell anyone of the sensations they experience,[b] or the treatment they received, including other Subjects, Investigators, outcome assessors, and Sponsor personnel.
- Subjects will be advised in the informed consent that the output parameters of the ReActiv8 IPG may be adjusted up or down at any time in a follow up visit.
- Use of carefully scripted Subject interaction with Investigators, coordinators and Sponsor personnel at each follow up visit.
- Investigators will be blinded as to randomization assignment of Subjects at all times until primary endpoint data are available (unless managing an AE requires unblinding of the Subject's randomization assignment).
- Persons performing interview based Subject assessments will be blinded as to Subject allocation.
- All members of the adjudication committee will be blinded as to Subject allocation.
- Subjects will be instructed to not compare notes with other Subjects in the Trial, and in particular to not use the internet to share experiences with other Subjects, as doing so a seriously prejudice the results of the Trial.
- During the clinical Trial prior to the primary outcome assessment, public information available from the Sponsor (e.g.: the web site) will be carefully worded with regard to sensations perceived with stimulation from the ReActiv8.

The primary outcome measure is average low back pain VAS completed alone by the Subject at the visits without assistance. Thus the endpoint assessment is inherently blinded since no assessor is involved.

After endpoint data collection at the Primary Endpoint Assessment Visit, all Subjects will complete a questionnaire to assess blinding. It is anticipated that the Treatment group will be

b Subjects will be advised that if they experience pain, discomfort, or any untoward effect, then they should contact the site research coordinator and not discuss with anyone else.

found to be predominantly unblinded because they will have felt muscle contraction and it is expected that those Subjects whose back pain has improved will assume they are in the Treatment group. It is anticipated that the Control group will be approximately 50% unblinded.

The blinding assessment questionnaire for Subjects is shown in Figure 4, and based on the methods suggested by Bang.[67]

Do you think you were in the Treatment or Control group?		
☐ Treatment	☐ Control	☐ No idea
How certain are you of your answer?		
☐ Strongly believe	☐ Somewhat believe	☐ No idea

Figure 4: Blinding Assessment Questionnaire

The Subject may experience an adverse event that requires the Investigator to be made aware of the Subject's randomization assignment. Unblinding should only occur in circumstances where there is a risk to Subject health or safety and every attempt should be made to contact the Sponsor before unblinding the Subject's randomization assignment. In addition, every attempt should be made to keep the Subject blinded to the randomization assignment, unless the Investigator believes that the Subject should be made aware in order to manage the adverse event. If it is necessary to unblind the Subject's randomization assignment, documentation of this will be provided through a study deviation case report form.

4.10. Crossover

The clinical effect is not reversible since removal of stimulation from a Subject who already has restored motor control is unlikely to result in return of the back pain or disability. Thus neither a double crossover nor a randomized withdrawal is possible. However, a single crossover is possible.

After collection of all endpoint data at the Primary Endpoint Assessment Visit, all Subjects in the Control group will have the ReActiv8 IPG programmed to deliver Subject appropriate stimulation to cause strong smooth contraction of the multifidus.

4.11. Data Collection

To avoid introduction of bias, all Subject reported endpoint data at Subject contact visits will be collected before any other intervention or interview during the Subject follow up. The data collection session shall not be attended by people not necessary for the data collection (e.g.: Investigator, the Subject's relatives or friends, or Sponsor personnel).

Programming the ReActiv8 and data collection via the Physician Programmer will be performed by the Investigator or delegate, with the assistance (if requested) of personnel from the Sponsor or CRO under Investigator direction and guidance.

4.12. Stimulation Compliance

Subjects will be required to deliver stimulation for 60 minutes per day up to the Primary Endpoint Assessment Visit, typically in two Sessions of 30 minutes each. The IPG contains data logging of the times for start and stop of each stimulation Session, and the data will be collected and recorded at each follow up visit.

Note: ReActiv8 does not allow stimulation greater than the maximum programmed number of minutes in any day (midnight to midnight), which is set at 60 by default.

Note: A Session can be prematurely stopped with the Magnet or the Activator, and stimulation can be restarted to complete the Session later in the day.

Following the Primary Endpoint Assessment Visit, Subjects in the Treatment group will be advised to continue to deliver stimulation for 60 minutes per day (in two 30 minute Sessions), but will be permitted to reduce the amount of stimulation as desired.

Subjects in the Crossover Group will be advised to continue to deliver stimulation for 60 minutes per day up to the Outcome Post Crossover Visit. Thereafter, Subjects will be advised to continue to deliver stimulation in two 30 minute sessions per day but will be permitted to reduce the amount of stimulation as desired.

Subjects should be encouraged to contact site personnel if they find that they are unable to complete a Session for any reason.

For the purposes of analyses, “stimulation compliance” will be defined as the amount of time spent delivering stimulation compared to the amount of time that stimulation could have been delivered in any period, expressed as a percentage. For the purposes of this analysis, “session compliance” will be defined as the number of Sessions during which 100% of the stimulation that could have been delivered actually was, during any period.

4.13. Statistical Plan

The Statistical Analysis Plan is a separate document which should be read in conjunction with this document.

Post-hoc analyses may be conducted but will not form part of the PMA submission.

4.14. Trial Schema

The Trial Schema is shown in outline in Figure 5. The summary data collection schedule is shown in Table 2.

Figure 5: Trial Schema

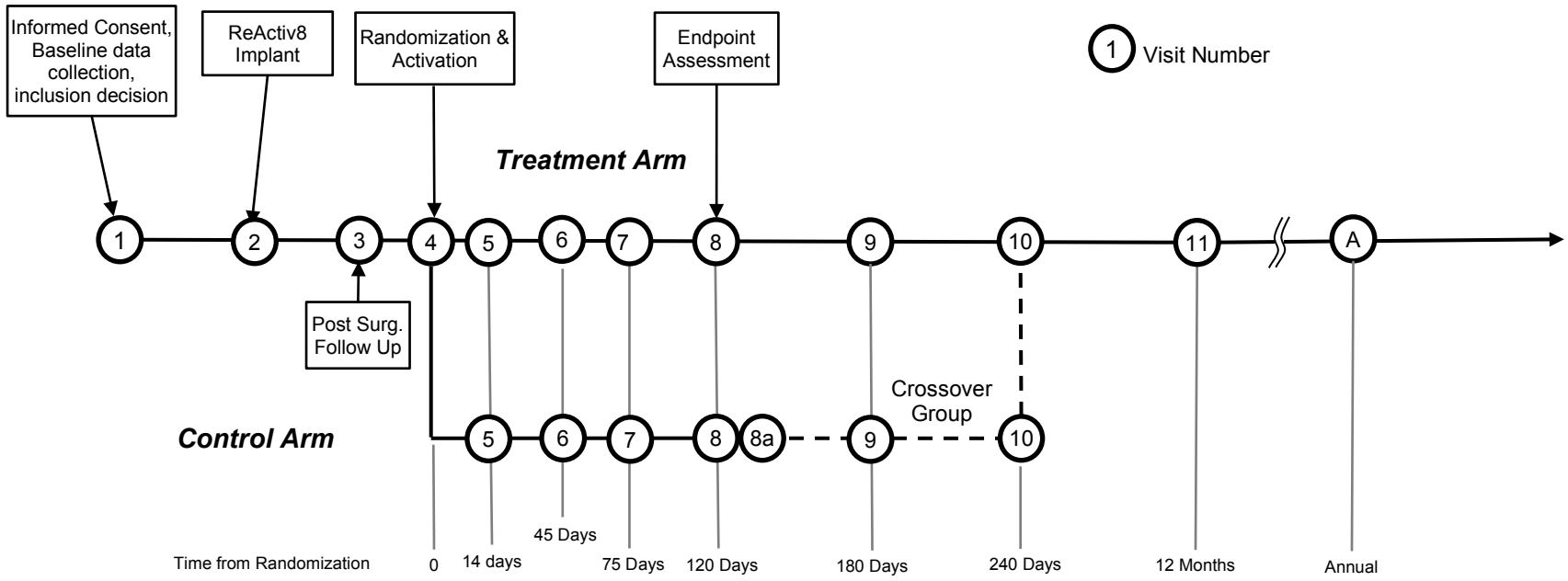

Table 2: Summary Data Collection Schedule

All Subjects T = Treatment Group Only	1 Informed Consent, Baseline Data, Inclusion decision	2 ReActiv8 Implant Procedure (1-45 days post inclusion)	3 Post-Implant Follow Up (7 -0/+10 days	4 Randomization and Activation (14 ± 3 days)	5 14±7 Days Post Randomization	6 45±7 Days Post Randomization	7 75±10 Days Post Randomization	8 Endpoint: 120 -0/+20 Days Post Randomization	8a Crossover and Activation (Crossover Group only)	9 180 ±30 Days Post Randomization	10 240±30 Days Post Randomization	11 12 Months -30/+60 Days Post Randomization	Annual Follow Up 360 ±60 Days Post Randomization	Unscheduled Visit
Screening data (including PIT) and MRI review	✓													
Psychological Assessment	✓													
ODI	✓						✓	✓		✓	✓	✓	✓	
Back Pain VAS (Journal)	✓					✓	✓	✓						
Back Pain VAS (Single Point)	✓				✓	✓	✓	✓		✓	✓	✓	✓	✓
Medications Questionnaire	✓	✓				✓	✓	✓		✓	✓	✓	✓	
EQ-5D	✓						✓	✓		✓	✓	✓	✓	
$DASS_{21}$	✓													
Low Back Pain Descriptive Characteristics	✓					✓	✓	✓		✓	✓	✓	✓	
Work Status Evaluation	✓					✓	✓	✓		✓	✓	✓	✓	
Percent Pain Relief							✓	✓		✓	✓	✓	✓	
Subject Global Impression of Change (SGIC)							✓	✓		✓	✓	✓	✓	
Treatment Satisfaction Questionnaire (TSQ)							✓	✓		✓	✓	✓	✓	
Clinical Global Impression (CGI)							✓	✓		✓	✓	✓	✓	
Health Care Utilization	✓									✓	✓	✓	✓	
Blinding Assessment Questionnaire								✓						
X-Ray (AP and Lateral)		✓			✓									?
Device Measurements & Stimulation thresholds		✓		T	T	T	T	T	✓	✓	✓	✓	✓	✓
Interrogate IPG for lead impedance & compliance					✓	✓	✓	✓		✓	✓	✓	✓	✓
Physical Exam & Surgical Site Exam	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy Test	✓													

5. Subject Selection and Withdrawal

5.1. Inclusion Criteria

1. Age ≥22[c] years, ≤75 years
2. 7 day recall of Average Low Back Pain VAS of ≥6.0cm and ≤9.0cm at baseline (on a 10cm scale)
3. Oswestry Disability Index score ≥21% and ≤60% at the Baseline Visit.
4. Chronic Low Back Pain defined as pain and discomfort localized below the costal margin and above the inferior gluteal fold (with or without referred leg pain) that has persisted >90 days prior to the Baseline Visit, which has resulted in pain in at least half of the days in the 12 months prior to the Baseline Visit, as reported by the Subject.
5. Evidence of lumbar multifidus muscle dysfunction by the Prone Instability Test (PIT).
6. Continuing low back pain despite >90 days of medical management including:
   a. At least one attempt of physical therapy treatment for low back pain, which may optionally be accomplished over multiple episodes or flare-ups of low back pain.

      NOTE 1: Subjects who start a physical therapy program but are unable to complete it are still eligible with regards to this inclusion criterion.

      NOTE 2: Subjects who participated in a physical therapy program in the past since the onset of low back pain but are unwilling or unable to participate in a new physical therapy program are still eligible with regards to this inclusion criterion;
   b. For Subjects with medications prescribed and used for chronic low back pain, usage shall be at a stable dose in the 30 days prior to the Baseline Visit as reported by the Subject.

      NOTE 3: A stable dose means the Subject reports no significant change in regular use of medications, which may include PRN use, in the 30 days prior to the Baseline Visit.
7. Be willing and capable of giving Informed Consent
8. Ability to comply with the instructions for use and to operate ReActiv8, and to comply with this Clinical Investigation Plan.
9. Suitable for ReActiv8 surgery as determined by the implanting physician prior to inclusion.

5.2. Exclusion Criteria

1. BMI > 35
2. Back Pain characteristics:
   a. Any surgical correction procedure for scoliosis at any time, or a current clinical diagnosis of moderate to severe scoliosis (Cobb angle ≥25°).
   b. Lumbar spine stenosis, as defined by an anterior-posterior diameter of the spinal canal of <10mm in Subjects with lower extremity pain.
   c. Neurological deficit possibly associated with the back pain (e.g. foot drop).
   d. Back pain due to pelvic or visceral reasons (e.g.: endometriosis or fibroids) or infection (e.g.: post herpetic neuralgia).
   e. Back pain due to inflammation or damage to the spinal cord or adjacent structures (e.g. arachnoiditis or syringomyelia).

[c] As per the FDA definition of an adult

f. Pathology seen on MRI that is clearly identified and is likely the cause of the CLBP that is amenable to surgery.
g. Back pain due to vascular causes such as aortic aneurysm and dissection.

3. An independent assessment of any current indication for back surgery according to appropriate guidelines, or has indications for back surgery but cannot undergo surgery for other reasons.
4. Leg pain described as being worse than back pain, or radiculopathy (neuropathic pain) below the knee.
5. Source of pain is the sacroiliac joint as determined by the Investigator.
6. Drug use per Subject report as follows:[d]
   a. Current baseline use of >120mg oral morphine equivalent per day of opioids.
   b. Current use of breakthrough dose of >60mg oral morphine equivalent per day
   c. Current requirement of opioids for treatment of a condition other than low back pain.
   d. History of any substance abuse at any time in the five years prior to the Baseline Visit.
   e. Currently taking >15mg Diazepam per day or equivalent. (See Table 3)
7. Surgical or other procedures exclusions:
   a. Any previous rhizotomy or rhizolysis procedure, including cryoablation, RF ablation or pulsed RF on the dorsal root ganglion (DRG) or the medial branch of the dorsal ramus nerve that crosses or lies below the T8 vertebra, within one year prior to the Baseline Visit.
   b. Anesthetic block of the DRG or medial branch of the dorsal ramus nerve that crosses or lies below the T8 vertebra or injection of epidural steroids for back pain in the 30 days prior to the Baseline Visit.
   c. Any previous back surgery including laminectomy or discectomy at or below segmental level T8, or spinal fusion at any level.
   d. Any previous thoracic or lumbar sympathectomy.
8. Any prior diagnosis of lumbar vertebral compression fracture, lumbar pars fracture, pars defect, or lumbar annular tear with disc protrusion that is amenable to surgery.
9. Planned surgery:
   a. Any major surgery (including elective surgery) planned in the twelve months following the Baseline Visit (does not include minor surgeries not expected to impact the lumbar spine (e.g. colonoscopy)).
   b. Any elective surgery of any kind (including, for example, tooth extraction, gynecological surgery, or cosmetic surgery) in the time between the Baseline Visit and the Primary Endpoint Assessment Visit.
10. Any co-morbid chronic pain conditions.
11. Other clinical conditions:
    a. Pregnant or planning to be pregnant in the next 12 months, at the time of inclusion.[e]
    b. Pregnancy at any time in the 6 months, or lactating in the 3 months, prior to the Baseline Visit.

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d The reason for exclusion of Subjects on high doses of narcotics or anti-depressants is that these doses may have altered the CNS to the extent that the therapy may not work, there is a possibility of addiction that may not resolve even after back pain symptoms are reduced or eliminated, and there is a possibility that a significant portion of the Subject's back pain symptoms are secondary to opioid induced hyperalgesia

e Subjects will be advised that if they become pregnant or plan to become pregnant after the Primary Endpoint Assessment Visit, the Activator will be withdrawn and the IPG programmed to OFF to prevent any stimulation delivery during pregnancy. The IPG may be reprogrammed and the Activator returned if the Subject requests following completion or termination of the pregnancy.

c. Any condition unrelated to the CLBP such as muscle wasting, muscle atrophy, other disability (e.g.: paraplegic, amputee, cerebral palsy) or muscular or skeletal disease (e.g.: arthritis in trunk or limbs, multiple sclerosis, rheumatoid arthritis) which, in the opinion of the Investigator, could limit physical movement or compliance with the protocol, or interfere with the assessment of efficacy of the investigational procedure.
d. Poorly controlled diabetes (Type I or Type II) determined by HbA1c >8.
e. Past or current neurological disorders (e.g.: known multiple sclerosis, motor neuron disease, Guillain-Barré syndrome, Parkinson's, Huntington's Disease, Alzheimer's, epilepsy, stroke, brain cancer, traumatic brain injury).
f. Cancer requiring treatment during the study.
g. Any drugs (e.g.: immunosuppressive drugs) or co-morbidity that might inhibit wound healing or electrode scarring, or drugs associated with reduced effectiveness of neuromodulation for other applications.
h. Any medical condition requiring anticoagulation (other than aspirin) that, in the opinion of the physician prescribing the anticoagulant, cannot be safely suspended for 5 days prior to device implantation surgery and an appropriate period after implantation surgery.
i. Any active infection in the vicinity of the implant site or any systemic infection.

12. Psycho-social exclusions
    a. Be involved in an injury claim under current litigation.
    b. Have a pending or approved financial compensation claim (e.g.: worker's compensation claim, long term disability claim) or any financial compensation (including social welfare payments) related to the Subject's CLBP.
    c. Current incarceration (prison or jail)
    d. Have an assessment of current active depression significant enough (DASS depression score >9) to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome.
    e. Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome (e.g.: active depression, bipolar disease, Alzheimer's disease) as determined by a psychologist or psychiatrist.
13. Protocol Compliance Exclusions
    a. Inability or unwillingness to comply with all protocol requirements.
    b. Inability to maintain the prone or side lying position in a relaxed manner for the duration of each stimulation session.
    c. Inability to operate the Activator, such as arthritis that limits arm or shoulder movement, or inability to learn how to operate.
    d. Inability to assess changes in pain intensity or perform wound care.
    e. Inability or unwillingness to complete the Journal.
14. General exclusions
    a. Any other active implantable device including an implantable device for back pain (such as an implantable drug pump or Spinal Cord Stimulator), pacemaker, implantable defibrillator, cochlear implant, deep brain stimulator, implantable drug pump, or other implanted neurostimulation device.
    b. Prior exposure to an implantable neurostimulator for treatment of pain, including spinal cord stimulation (including trial implant of SCS leads), occipital nerve stimulation or peripheral nerve stimulation.
    c. A condition currently requiring or likely to require use of MRI or diathermy while implanted with the ReActiv8.

d. Therapy with any other investigational intervention (drugs, devices, or procedures) for the treatment of back pain at the time of the Baseline Visit, or at any time in the past if the past investigational intervention did not subsequently gain regulatory approval.
e. Current or planned participation in any other clinical trial during participation in this Trial.
f. Life expectancy <1 year

Table 3: Benzodiazepine Equivalents

Drug	Dose Equivalent to 15mg Diazepam (mg)
Alprazolam	1.5
Alprazolam extended release	1.5
Chlordiazepoxide	30
Clonazepam	0.75
Clorazepate	22.5
Estazolam	0.9
Flurazepam	15
Lorazepam	3
Oxazepam	45
Prazepam	45
Quazepam	15
Temazepam	15
Triazolam	0.3

5.3. Other Therapy During the Trial

5.3.1. Medication

Subjects shall be advised to not make any change to medications for treatment of low back pain at the time of the Subject's inclusion in the Trial until the Primary Endpoint Assessment Visit. This includes medications for pain and muscle relaxants. Subjects will be informed that they may reduce, increase or discontinue medications for low back pain following the Primary Endpoint Assessment Visit.

Subjects will be informed that if they believe they need any change in prescription medications for treatment of low back pain during the Trial, then they should contact the Investigator who will arrange for modification of type or dose of pain medications, as clinically necessary, and the data will be recorded. Subjects will be told that they should not request modification to prescribed drugs for their low back pain from any non-study physician during the period from baseline until the Primary Endpoint Assessment Visit. Any change in medications for other conditions (e.g.: hypertension) are allowed if prescribed by the Subject's regular treating physician.

All Subjects shall continue on any and all prescribed medication deemed medically necessary and not prescribed for the indication of CLBP (e.g.: antihypertensive medicines, statins, thyroid medications, diabetes medication, and low-dose aspirin).

Any change in pain medication prescribed and taken over the 14 days prior to the 120 day visit shall be reported by the Subject at the visit. If the prescribed dose is PRN, the Subject shall report the use of the drug over the prior two weeks if it changed from that taken at baseline.

5.3.2. Physiotherapy & Exercise

Subjects will be instructed to go about their daily lives as best as possible, and encouraged to be active.

If the Subject has previously participated in an exercise program or other physical activity (e.g.: aerobic exercises, weight training, home exercise machine, team or solo sports) then that exercise may continue or resume at the discretion of the Investigator, following the Randomization Visit. Such exercise should not be performed between Implant and the Randomization Visit to allow time for healing of the surgical scar.

Any additional exercise is to be allowed at the discretion of the Investigator, subject to the Subject's ability to perform exercise. To avoid bias, no specific physiotherapy or other exercises to treat CLBP are allowed between the Baseline and Primary Outcome Assessment Visit.

Strenuous activity that could exacerbate the underlying condition of low back pain shall be forbidden until after the Primary Endpoint Assessment Visit (e.g.: chopping wood, rowing, heavy weight lifting, and wrestling).

5.3.3. Other Devices or Therapy

Use of other devices or therapy is likely to confound the results of the Trial. Therefore, with the exception of medication, all therapies targeted at the low back pain will be prohibited during the Trial. Subjects should be instructed to not use any other devices such as braces, belts, TENs devices, acupuncture, chiropractic manipulation, massage or anything else which is not specifically required by this protocol.

It is especially important that the following procedures *not* be performed during the Trial because they will directly affect the device itself and/or its ability to interact appropriately with the body, or may affect endpoint assessment:

- Epidural injections
- Nerve ablations of any kind for low back pain
- Any other interventional pain procedures for low back pain (e.g.: nerve blocks)
- Any physical procedure (e.g.: back or gluteal massage or chiropractic adjustment) that carries a risk of dislodging leads

6. Subject Contact and Data Collection Schedule

Subject contact will be according to the following schedule. Any unscheduled visits will be recorded.

Note: All data collection shall be done as the first thing in the follow up visit, prior to any other procedures.

Note: Adverse event data will be collected at each visit after the Baseline Visit.

6.1. Visit 1: Informed Consent, Baseline Data, Inclusion Decision

The process for obtaining informed consent shall be in compliance with FDA regulations (21CFR 50) and ISO 14155.

Subjects will be provided with the Subject Information and Informed Consent Form which advises that data will be collected for evaluation of eligibility for inclusion in the Trial. Subjects are told that if the criteria are met and the Subject consents, then the ReActiv8 will be implanted.

If the Subject agrees to inclusion for data collection, the Subject Informed Consent will be signed and recorded in the Subject's records at Visit 1.

The Subject will be assigned a unique study identifier.

Data to be collected during the visit:

- Screening data as required by the inclusion/exclusion criteria documented in Subject study records
- Medical History (including Physical Exam)
- Low Back pain descriptive characteristics
- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Work status evaluation
- Medications (all medications including indication)
- ODI
- EQ-5D
- $DASS_{21}$
- Healthcare Utilization

Activities to be performed:

- Journal:
  - Instruct the Subject in the use of the Journal and provide the Journal.
- Prone Instability Test to assess lumbar multifidus dysfunction.
- Answer any questions the Subject may have, and confirm willingness to proceed if the baseline criteria are verified.
- Verify that the inclusion/exclusion criteria are satisfied.

- An MRI of the lumbar region of the low back will be performed or ordered if there are no MRI images from more recently than 180 days prior to Visit 1. MRI images will be reviewed[f] to assess conditions that may be a possible cause of low back pain and to rule out possible surgical candidates by institutional guidelines.
- Pregnancy test in women of child bearing potential.
- Assessment by the Investigator of the Subject's suitability for ReActiv8 implant which includes review of the psychological assessment (e.g. mental fitness).

  NOTE: The surgical assessment and other required assessments may be performed at any time prior to Visit 2, and still be included in the Visit 1 data collected. If the implanting physician determines that the Subject is not a suitable candidate for the procedure, then the Subject shall not be scheduled for implant, will be withdrawn from the Trial, and will not be included in the analysis.

- If the Subject meets the inclusion criteria, schedule the surgery for the ReActiv8 implant and discuss with the Subject. Ensure that all hardware necessary for the procedure is available, and schedule support staff.

6.2. Visit 2: Implant Procedure

The implant procedure should take place as soon as possible following the verification of baseline criteria, at a minimum of 1 day and maximum of 45 days following Visit 1. The duration of the implant procedure visit depends on local institutional practices and Subject condition post-implant, and may be as short as a few hours (e.g.: for an outpatient procedure), or as long as several days.

Data to be collected prior to implant:

- Medications

Data to be collected during or post implant:

- Surgical notes
- Adverse Events (including Adverse Events prior to the Implant Procedure, and any adverse events associated with the Implant Procedure).
- Measurement and recording of electrode impedance and stimulation thresholds as defined in the Implant and Programming Manual

  NOTE: The Subject should preferably be unconscious (i.e.: general anesthesia) during assessment of electrode impedance and stimulation thresholds. If local anesthesia is used, then appropriate medication should be administered to minimize the chance that the Subject will remember the procedure.

Activities to be performed after implant procedure:

- Make a (de-identified) digital record of fluoroscopic images taken during the implant procedure[g] including at least bi-plane (AP and lateral) radiographic images of electrode position that shows the entire implanted system from the distal tip of the electrodes to the whole IPG.

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f All Images to be de-identified and included in the data record for the Subject in an electronic format to allow analysis at a later date. A core lab may be used for evaluation of MRI images as part of the supplementary data analysis.

g It is a requirement for a site to participate in the trial that digital recording of fluoroscopic images should be available

- Inspect the surgical site prior to hospital discharge
- Program IPG to OFF (i.e.: default state is no electrical output from the IPG).

NOTE: Regular post-surgical follow up per institutional guidelines in the first 7 days post-implant are included in the Implant Procedure Visit.

6.3. Visit 3: Post-Implant 7 -0+10 Days

A Post-Surgical Follow Up visit should be performed between 7 and 17 days post-implant.

Data to be collected

- Adverse Events

Activities to be performed:

- Examination of the surgical wounds (Physical Exam and Surgical Site Exam)
- General post-surgical clinical care
- Removal of sutures (Note: it is recommended that sutures be removed no sooner than 11 days post-implant to reduce the risk of infection)

6.4. Visit 4: Randomization & Activation Visit 14 ± 3 days Post Implant

Randomization shall be 14 ± 3 days from the date of implant (to allow for scheduling). Visit 3 and Visit 4 may be combined.

If the Subject is unable to use the device for any reason (e.g.: injury, infection, other new clinical condition) at the time of the Randomization Visit, then the Randomization Visit may be postponed up to 30 days to allow the issue to resolve without incurring a protocol deviation.

Note: A decision to delay randomization must be done before the Subject is randomized.

Data to be collected:

- Adverse events

Activities to be performed:

- Inspect surgical wound to verify healing, and remove sutures (if not previously removed). Address any clinical issues associated with the surgical procedure (Physical Exam and Surgical Site Exam)
- Confirm Subject allocation to Treatment or Control group has been completed.

For Subjects in the Treatment Group Only:

- Perform electrode impedance and threshold measurements and record results
- Program IPG to Subject appropriate levels

For Subjects in the Control Group Only:

- Program IPG to Control

For all Subjects:

- Train in use of the Activator and document assessment of Subject's ability to self-administer therapy twice a day starting the next day.
- Train in the procedure to deliver stimulation, including time of day and Subject positioning.

- Provide encouragement to contact site personnel if any difficulty is encountered delivering stimulation or completing a Session.

6.5. Visit 5: 14±7 Days Post Randomization

Data to be collected:

- Single point average low back pain VAS over previous week as reported by the Subject
- Adverse events
- AP and lateral X-Rays that clearly shows the entire implanted system from the distal tip of the electrodes to the whole IPG.

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site Exam)
- Provide the pain Journal and instruct the Subject in the use of the Journal for 7 days prior to the next scheduled visit.
- Remind Subject to continue to lie down and activate therapy twice daily.
- Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements

Note: Provide encouragement to all Subjects to continue to apply therapy using the Activator twice a day. If compliance assessment shows <90% compliance, additional counseling may be provided.

For Subjects in the Treatment Group Only:

- Device activities:
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.6. Visit 6: 45±7 Days Post Randomization

Data to be collected:

- Pain Journal:
  - VAS for daily average low back pain
- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Pain medications prescribed and taken
- Low Back Pain descriptive characteristics
- Work status evaluation
- Adverse events

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site Exam)
- Collect Journal, and provide new Journal and instruct the Subject to continue to complete Journal assessments 7 days prior to the next scheduled visit.
- Remind Subject to continue to lie down and activate therapy twice daily.
- Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements

Note: Provide encouragement to all Subjects to continue to apply therapy using the Activator twice a day. If compliance assessment shows <90% compliance, additional counseling may be provided.

For Subjects in the Treatment Group Only:

- Device activities:
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.7. Visit 7: 75±10 Days Post Randomization

Data to be collected:

- Pain Journal:
  - VAS for daily average low back pain
- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Low Back Pain descriptive characteristics
- Work status evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Adverse events
- Subject Global Impression of Change (SGIC)
- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site)
- Collect Journal, and provide new Journal and instruct the Subject to continue to complete Journal assessments 7 days prior to the next scheduled visit.
- Remind Subject to continue to lie down and activate therapy twice daily.
- Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements

Note: Provide encouragement to all Subjects to continue to apply therapy using the Activator twice a day. If compliance assessment shows <90% compliance, additional counseling may be warranted.

For Subjects in the Treatment Group Only:

- Device activities:
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.8. Visit 8: 120 -0/+20 Days Post Randomization

This Primary Endpoint Assessment Visit must be performed no sooner than 120 days post randomization to ensure all Subjects have at least 120 days of treatment or control. At this visit Subjects in the Control group may now be programmed to appropriate stimulation levels and will be considered part of the Crossover group.

Data to be collected:

- Pain Journal
  - VAS for daily average low back pain
- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Low Back Pain descriptive characteristics
- Work status evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Subject Global Impression of Change (SGIC)
- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)
- Adverse events
- Blinding Assessment

Activities to be performed after endpoint data collection:

- Collect Subject's Journal
- Inspection of surgical site (Physical Exam and Surgical Site Exam)
- Device activities:
  - Electrode impedance and threshold measurements
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements
  - Adjustment of stimulation configuration and amplitude as appropriate
- For Subjects in the Control group, assessment of thresholds and programming of the ReActiv8 IPG to a Subject appropriate level that result in strong smooth contractions of the multifidus. These Subjects now form the Crossover Group.

Note: At the Primary Endpoint Assessment Visit, all Subjects are advised that they can vary their medications for back pain as needed or desired.

6.9. Visit 8a: Crossover and Activation

Subjects in the Crossover Group require additional activities and data collection, which may be done as part of Visit 8 or can be scheduled as an additional visit.

Data to be collected:

- Adverse events (after threshold assessment and IPG programming)

Activities to be performed:

- Device activities (if not already done):
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements

- Electrode impedance and threshold measurements, and data collection

Adjustment of stimulation configuration and amplitude as appropriate

6.10. Visit 9: 180 ± 30 Days Post Randomization

Data to be collected:

- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Low Back Pain descriptive characteristics
- Work status evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Adverse event
- Device measurements and stimulation thresholds
- Subject Global Impression of Change (SGIC)
- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)
- Health care Utilization

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site Exam)
- Device activities:
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.11. Visits 10: 240 ± 30 Days Post Randomization

Data to be collected:

- 7 day recall of Average Low Back Pain VAS over previous week as reported by the Subject
- Low Back Pain descriptive characteristics
- Work status evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Adverse event
- Device measurements and stimulation thresholds
- Subject Global Impression of Change (SGIC)
- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)
- Health care Utilization

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site)

- Device activities:
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.12. Visits 11: 12 Months 0-30/+60 Days Post Randomization

Data to be collected:

- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Low Back Pain descriptive characteristics
- Work status evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Adverse events
- Device measurements and stimulation thresholds
- Subject Global Impression of Change (SGIC)
- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)
- Health care Utilization

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site Exam)
- Device activities:
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.13. Annual Follow Up

All Subjects will be scheduled for an Annual Follow Up following Visit 11 until such time as ReActiv8 obtains US regulatory approval or the Trial is abandoned. Following US regulatory approval, all Subjects who continue with ReActiv8 implanted will have continuing Annual Follow Up for 7 years from the date of randomization.

Data to be collected:

- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Low Back Pain descriptive characteristics
- Work Status Evaluation
- Oswestry Disability Index
- EQ-5D
- Pain medications prescribed and taken
- Percent Pain Relief
- Adverse events
- Subject Global Impression of Change (SGIC)

- Treatment Satisfaction Questionnaire (TSQ)
- Clinical Global Impression – Global Improvement (CGI-I)
- Health care Utilization Inspection of surgical site (Physical Exam and Surgical Site)
- Device measurements and stimulation thresholds
- Device activities:
  - Readout from IPG of stimulation delivery times and duration (compliance assessment), battery state, and stored impedance measurements
  - Electrode impedance and threshold measurements, and data collection
  - Adjustment of stimulation configuration and amplitude as appropriate

6.14. Unscheduled Visits

If an unscheduled visit occurs for any reason, the following data will be collected prior to any other activities.

- 7 day recall of Average Low Back Pain VAS as reported by the Subject
- Adverse events

Activities to be performed:

- Inspection of surgical site (Physical Exam and Surgical Site Exam)

If an unscheduled visit occurs because of a suspected Adverse Device Effect (ADE) related to stimulation, then device testing shall be performed to investigate a suspected device failure.

Other activities to investigate the suspected ADE (e.g.: X-Ray imaging) may be performed at the discretion of the physician.

If an unscheduled visit occurs to perform a device explant for any reason (e.g.: infection necessitating device removal, elective removal at the request of the Subject), then additional data including surgical notes may be collected. Furthermore, any explanted devices or components shall be returned to the Sponsor following appropriate decontamination procedures.

Note: If an unscheduled visit occurs prior to the Endpoint Data Assessment Visit for a Subject in the Control group, then all efforts shall be made to avoid potential unblinding of the Subject, particularly as a result of IPG testing which may inadvertently result in delivery of stimulation leading to Subject-perceived muscle contraction.

6.15. Telephone Calls or Electronic contact

The study coordinator will contact Subjects by telephone (or electronically) prior to each study visit starting with the 75 day visit through the 12 month visit. This contact will be to check on the well-being of the Subject, remind the Subject of the upcoming visit, remind Subjects to contact the Investigator/staff should he/she have any questions or concerns, remind Subjects to keep their pain medications the same as those taken at baseline, and to complete the pain Journal 7 days prior to the 120 day visit. The telephone calls (or electronic contact) should be made within 15-25 days prior to the scheduled visit date.

6.16. Revision/Explant Procedure

Data to be collected prior to revision/explant:

- Medications
- Measurement and recording of electrode impedance as defined in the Implant and Programming Manual (system to be revised/explanted)

Data to be collected during or post revision/explant procedure:

- Surgical notes
- Adverse Events
- Measurement and recording of electrode impedance and stimulation thresholds as defined in the Implant and Programming Manual (newly implanted system)

  NOTE: If the procedure occurs prior to 120 days, then the Subject should preferably be unconscious (i.e.: general anesthesia) during assessment of electrode impedance and stimulation thresholds. If local anesthesia is used, then appropriate medication should be administered to minimize the chance that the Subject will remember the procedure.

Activities to be performed after revision procedure:

- Make a (de-identified) digital record of fluoroscopic images taken during the implant procedure[h] including at least bi-plane (AP and lateral) radiographic images of electrode position that shows the entire newly implanted system from the distal tip of the electrodes to the whole IPG
- Inspect the surgical site prior to hospital discharge
- Program IPG to OFF (i.e.: default state is no electrical output from the IPG)
- Continue with study required visits.

Activities to be performed after explant procedure:

- Explant <120 days post randomization
  - Subject will be followed until the 120 day visit and then exited.
- Explant >120 days post randomization
  - Adverse events will be collected over the last 30 days prior to exiting the study

h It is a requirement for a site to participate in the trial that digital recording of fluoroscopic images should be available

7. Anticipated Benefits and Risks

7.1. Anticipated Benefits

The purpose of electrical stimulation of the medial branch of the dorsal ramus nerve with the ReActiv8 is to help restore neural drive to the lumbar multifidus muscle (LM). There are known clinical benefits to the restoration of neural drive to and rehabilitation of the LM when delivered by guided physical therapy with image guided biofeedback including:

- Improvements in the disabling effect of low back pain
- Improvements in severity of low back pain
- Reduction in recurrence of low back pain
- Improvement in ability to handle regular daily activities, including return to work
- Improvements in Quality of Life

Based on the Feasibility Study performed with other devices, there are expected benefits from the stimulation to be delivered by the ReActiv8, including decrease in low back pain, decrease in disability, and improvements in quality of life.

There may be no benefits to the Subject as a result of participation in this Trial.

7.2. Anticipated Risks

All medical device treatments have the potential to cause adverse events or side effects. Adverse events are expected to be similar to other neurostimulation devices for treatment of back pain, such as spinal cord stimulators. Listed in this section are both known risks with spinal cord stimulators and peripheral nerve stimulators as well as theoretical risks for the ReActiv8.

Additional information on risks and anticipated adverse events is to be found in the Implant and Programming Manual, which also includes warnings and precautions.

Anticipated Adverse Events include:

- AEs associated with the surgical procedure, including implant, revision, replacement and removal.
  - Acute or persistent pain including more pain than anticipated after surgery or worsened low back pain
  - Accidental injury to adjacent tissues, e.g. piercing structures such as muscle, blood vessels, nervous tissue, or organs
  - Anxiety about surgical procedure or outcome of therapy (beyond what is reasonably expected)
  - Infection, including local infection of the device or surgical site, systemic infection and sepsis
  - Respiratory arrest, e.g. apneic spell during surgery
  - Slow, abnormal or inadequate wound healing including swelling, hematoma, seroma, or wound dehiscence, which may require surgical repair
  - Nerve irritation, impingement or damage, including pain, paralysis, sensory deficits or changes to bowel, bladder or reproductive function
  - Scarring or inflammation associated with the surgical site (beyond what is reasonably expected)
  - Stiffness or restriction in movement
  - Death

- Risks associated with any surgical procedure, regardless of type, including prolonged procedure or sequelae of anesthesia
- Bleeding, hematoma, and bruising
- Swelling (beyond what is reasonably expected), seroma, or cyst
- Abandonment of implant procedure, including due to failure to achieve suitable stimulation thresholds in one or both leads
- Intraoperative difficulties implanting the device, such as inadequately seating lead into connector or damage to lead insulation
- Tissue reaction to the presence of the implanted device or materials in/on the implanted device such as response to residual material on device or an allergic response, e.g. previously unknown nickel or titanium allergy. Reaction may be local or systemic.

- AEs associated with presence and use of the device. This includes AEs associated with chronic implant whether or not the device is turned on.
  - Migration of the lead, which may result in surgical revision, replacement or removal of device
  - Device failure including failure of the IPG, failure of the lead, or failure of any other implanted component which may necessitate surgical revision, replacement, or removal of the device or components of the device.
  - Nerve irritation, impingement or damage, including that resulting from mechanical presence of device, exposure to electricity including electrical stimulation, or migration of the leads, suture sleeve or IPG. This may lead to pain, paralysis, sensory deficits or changes to bowel, bladder or reproductive function
  - Device extrusion
  - Erosion, threatened erosion or fistula formation in skin overlying device components
  - Excessive fibrotic tissue growth, including fibrotic tissue growth which may complicate device removal.
  - Hematoma, seroma, cyst or swelling
  - Acute or persistent pain including worsened low back pain and/or pain and discomfort due to presence of the device
  - Undesired sensations such as uncomfortable paresthesia, numbness, vibration, pressure, prickling, or uncomfortable contraction of the multifidus
  - Overstimulation of tissue, resulting in symptoms such as painful muscle contraction, paresthesia, jolts or shocks. In addition, injuries that occur as a consequence of stimulation, e.g. accidents that occur as a result of being startled or back injuries that occur due to diminished motor control
  - Infection, including local infection of the device or surgical site, systemic infection and sepsis
  - Death
  - Tissue reaction to the presence of the implanted device or materials in/on the implanted device such as response to residual material on device or an allergic response, e.g. previously unknown nickel or titanium allergy. Reaction may be local or systemic.
  - Skin irritation as a result of contact with the Activator
  - Tissue damage due to mechanical presence of device, or exposure to electricity including electrical stimulation
  - Contraction of muscles other than the target muscle(s)
  - Muscle fatigue, spasm or injury
  - Malfunction of other medical equipment such as a pacemaker due to device interactions
  - Stiffness, including restricted motion due to adhesions to the device
  - Psychiatric disturbance, such as anxiety or depression or complications of depression such as suicide

- Symptoms in unrelated systems such as nausea, insomnia, urinary retention or undesired weight changes, including as a sequelae of stimulation of the Subject.
- Inability to deliver therapy, including inadequate doses of therapy. Sources include lead migration, device malfunction or exposure to electromagnetic fields, e.g. security screening devices
- Electrical shock
- Inability to stop therapy, with possible sequelae such as anxiety, restriction of movement, pain, muscle fatigue, postural changes, difficulty in walking, sitting or physical activity
- Accidents, injuries, body movements, body positions or biological process which lead to device complications such as a fall which causes injury to the IPG, sit-ups or severe coughing leading to migration of the lead, or bony fracture leading to device migration or fracture.

Subjects may also undergo medical/and or surgical intervention to treat the issues identified above.

The ReActiv8 includes features that provide protection from EMI. Most electrical devices and magnets encountered in a normal day are unlikely to affect the operation of the ReActiv8. Sources of strong EMI can exist near high power amateur radio transmitters, near television towers or other equipment. Generally, the amount of EMI present in publicly-accessible areas is reduced to a level that is not likely to impact the ReActiv8. Exposure to strong sources of EMI can result in the following effects:

- Serious injury or death, resulting from heating of the implanted components of the ReActiv8 and damage to surrounding tissue.
- Damage to the ReActiv8, resulting in a loss of or change in stimulation delivery and requiring surgical replacement.
- Operational changes to the ReActiv8 IPG, causing it to turn ON or OFF (particularly if the IPG is enabled for magnet use) or to reset, resulting in loss of stimulation and requiring reprogramming by a clinician.

Equipment such as retail theft prevention systems and airport metal detectors may interfere with the ReActiv8. The Subject should be instructed to walk directly through such systems and not remain near them any longer than necessary. The presence of an implantable pulse generator in the body may set off security screening devices (e.g.: at airports), so it will be necessary for the Subject to carry a card to identify themselves to security screeners as carrying an IPG.

Subjects with either the study device implanted or parts of the study device still implanted will not be able to have a magnetic resonance imaging (MRI) scan, since this test may damage the study device and may cause serious injury. This risk is unchanged as long as the system (IPG and leads) remains implanted.

7.3. Risk Minimization

Additional risks may exist. Risks can be minimized through the use of strict compliance with this CIP, and adherence to the guidelines for Subject selection, site training, and close monitoring of the Subject's physiologic status at follow-up visits. In addition, the product labeling (including the Implant and Programming Manual and the User Manual) details warnings and precautions which must be followed to minimize risk to Subjects.

8. Safety

The following definitions are used:

Adverse Event (AE):

An adverse event is defined as any undesirable clinical occurrence that affects the health or safety of the Subject.

If an adverse event leads to multiple outcomes that sequentially worsen, only the worst adverse event is reported. For example, a hematoma leading to infection would be reported as a single AE for the infection.

Serious Adverse Event (SAE):

A Serious Adverse Event is defined as an adverse event that led to death, or led to serious deterioration in the health of the Subject, that either resulted in:

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient or prolonged hospitalization,
4. congenital anomaly/birth defect, or
5. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol (e.g., the index implant procedure, or device replacement due to normal battery depletion), without serious deterioration in health, is not considered a serious adverse event.

Unanticipated Adverse Device Effect (UADE):

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

For all adverse events the Investigator must determine whether the event was related to the device and/or procedure and document this on the eCRF. Individual events may be related to more than one category, e.g. an injury due to a tunneling tool may be related to Device Hardware and Procedure. The categories used for relatedness are listed in Table 4.

Table 4: Adverse Event Relatedness Categories

Related to Device Hardware	Events reasonably anticipated to be related to the physical presence of the device, e.g. erosion, a device deficiency, loss of power.
Related to Device Stimulation	Events reasonably anticipated to be related to electrical stimulation, especially those that appear when the device is on and disappear when the device is off, e.g. undesired sensation experienced only when the device is turned on.
Related to Procedure	Events reasonably anticipated to be related to procedures described in this protocol.

All AEs will be collected from the time of informed consent through the end of the study. Death should not be recorded as a separate adverse event, but rather as an outcome of the specific SAE which led to the Subject's death.

Adverse Events that would be reasonably expected to be associated with any surgical procedure (e.g.: anesthesia associated nausea, surgical site pain) will not be categorized as procedure or device related in the 30 days post the surgical procedure (to be adjudicated by the Adjudication Committee).

The Adjudication Committee will review and adjudicate all Adverse Events that occur, including relatedness. The Committee will also review and adjudicate all reported hospitalizations, regardless of whether they are classified by the Investigator as an adverse event. Safety Analysis will be performed on adjudicated events only.

Notes:

1. Any current condition that is recorded as a pre-existing condition is not an AE, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
2. Technical observations – an undesirable device event that does not result in a medically undesirable situation for the Subject – is not an AE.
3. Normal end of battery life of the IPG is not an AE.
4. Suspending or stopping use of ReActiv8 due to pain relieved is not an AE.
5. ReActiv8 removed due to pain relieved is not an AE.
6. Planned hospitalization for a procedure required by this protocol is not an AE. However, complications during the course of that planned hospitalization that prolong the anticipated duration of the hospitalization do constitute SAEs.
7. Elective hospitalization for a pre-existing illness does not constitute an SAE unless the illness has worsened in the nature, severity or degree of the condition with respect to baseline.
8. Device migration will not be collected as an AE, but rather as a device deficiency. If device migration results in a clinical symptom, report this as an AE in addition to the device deficiency report documenting device migration.
9. Experiencing unusual sensations is a normal part of programming a neurostimulation device. Accordingly, symptoms felt during a programming session are not considered AEs unless they are caused by the final programming parameters and persist after completion of the programming session.
10. Lack of efficacy or diminished therapeutic response does not constitute an AE since failure to receive therapeutic benefit is an issue of efficacy, not safety. This includes symptoms that recur in the context of device deficiency leading to loss of therapy. If the recurring symptoms are not worse than at baseline, record the event as a device deficiency but not as an adverse event.
11. Removal and/or replacement of any part of the device due to malfunction would be considered a device related adverse event.

8.1. Adverse Event Reporting

The Investigator will monitor the occurrence of adverse events for each enrolled Subject. Adverse events reported by the Subject to the Investigator, confirmed by the Investigator, and documented in medical records must be reported on the adverse event form based on the requirements of the study CIP.

All Adverse Events, all Serious Adverse Events, and all Unanticipated Adverse Device Effects will be reported to all Investigators and IRBs and/or Ethics Committees participating in the study

per their reporting requirements. This is done by means of an interim report or a final study report prepared by the Sponsor.

8.2. Adverse Event Outcome Status

Adverse Events, when reported, are assigned a status by centers depending on the nature of the event or the corrective action involved. When clinically appropriate, centers should work to close events whose underlying clinical condition may not be resolvable during the term of the investigation.

Centers may move outcome status to “closed” or alternatively, add text to the adverse event description at a follow-up visit addressing that adverse event stating that the adverse event is ongoing but for study purposes and outcome data, the event is considered closed.

8.3. Device Deficiencies

A ***device deficiency*** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. All suspected investigational device deficiencies should be documented on the appropriate CRF. The Sponsor will investigate all suspected device deficiencies.

Note: a device deficiency can include a device malfunction (i.e.: failure to perform to specifications), and may also include other deficiencies (e.g.: ambiguity of labelling).

For the implanted components of ReActiv8, note that not all device deficiencies will lead to an explant. For example, loss of stimulation on one electrode may be resolved by reprogramming such that stimulation can be delivered on a different set of electrodes. Thus a device deficiency may not necessarily lead to an AE or SAE.

If possible, a device with a suspected malfunction should be returned to Mainstay for analysis, including any explanted components. If it is not possible to return the device, the reason it could not be returned as well as its final disposition should be documented.

Note that reporting of device deficiencies shall be separate from adverse event reporting. If there should be an adverse event associated with the device deficiency, then that adverse event should be reported on an adverse event CRF.

8.4. Subject Deaths

A Subject death during the study should be reported to the Sponsor as soon as possible and, in any event, within two working days of notification to the Investigator. The center’s IRB or Ethics Committee must be notified of any deaths in accordance with that center’s IRB or Ethics Committee policies and procedures.

Notification of death should include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized Sub-Investigator. The death letter should include all of the following:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether or not the death was witnessed
- Device status and/or activity at the time of death, if known
- Any other circumstances surrounding the death

- Approximate time interval from the initiating event to death (temporal course)
- Investigator or sub-Investigator signature and date

Any information listed above that is unavailable or unknown must be specified as such in the death letter.

If the Subject expired in the hospital, the following documentation should also be submitted:

- A copy of the medical records for that admission (e.g., consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the Subject expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to the Sponsor)
- Death certificate (if available)

As applicable per local country regulation, the event should be reported by the Investigator to the appropriate regulatory bodies.

Note that in the event of the death of a Subject with an implanted IPG, if cremation is planned, then the IPG must be explanted prior to cremation. The internal battery may explode when exposed to extreme heat.

9. Data Management

9.1. Study Assessments

The Sponsor will be responsible for collection of the data required for this study in accordance with record and reporting requirements listed in FDA 21CFR812 and Part 11. The Sponsor will use an electronic clinical database which shall have written procedures and document requirements. The Sponsor or its designated CRO(s) will verify and validate that the requirements for an electronic data system to receive and process data can be consistently met. Security, reliability, consistency of the data will be maintained throughout the study. Electronic CRF's will be used on this study. Only those staff at each site that are identified and designated by the Investigator and trained on eCRF data entry system will be allowed access to the eCRF system. Any study assessment questionnaires that required the Subject to complete directly, will be done on paper CRF's then transferred to the eCRF system by the designated study site personnel.

The electronic case report forms, and paper CRFs will reflect the contents of this study protocol. The CRF's and any amendment to them will bear a version date and each page will be identifiable by the study, site and Subject identification numbers. If it is necessary to amend the CRF's, the Sponsor will review the study protocol to determine whether or not an amendment to the protocol is necessary. Study assessments may be recorded using paper notes from which data are transcribed into the eCRF, may include data recorded as per institutional practice (hard copy or electronic), or may be recorded directly into the eCRF, as appropriate.

9.1.1. Medical History

Medical history collected will include characteristics of the Subject's low back pain such as diagnosis and duration, as well as number of episodes of low back pain as well as the medications and procedures for treatment of low back pain that the Subject has failed.

The medical history will include baseline demographics as well as a small set of clinical data that would be collected at a typical visit to a general practitioner.

Collection Method: Information transferred to paper CRFs or eCRF

9.1.2. Subject Screening/Baseline

Subject baseline and screening data collected shall include basic information (e.g., Subject identifier, date of enrollment, etc.) as well as a review of inclusion criteria, and a review of exclusion criteria.

Additional data such as results of a pregnancy test (if applicable) and MRI shall be recorded as per institutional practice and the results included in the eCRF.

Collection Method: Information transferred to paper CRF or eCRF if part of the site source documents.

9.1.3. Depression Anxiety Stress Scale ($DASS_{21}$)

The $DASS_{21}$ is a paper questionnaire completed by the Subject alone and without assistance and results are recorded in the eCRF. Validated language specific versions are available.

Collection method: Completed by the Subject on a paper questionnaire then transferred to the CRF or eCRF.

9.1.4. Surgical Procedure

Surgical procedure data collected shall include relevant information during and following the procedure.

Collection Method: Transferred from source documents and surgery worksheets to paper CRF or eCRF

9.1.5. Post-Operative Evaluation

Evaluation of Subject post-operative status will be collected at the Post-Implant Follow-up.

Collection Method: Transferred from source documents to paper CRF or eCRF

9.1.6. Physical Exam and Surgical Site Exam (Post Implant)

After implant, inspect the surgical site and note if healing is normal and as expected. Other elements of the physical exam include weight and information on any new clinical conditions not associated with the Trial.

Collection Method: Transferred from source documents to paper CRF or eCRF

9.1.7. Oswestry Disability Index

The Oswestry Disability Index is a paper questionnaire completed by the Subject alone and without assistance and results are recorded in the eCRF. Validated language specific versions are available.

Collection method: Completed by the Subject on a paper questionnaire then transferred to the CRF

9.1.8. Low Back Pain VAS

Low back pain VAS will be collected at each visit.

Collection Method: Subject completes a form without assistance, and the results are transferred to the eCRF.

9.1.9. Medication

All prescribed medications used, regardless of indication, will be collected at the time of Subject Screening/Baseline Visit.

Medication endpoints will use the subset of this data comprised of prescribed pain medications and muscle relaxant

- Primary endpoint assessment - the metric will be based on all prescribed pain medications or muscle relaxants taken.
- Secondary endpoint assessment - the metric will be limited to opioids taken for treatment of low back pain.

Collection Method: Question asked by the Study Coordinator and recorded then transferred to the eCRF.

9.1.10. Treatment Satisfaction Questionnaire

Treatment Satisfaction Questionnaire will consist of the questions shown in Figure 6.

Are you satisfied with the outcome of your treatment?
☐ Definitely yes ☐ Maybe ☐ Definitely not
Knowing what you know now, would you want this treatment again?
☐ Definitely yes ☐ Maybe ☐ Definitely not
Would you recommend this treatment to another person with chronic low back pain?
☐ Definitely yes ☐ Maybe ☐ Definitely not

Figure 6: Treatment Satisfaction Questionnaire

Collection Method: Subject completes a paper form and results are transferred to paper CRF or into the eCRF

9.1.11. Subject Global Impression of Change

Subject Global Impression of Change consists of the questionnaire as detailed in 4.6.5.

Collection method: Subject completes a paper form and results are transferred to paper CRF or eCRF

9.1.12. Clinical Global Impression – Global Improvement

Clinical Global Impression – Global Improvement consists of the questions that are to be completed by the Investigator as shown in Figure 3 on Page 28.

Collection method: Physician completes on a paper CRF which is transferred to eCRF

9.1.13. EQ-5D

The EQ-5D-5L[i] Quality of Life questionnaire is completed by the Subject. Validated language specific versions are available.

Collection method: Subject completes a paper form and results are transferred into the eCRF

9.1.14. Adverse Events

All transient and long-term adverse events will be collected throughout the course of the study. Assessment will include Investigator-assessed relationship to device, relationship to procedure, severity (i.e.: AE or SAE), subsequent treatment/intervention required and resolution status at each follow-up visit until the event is resolved or closed because of chronic nature of the event. Note that a Subject death automatically closes any outstanding adverse events for that Subject.

Collection Method: Paper CRF or eCRF

9.1.15. Device Deficiency

Device deficiency data collection will include all device deficiencies, including suspected device malfunctions and deficiencies.

Collection Method: Paper CRF or eCRF

9.2. Management of Protocol Deviations

An Investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this investigational plan, applicable laws and applicable national regulations, and any conditions of approval imposed by the reviewing IRB or Ethics Committee and regulatory agency (e.g.: FDA or Competent Authority).

Protocol deviations are a fact of life with any clinical trial. Deviations may be anticipated (e.g.: known delay in a follow up visit), inadvertent (e.g.: unplanned delay or miss of a follow up visit due to a family emergency), or unanticipated on an emergency basis (e.g.: trauma may require device removal to allow an MRI, or other contraindicated procedures).

Except in emergency situations, protocol deviations require prior Sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of Subjects, prior IRB or Ethics Committee approval is required.

An Investigator shall notify the Sponsor and the reviewing IRB or Ethics Committee of any deviation from the investigational plan to protect the life or physical well-being of a Subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred.

All deviations from the investigational plan must be reported to the Sponsor together with the reason for the deviation and possible corrective actions for the deviations. In some circumstances, the center may be required to notify the center’s IRB or Ethics Committee, and the Sponsor will notify the appropriate regulatory agencies.

i See http://www.euroqol.org/

9.3. Informed Consent

Informed Consent is required from all Subjects (or their legal representatives) prior to the Subject's participation in the study. The process of obtaining Informed Consent shall comply with the Declaration of Helsinki, FDA 21CFR 50, ISO 14155-2011 and applicable national regulations (local IRB, Ethics Committee and/or Regulatory bodies, as applicable).

The process of obtaining informed consent shall

a) Avoid any coercion of or undue influence of Subjects to participate,
b) Not waive or appear to waive Subject's legal rights,
c) Use native language that is non-technical and understandable to the Subject or his/her legal representative,
d) Provide adequate time for the Subject to consider participation and ask questions if necessary,
e) Informed consent shall always be signed and personally dated by the Subject or legal representative and by the Investigator or delegate.

The original signed Informed Consent must be retained on file by the Investigator and a copy given to the Subject (Investigator's responsibility).

9.4. Subject Classification

All Subjects are classified as one of the following:

- Baseline withdrawal – refers to a Subject who has been enrolled but then is withdrawn from the study before the device implant process has been initiated. The original Informed Consent form for intent Subjects should be maintained in the Centre's administrative files. There are no follow-up requirements for Baseline withdrawal Subjects.
- Attempt – refers to a Subject who has been enrolled, and in whom a ReActiv8 implant was attempted (i.e.: attempt to place at least one lead) but was not completed.[j] All Subjects in whom the implant was unsuccessful will be followed for at 30 days following the implant attempt. If there are any AEs or SAEs associated with the attempted implant, the Subject will be followed until resolution or closure of the AE or SAE.
- Implant – refers to an enrolled Subject whose implant was completed (i.e.: device remains implanted and the surgical wound is closed and dressed).
- Withdrawal post implant – refers to a Subject who is determined to be inactive in the study due to physician discretion, Subject choice, lost to follow-up, or Subject death. Final status information will be included on all Subjects as available per the Informed Consent document.

9.5. Subject Data Confidentiality

Throughout the study, confidentiality shall be maintained at all times, by all parties involved, and all data shall be secured against unauthorized access. Confidentiality of each Subject shall be preserved in reports and any publication of the results. Only authorized personnel and their designees will have access to these confidential files. Subject data may be made available to national and foreign regulatory agencies, health or other governmental authorities, under strict confidentiality condition. The investigational sites shall ensure that data (e.g. worksheets,

j Only one procedure for ReActiv8 implant should be attempted for each Subject, although each procedure may include multiple attempts to implant, e.g.: to allow for surgical challenges and need for lead repositioning.

programmer printouts, medical records, digital images) forwarded to the Sponsor do not contain any Subject identifying data (such as name and birth date) other than the Subject ID.

It is required that CRFs be entered in the electronic data entry system provided by the Sponsor. All CRFs require the Investigator's signature or the Investigator's designee.

Source documents as per FDA 21CFR 812 and ISO 14155-2011 are printed, optical or electronic documents including the information in original records and necessary for the reconstruction and evaluation of the clinical investigation. Original source data should remain at the investigational site.

Any changes of the reported data should be reported to the Sponsor. When available, changes should be entered into the electronic discrepancy management system provided by the Sponsor. A participating Investigator shall provide direct access to source data and documents for Trial-related monitoring, audits, IRB or Ethics Committee review, and regulatory inspection.

All Subjects' health information will be kept confidential in accordance with all applicable laws and regulations. Subjects' health information may be used to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of products, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to Subjects; Subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

9.6. Record Keeping

Investigators are required to maintain on file the accurate, complete, and current records relating to this investigation:

- All correspondence with another Investigator, an IRB or Ethics Committee, Mainstay Medical, a monitor, or FDA or Competent Authority including required reports
- The signed CIP with any and all amendments
- The approved template of the Subject informed consent form
- Records showing receipt, use, and disposition of all devices (including software), including:
  - Date, quantity, and serial numbers of devices received
  - Names of all persons who received, used or disposed of each device
  - Dates and serial numbers of devices returned to the Sponsor and the reason(s) for return
- IRB or Ethics Committee approval of the CIP and any amendments and renewals
- Competent Authority Approval in those countries where is applicable
- The Investigators' agreement and the fee agreement (separate or combined)
- The Report of Prior Investigations and/or the Investigator's Brochure
- The insurance certificate
- The Implant and Programming Manual and any other documentation provided with the device
- Current curriculum vitae for the principal Investigator and all Sub-investigators
- Monitoring letters (if applicable)
- Interim/final reports
- Study initiation forms
- Study closure documents

In addition, to the study administrative documents, Subject records shall be appropriately filed, including the following:

- Signed informed consent forms
- Source documents used for recording data (e.g., device characteristics at implant and follow-up)
- Records of any adverse event, including supporting documentation
- Records pertaining to Subject deaths during the study
- Relevant source data
- Any other records required by the Sponsor
- Documents showing the dates and reasons for each deviation from the CIP

10. Study Management

10.1. Committees and Independent Review

10.1.1. Data Monitoring Committee

A Data Monitoring Committee (DMC, or sometimes referred to as a Data and Safety Monitoring Board or DSMB) will be established according to ISO 14155, FDA and NIH guidelines, and will consist of experienced and knowledgeable professionals who are not Investigators. The DMC will meet periodically, or as needed, to review the results of the study and to provide safety oversight and professional input to make recommendations for the continuation or termination of the study based on data analysis and study related adverse events. The members of the committee will have access to all adverse event data and any other requested study data that would be necessary in order for the group to make an assessment relative to Subject safety.

10.1.2. Adjudication Committee

As per ISO 14155, the Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation.

An Adjudication Committee will be established to adjudicate reported AEs.

The Adjudication Committee will consist of at least three independent physicians (i.e.: not Investigators), of whom two will form a quorum, and none are also members of the DMC. The activities will be governed by a Charter.

10.1.3. Independent Assessment of Surgical Candidacy

If the site determines that the subject is not excluded based on the MRI assessment, the site will upload the relevant images to a Core Lab for storage and preparation for review by an Independent Physician Reviewer. An appropriately trained independent physician will review the Subject's MRI to assess any current indication for back surgery according to appropriate evidence or guidelines (e.g.: Evidence Informed Management of Chronic Low Back Pain with Surgery,[68] the Guidelines of the American Pain Society,[69] or the European Guidelines for Management of Chronic Non-Specific Low Back Pain[2]). The activities will be governed by a Charter.

10.2. Study Principal Investigator Review

The Study Principal Investigator will review Baseline data for all subjects to confirm that they meet the eligibility criteria for the trial. This review will take place prior to the study implant procedure (Visit 2) and will be communicated to the Site Principal Investigator and study staff. The review may be performed by the Study PI or an alternate physician designated by the Study PI.

10.3. Procedures to Amend the Clinical Investigation Plan

From time to time, an Investigator or the Sponsor may propose changes to the Clinical Investigation Plan. The Sponsor shall have final authority to make such changes or not.

From time to time, the DMC may mandate or recommend changes to the Clinical Investigation Plan. From time to time, regulatory authorities may mandate or recommend changes to the Clinical Investigation Plan.

All amendments to the CIP shall be agreed upon by the Sponsor and the Investigators and be recorded with a justification for the amendments. In all cases of changes to the Clinical Investigation Plan, the local rules for approval of modifications shall be followed, including by way of example a submission to the IRB or Ethics Committee (either in full or to the Chairman), and modifications to the clinical Trial contract with the institution if applicable.

10.4. Device Accountability

Device accountability shall be in compliance with ISO 14155 and FDA regulations.

The Sponsor will control the availability of all investigational devices (including software) by shipping devices only to trained representatives or study Investigators who have IRB or Ethics Committee, and Sponsor approval. The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. Devices are not transferable between Investigators unless prior approval is obtained from the Sponsor. Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigation Plan.

The site Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

1. the date of receipt,
2. identification of each investigational device (batch number/serial number or unique code),
3. the expiry date, if applicable,
4. the date or dates of use,
5. Subject identification,
6. date on which the investigational device was returned/explanted from the Subject, if applicable, and
7. the date of return of unused, expired or malfunctioning investigational devices, if applicable.

An out-of-service product is defined as any implantable products (e.g. device, lead) removed or rendered inactive. Out-of-service product includes but is not limited to devices that do not function appropriately at implant and explanted product. Whenever possible, any out-of-service product should be returned to the Sponsor for analysis. In the event of a Subject death, every effort should also be made to return product to Mainstay Medical.

10.5. Labeling

All investigational devices will have a clinical investigation label, which will be visible on the pertinent shipping cartons and storage containers. The required labels or manuals will bear the following information:

- Model and serial number of the device (the magnet does not have a serial number)
- Name of the device and the address of Mainstay Medical as the manufacturer
- Caution statement regarding investigational device

- All relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings and precautions

10.6. Data Monitoring Plan

It is the responsibility of the Sponsor to ensure proper monitoring of the study per regulations. Appropriately trained Sponsor personnel or delegates appointed by the Sponsor will perform study monitoring at the investigation site in order to ensure that the study is conducted in accordance with the CIP, the signed Clinical Trial Agreement, and applicable regulatory requirements. The Sponsor must therefore be allowed access to the Subjects' clinic and hospital records when so requested as per the consent form, Privacy Authorization (US only) and Clinical Trial Agreement. Procedures required in this CIP require source document verification for this study. A separate Monitoring Plan will detail levels of source verification for this study.

Monitoring visits will be conducted periodically to assess study progress, the Investigator's adherence to the CIP and regulatory compliance. This includes but is not limited to IRB/EC approval and review of the study, maintenance of records and reports, review of the consent process and review of source documents against Subject case report forms to ensure data points are correct and that adverse events are being reported. Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Communication with the site personnel occurs during the visit and following the visit via a written follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

Frequency of monitoring visits will occur based on Subject enrollment, timing of the study visits, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. All data used for a regulatory submission will be monitored against source documentation prior to the PMAA submission.

All active sites will have a closure visit. A closure visit is a visit that occurs after a site's last required follow-up visit. Closure visit activities may include source verification of the data and closure of any findings and/or study-related activities.

Storage and accountability of investigational product used for this study will be assessed and monitored throughout the study at each site.

10.7. Sponsor Responsibilities

MML US Inc. (a subsidiary of Mainstay Medical Limited, Ireland) ("Mainstay") is the Sponsor of this study, where a Sponsor is defined as an individual or organization taking the responsibility and liability for the intention or implementation of a clinical investigation.

It is the responsibility of the Sponsor to ensure proper monitoring of the study and to see that all clinical requirements are met. In addition, Sponsor representatives may participate in the conduct of the Trial to the extent described in the following section on the role of the Sponsor representatives. In this study Sponsor representatives are not blinded to the study results, particularly since Sponsor representatives may be involved in device programming. Participation in the study will be limited to Sponsor personnel who are appropriately qualified and trained such as those personnel with an engineering, technical or nursing degree or equivalent training, or significant experience within the implantable device industry. All Sponsor personnel will be trained on the appropriate clinical study regulations and guidelines for medical device trials.

It is the responsibility of the Sponsor to ensure appropriate training of all individuals involved in the clinical Trial. This includes Investigators and other health care professionals at the investigational sites, Sponsor personnel, and contractors if applicable.

10.8. Role of the Sponsor Representatives

Sponsor personnel can provide technical support to the Investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the CIP, and follow-up visits. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of Mainstay Medical equipment (including programmers and other support equipment) or the procedures and forms related to the CIP.

At the request of the Investigator and while under the Investigator's supervision, Sponsor personnel may operate equipment during implant or follow-up visits, assist with the conduct of testing specified in the CIP, and interact with the Subject to accomplish requested activities. Typical tasks may include:

- Interrogating the device or programming device parameters to physician requested settings
- Performing lead diagnostic testing using a programmer to obtain thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the Investigator or other health care personnel
- Assisting with the collection of study data from programmers and other equipment
- Entering data on study worksheets as long as the responsible study Investigator verifies and signs the completed worksheet

In addition, Sponsor representatives or designated technical personnel can perform certain activities to ensure study quality. These activities include:

- Observing testing or medical procedures to provide information relevant to CIP compliance
- Reviewing collected data and study documentation for completeness and accuracy

At no point shall personnel from the Sponsor or CRO:

- Practice medicine;
- Discuss with the Subject the Subject's diagnosis or recommend treatment;
- Enter data into the eCRF; or
- Discuss the Trial with the Subject.

10.9. Clinical Investigators

This study will be conducted in accordance with FDA Regulations 21CFR 812 and ISO 14155-2011. A detailed list of the Investigators' responsibilities can be found in 21CFR 812 and ISO 14155-2011. The Investigator is responsible for conducting the study in accordance with the investigational plan, the latest version of the Declaration of Helsinki, the signed Investigator Agreement and other agreements, applicable laws and regulations, and any conditions of approval imposed by the reviewing IRB or Ethics Committee, and FDA or Competent Authority. To ensure compliance with the guidelines, the Sponsor, an independent body, or a regulatory agency may audit the study. By agreeing to this CIP, the Investigators and their institutions accept to allow monitoring, audits, IRB or Ethics Committee review, and regulatory inspections that are related to the study. They also agree to provide authorized individuals with access to

source data and documentation as well as the right to copy records, provided such activities do not violate Subject consent and Subject data confidentiality.

The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care, and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is obtained in accordance with this investigational plan, applicable regulatory requirements, and local IRB or Ethics Committee requirements. The Investigator or sub-Investigator may request the presence of Sponsor personnel at device-related procedures.

A list of Investigators and institutions participating in this study will be available upon request.

10.10. Investigator Selection

In accordance with 21CFR 812 and ISO 14155-2011 the role of the site principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the Subjects involved in the clinical investigation.

If the Sponsor contracts an institution to conduct the clinical investigation, the institution shall appoint an appropriately qualified person to be Site Principal Investigator.

The Site Principal Investigator shall:

- Be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation; evidence of such qualifications of the principal Investigator and key members of the investigation site team shall be provided to the Sponsor through up-to-date CVs or other relevant documentation
- Be experienced in the field of application and trained in the use of the investigational device under consideration
- Disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical investigation or interpretation of results, and
- Be knowledgeable with the method of obtaining informed consent.

A Site Principal Investigator and any Sub-Investigator(s) must be experienced in and responsible for the following:

- Subject well-being
- Strict adherence to the Investigational CIP, which includes all testing requirements to provide for optimal safe and efficacious use of the investigational device
- Return of explanted devices, if applicable
- Providing the Subject with comprehensive information about the study and documenting Subject consent and data during the study
- Addressing medical questions which might be asked, either by the Sponsor or by external Regulatory Agencies, during or after the study.
- Notifying the Sponsor of any deviation from the Protocol with an explanation for the deviation. This notice shall be given as soon as possible, but in a timely manner after the deviation occurred.
- The Investigator will ensure that any Adverse Event is reported according to Section 8.1.
- Subject death during the study should be reported to the Sponsor as outlined in Section 8.4.
- Submission of death letters, notes, etc. if applicable

It is acceptable for the Site Principal Investigator to delegate one or more of the above functions to an associate or sub-Investigator. However, the Site Principal Investigator remains responsible for proper conduct of the study. The study is not transferable to other centers attended by the Investigator unless prior approval is obtained from the appropriate reviewing IRB or Ethics Committee, the Sponsor, and the appropriate regulatory authority (if applicable).

10.11. Publication Policy

A Publication Plan will be developed by the Sponsor and Investigators following approval of the Study, and for the duration of the Trial, the Publication Plan shall determine what information is to be submitted for publication, to which journal and/or meeting, and by whom. Publications shall have the order of authors as determined by the Publication Plan.

Should presentation or publication be contemplated, the Sponsor shall be provided with copies of any abstracts, papers or manuscripts for review and approval within a reasonable period prior to submittal for publication or presentation. The Sponsor shall limit its review to a determination of whether Confidential Information is disclosed and shall not attempt to censor or in any way interfere with the presentation or publication beyond the extent necessary to protect Confidential Information or to allow the Sponsor to protect its rights in patentable or copyrightable material.

Authorship of publications shall follow the recommendations of the International Committee of Medical Journal Editors[k], which may result in employees of the Sponsor being included as authors.

10.12. Payment of Subjects

Subjects will be reimbursed for reasonable transportation costs according to local institutional guidelines and regulatory requirements of up to US$550 (in local equivalent) in any calendar year.

10.13. Maintaining Compliance

The study will be conducted according to the stipulations of the FDA, the Declaration of Helsinki, ISO 14155-2011 and all other applicable regulations determined by country.

10.13.1. Study Monitoring

Monitoring will be performed during the study to ensure that compliance with the CIP and applicable regulations are maintained, that data are collected in a timely, accurate and complete manner and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively.

Monitors are individuals who are designated to oversee the progress of a study. These individuals are appropriately trained and qualified to monitor the progress of a study. Monitors will be selected and assigned by Mainstay Medical.

k http://www.icmje.org/ethical_1author.html

10.13.2. Review of Submitted Data

In addition to the site monitoring visits the case report forms submitted by the Investigators will be reviewed. The following activities will occur:

- All case report forms will be reviewed for completeness and accuracy upon receipt or after entry into the electronic data capture system
- The Investigators and/or their clinical investigation representative and/or the Mainstay Medical designated personnel will be contacted regarding any missing or unclear data

10.13.3. Securing Compliance

In the event of repeated noncompliance, as determined by the Sponsor, a Sponsor or CRO representative will attempt to secure compliance by one or more actions:

- Visiting the Investigator
- Telephoning the Investigator
- Corresponding with the Investigator

If an Investigator is found to be repeatedly noncompliant with the signed agreement, the study CIP, applicable regulatory requirements, or any other conditions of the study, the Sponsor may, at its sole discretion, terminate the Investigator's participation in the study. In the event of termination of Investigator participation, study devices will be returned to the Sponsor unless this action would jeopardize the rights, safety, or welfare of the Subject.

10.14. Study Completion

The Sponsor will notify each Investigator of the completion or termination of the investigation or of the Investigator's participation in the study. At the Sponsor’s request, an Investigator will return any devices in his or her possession. The Investigator will provide a summary to the Sponsor and reviewing IRB or Ethics Committee of their investigation within 3 months of study termination.

The Study Completion plan which details actions and responsibilities is shown in Table 5.

10.15. Suspension or Premature Termination of the Trial

The procedure to be followed as a result of suspension or premature termination of the Trial shall be in compliance with 21CFR 812 and ISO 14155.

- The Sponsor may suspend or prematurely terminate either the clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.
- A principal Investigator, IRB or Ethics Committee, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigational sites for which they are responsible.
- If suspicion of an unacceptable risk to Subjects arises during the clinical investigation, or when so instructed by the IRB or ethics Committee, or regulatory authorities, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed.
- The Sponsor shall consider terminating or suspending the participation of a particular investigation site or Investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal Investigator and Sponsor shall keep each other informed of any communication received from either the IRB or Ethics Committee, or the relevant regulatory authority.

If the Sponsor makes a decision to discontinue the study for any reason (e.g., slow enrollment, significant change in risk/benefit due to unanticipated adverse device effect, or other scenario), then the Sponsor will promptly inform all Investigators, IRBs or Ethics Committees, and relevant regulatory bodies along with detailed information on how enrolled Subjects should be managed thereafter. All Subjects enrolled in the Trial will continue to be followed according to the investigational plan unless the Sponsor notifies the investigational centers otherwise.

An Investigator may also discontinue participation in the study with suitable written notice to the Sponsor. Should either of these events occur, the Investigator shall:

- return all documents and devices to the Sponsor
- provide a written statement as to why the premature termination has taken place
- notify the IRB or Ethics Committee and the regulatory authority (if applicable)

If suspension or premature termination occurs:

1. the Sponsor shall remain responsible for providing resources to fulfill the obligations from the Clinical Investigation Plan and existing agreements for following up the Subjects enrolled in the clinical investigation;
2. the principal Investigator or authorized designee shall promptly inform the enrolled Subjects at his/her investigation site, if appropriate;
3. the Sponsor shall arrange, and each site shall cooperate, to remove all investigational devices from investigational sites, and
4. the database from the clinical Trial at the time of termination shall be locked and made available for inspection by regulatory authorities or publication at a later date.

Table 5: Study Completion Plan

Time of Completion	**After Subject reaches final study visit**			**If study closed before Subject reaches final study visit . . .**		**If Subject ends participation before final study visit . . .**	
Note: All days are calendar days	ReActiv8 PMA Approval	Decision to not pursue PMA Approval	PMA Approval not Granted	Study closed for safety reasons	Study closed for other reasons	Subject withdrawal	Subject lost to follow-up
Site must notify Subjects of the study completion plan within	45 days	45 days	45 days	45 days	45 days	n/a	45 days
Will Sponsor provide ongoing support?	Yes	No	No	No	No	No	No
IPG to be turned OFF (disabled)?	No	No*	No*	Yes	No*	No	No
Will external devices be collected?	No	No*	No*	Yes	No*	No	No
Explant required?	No	No	No	No*	No	No	No
Will Sponsor pay for explant procedure if needed?	No	Yes, for up to 6 months	Yes, for up to 6 months	Yes, for up to 6 months	Yes, for up to 6 months	Yes, for up to 6 months	Yes, for up to 6 months
What other surgical costs will Sponsor pay for?	None	None	None	None	None	None	None
Sponsor will pay for what type of clinic visits	None	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals	One visit to 1. inform of completion 2. Turn off IPG 3. collect externals
How should symptoms related to the device be reported?	Submit Complaint	Submit Complaint	Submit Complaint	Submit Complaint	Submit Complaint	Submit Complaint	Submit Complaint

* Subject and Investigator to discuss

11. Administrative Data

11.1. Name and Address of the Sponsor

MML US Inc.
6601 Shingle Creek Parkway
Brooklyn Center, MN 55430

MML US Inc. is a subsidiary of

Mainstay Medical Limited
Clonmel House
Swords, K67F2K3
County Dublin,
Ireland

Sponsor's Contact:

Ms. Diane Burnside
Vice President Clinical Affairs
diane.burnside@mainstay-medical.com
Office: +1 763 270-5303
Mobile +1 (763) 772-7637

11.2. Investigators

Each Investigational Site shall have a Site Principal Investigator. Subject to Sponsor approval, a Site Principal Investigator shall delegate some or all of the Subject interaction and data collection to one or more Sub-investigators.

The overall Study Principal Investigator is:

Chris Gilligan MD MBA

Chief, Division of Pain Medicine
Department of Anesthesia, Critical Care and Pain Medicine
Brigham Pain Center
Boylston Street, MA

Dr. Gilligan was also Chairman of the DMC for the European Feasibility Study and the Chairman of the DMC for the ReActiv8-A Trial.

11.3. Data Monitoring Committee

The list of members, affiliations and roles and responsibilities of the DMC will be described in the DMC Charter, which will be stored as a part of the Trial Master File.

11.4. Adjudication Committee

The list of members, affiliations and roles and responsibilities of the Adjudication Committee will be described in a Charter, which will be stored as a part of the Trial Master File.

11.5. Clinical Research Organizations (CROs)

Data collection will be performed with an electronic Case Report Form (eCRF). A CRO will manage the clinical database and will be responsible for randomization. The Sponsor will determine the data monitoring staff using the Sponsor's and the CRO's personnel. Subsidiary CROs may be used in certain countries.

11.6. Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

This clinical investigation shall be conducted compliance with FDA regulations, ISO 14155 and any regional or national regulations, as appropriate.

The clinical investigation shall not begin until the required approval or favorable opinion from the FDA, IRB (or Ethics Committee), and any other regulatory body as appropriate and necessary in other countries.

Any additional requirements imposed by the IRB, Ethics Committee, FDA or Competent Authority shall be followed, if appropriate.

Appendix 1: Acronyms and Definitions

AE	Adverse Event - any undesirable clinical occurrence that affects the health or safety of the Subject
ALBP	Axial Low Back Pain
AMI	Arthrogenic Muscle Inhibition – the physiological mechanism by which pain in a skeletal joint can inhibit activation of the muscles that surround or stabilize that joint
BMI	Body Mass Index
CGI-I	Clinical Global Impression – Global Improvement
CIP	Clinical Investigation Plan (this document). A document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. NOTE The term "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. Therefore, the term CIP is used in ISO 14155.
CLBP	Chronic Low Back Pain
CRF	Case Report Form(s) - set of printed, optical or electronic documents for each Subject on which information to be reported to the Sponsor is recorded, as required by the CIP (ISO 14155)
CRO	Contract Research Organization - person or organization contracted by the Sponsor to perform one or more of the Sponsor's clinical investigation-related duties and functions (ISO 14155)
CV	Curriculum vitae
Deviation	instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP (ISO 14155).
DD	Device Deficiency. An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
DMC	Data Monitoring Committee - independent committee that may be established by the Sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the Sponsor whether to continue, suspend, modify, or stop the clinical investigation (ISO 14155)
DRG	Dorsal Root Ganglion – is a cluster of nerve cell bodies located in the posterior region of the various vertebrae along the spine. It is adjacent to the dorsal nerve root, which exists as part of a pair of nerve roots exiting at each level of the spine.
EC	Ethics Committee - independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human Subjects participating in a clinical investigation (ISO 14155 - NOTE For the purposes of ISO 14155, "ethics committee" is synonymous with "research ethics committee", "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMG	Electromyogram
EQ-5D	European Quality of Life Assessment
FDA	Food and Drug Administration
HCP	Health Care Personnel
IB	Investigator's Brochure - compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation (ISO 14155)

ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IPG	Implantable Pulse Generator
IRB	Institutional Review Board (equivalent to Ethics Committee)
Labeling	Per 21 CFR Part 801, 21 CFR Part 812, and 21 CFR Part 820, Section 201(m) defines 'labeling' as: 'all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article' at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.' Labeling thus includes package labeling and accompanying manuals.
Malfunction	failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP (ISO 14155)
MF	Multifidus muscle of the lumbar spine (see also LM)
Monitoring	Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, ISO 14155, and the applicable regulatory requirements (ISO 14155)
NRS	Numerical Rating Scale
NSLBP	Non-Specific Low Back Pain
NSAID	Non-Steroid Anti-Inflammatory. A class of drugs, sometimes used for low back pain.
ODI	Oswestry Disability Index
OTC	Over the Counter – refers to non-prescription medications
PI	Principal Investigator. A qualified physician who takes overall responsibility for conduct of the trial according to the protocol and regulations.
PMA	Pre-Market Approval
PMCF	Post-Market Clinical Follow Up
PRO	Patient Reported Outcome
QOL	Quality of Life
Re-implant surgery	A surgical procedure in which a new device is implanted to replace a device removed in a prior surgical procedure.
Removal Surgery	A surgical procedure in which at least one of either the leads or IPG is removed and not replaced with a device of the same type during the same surgical procedure
Replacement Surgery	A surgical procedure that involves removal of one device component and implantation of a new device component of same type, e.g. lead, during a single surgical procedure
Revision Surgery	Surgical procedure performed on a currently implanted device, e.g. repositioning a dislodged lead
SAE	Serious Adverse Event. an adverse event that led to death, or led to serious deterioration in the health of the Subject, that either resulted in:

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient or prolonged hospitalization,
4. congenital anomaly/birth defect, or
5. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol (e.g., the index implant procedure, or device replacement due to normal battery depletion), without serious deterioration in health, is not considered a serious adverse event.

SAP	Statistical Analysis Plan

SCS	Spinal Cord Stimulator
SGIC	Subject Global Impression of Change
Site PI	Site Principal Investigator - qualified person responsible for conducting the clinical investigation at an investigation site (ISO 14155)
Sponsor	Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation. For this Trial, it is Mainstay Medical Limited.
Subject	An individual who participates in a clinical investigation. A Subject can be either a healthy volunteer or a patient. (ISO 14155)
TENS	Transcutaneous Electrical Nerve Stimulation
TSQ	Treatment Satisfaction Questionnaire
UADE	Unanticipated Adverse Device Effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects.
VAS	Visual-Analogue Scale

Appendix 2: Bibliography

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