Title: ReActiv8 Stimulation Therapy vs Optimal Medical Management: A Randomized Evaluation

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ReActiv8 Stimulation Therapy vs Optimal Medical Management: A Randomized Evaluation (RESTORE)

Clinical Protocol

Post Market Study

Sponsor

MML US Inc.
2159 India Street, Suite 200
San Diego, CA 92101

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Revision History

Rev	Change Description	Effective Date
A	Initial release to production	12-Mar-2021
B	• Remove EQ-5D eligibility criterion • Correct Age criterion • Add Leg Pain description and NRS • Add EQ-5D sub-analysis • Aligned study visit activities throughout the document • Other minor edits	11-Aug-2021
C	• Increase number of sites to up to 30 sites • Clarify that visit windows are a guideline, not a strict requirement • Clarify timing of implant procedure in the Control group • Remove the additional 30 days after randomization for the start of visit timing in the Control group • Clarification of endpoint hypotheses • Other minor edits	7-Sep-2022
D	• Update sponsor address and contact. • Correct typo in EQ-5D hypotheses	11-Jan-2024

Investigator Signature Page

Investigator Acknowledgement Signature:

I have received and reviewed this Clinical Protocol. I will conduct the study as described.

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

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1. Background

Back pain is the largest cause of years lived with disability globally,[1] the leading driver of work absenteeism,[2] and a leading reason for chronic opioid use.[3,4,5] 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."[6] Annual direct and indirect costs related to low back pain in the US society are estimated to be as high as $296 billion annually.[7,8]

Acute low back pain usually improves within a matter of weeks, but recurrences are common, and pain and disability can become chronic.[9] Back pain is generally stated to have become "chronic" if it has persisted for more than 3 months. The NIH Task Force on Research Standards for Chronic Low Back Pain recommended that Chronic Low Back Pain (CLBP) 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.[10]

Although much attention and investment have been applied to surgical treatments for CLBP, only 20% or less of CLBP patients present with a pathophysiology that can be addressed by additional surgical options.[11] For the remainder, the most common cause of the CLBP is thought to be musculoskeletal or mechanical in nature.[12] Depending on local convention and physician preference, various terms are used for this type of CLBP: "mechanical chronic low back pain," "musculoskeletal chronic low back pain," "non-specific low back pain" (NSLBP), or "axial low back pain." There are European clinical practice guidelines for chronic NSLBP[13] and UK guidelines for management of patients with chronic NSLBP (published by the National Institute for Health and Care Excellence – NICE).[14] US guidelines for acute and chronic low back pain are similar to the European guidelines.[15]

It is important to differentiate the two most clinically relevant types of chronic low back pain: mechanical CLBP, as noted above, and neuropathic CLBP, frequently a component of the failed back surgery syndrome (FBSS). As described below, the pathophysiology of these types of CLBP is very different, as are the potentially available therapeutic approaches.

- Neuropathic CLBP, frequently a component of FBSS that does not respond to non-opioid medications or physical therapy is well treated with spine surgery and a number of neuromodulation modalities including spinal cord stimulation[16] and dorsal root ganglion stimulation.[17]
- Mechanical CLBP, which is predominantly nociceptive pain that results from tissue injury and inflammation, has no known effective treatment should physical therapy and non-opioid medications fail, and outcomes from opioid therapy are poor.[18,19] Interventional pain approaches including nerve blocks, facet blocks, and radio-frequency ablation may provide transient relief but rarely result in long-term relief.[20,21,22,23,24,25] To our knowledge, no studies have been published demonstrating the effectiveness of spinal cord stimulation or dorsal root ganglion stimulation for the treatment of this nociceptive pain syndrome.[26]

Non-Invasive Therapies

Recently, a series of systematic reviews of therapies for Low Back Pain were performed to update the Clinical Practice Guideline for the American College of Physicians (ACP) and the American Pain Society (APS).[27,28] With respect to nonpharmacological non-invasive therapies, the authors concluded that: "Several nonpharmacologic therapies for primarily chronic low back pain are associated with small to moderate, usually short-term effects on pain; findings include new evidence on mind-body interventions."[29]

Exercise therapy is frequently prescribed for low back pain. Systematic reviews of the literature show that the effectiveness of exercise for chronic low back pain is limited, except for certain types of exercise therapy that can be effective in a small subset of patients.[30,31]

Many non-invasive conservative therapies have been tried with modest or no success, and several reviews are available.[32,33,34] Therapies include lumbar extensor strengthening exercises,[35] watchful waiting (i.e., no therapy),[36] traction therapy,[37] the McKenzie Method of exercise therapy,[38] various types of energy application including ultrasound, transcutaneous electrical nerve stimulation (TENS),[39] osteopathic therapy,[40] thermotherapy,[41] and lumbar stabilization exercises.[42]

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

Pharmacological Therapy Including Opioids

With respect to pharmacological therapies, the recent systematic review by the ACP guideline group (Figure 1) noted that: "Several systemic medications for low back pain are associated with small to moderate, primarily short-term effects on pain. New evidence suggests that acetaminophen is ineffective for acute low back pain, and duloxetine is associated with modest effects for chronic low back pain".[43]

Table 3. Pharmacologic Therapies Versus Placebo for Chronic Low Back Pain

Drug	Pain			Function		
	Magnitude of Effect	Evidence	SOE	Magnitude of Effect	Evidence	SOE
Acetaminophen	No evidence	–	–	No evidence	–	–
NSAIDs	Small to moderate	1 SR (4 RCTs), 2 RCTs	Moderate	None to small	4 RCTs	Low
Opioids (strong opioids)	Small	1 SR (6 RCTs), 4 RCTs	Moderate	Small	1 SR (4 RCTs), 4 RCTs	Moderate
Opioids (buprenorphine patch or sublingual)	Small	3 RCTs	Low	Unable to estimate	3 RCTs	Insufficient
Tramadol	Moderate	1 SR (5 RCTs), 2 RCTs	Moderate	Small	1 SR (5 RCTs), 2 RCTs	Moderate
Skeletal muscle relaxants	Unable to estimate	3 RCTs	Insufficient	–	–	–
Benzodiazepines: tetrazepam	Failure to improve at 10–14 d: relative risk, 0.71 (95% CI, 0.54–0.93)	1 SR (2 RCTs)	Low	–	–	–
Tricyclic antidepressants	No effect	1 SR (4 RCTs)	Moderate	No effect	1 SR (2 RCTs)	Low
Antidepressants: selective serotonin reuptake inhibitors	No effect	1 SR (3 RCTs)	Moderate	–	–	–
Antidepressants: duloxetine	Small	3 RCTs	Moderate	Small	3 RCTs	Moderate
Gabapentin/pregabalin	Unable to estimate	2 RCTs	Insufficient	Unable to estimate	2 RCTs	Insufficient

NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; SOE = strength of evidence; SR = systematic review.

From Chou et al., 2017

Figure 1: Review of Pharmacological Therapy

The ACP also stated "For opioids, evidence remains limited to short-term trials showing modest effects versus placebo for chronic low back pain (moderate strength of evidence).[44] Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow-up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design, which could underestimate harms.[45] Observational studies have found an association between prescribed opioids and serious harms, such as overdose,[46] and clinical guidelines recommend risk assessment, careful patient selection, use of lower doses, and close monitoring and follow-up of patients prescribed these drugs."[47,48]

According to the 2009 to 2010 National Health and Nutrition Examination Survey, opioids are the most common prescription drug taken by US adults with CLBP.[49] However, outcomes from opioid therapy for CLBP are poor.[50,51] Concerns about serious avoidable harms, including the development of opioid use disorder (OUD), have led the National Institute for Health and Care Excellence in the UK to explicitly advise against the use of opioids for CLBP (NICE NG 59), citing effects on pain and function that are too small to be clinically important. [52] Despite the lack of evidence for effectiveness, surveys show that opioids are prescribed to 45% of patients presenting with CLPB to emergency care departments in the US.[53]

Data from the first randomized clinical trial with long-term outcomes demonstrated that opioid treatment did not confer significantly better benefit with respect to pain-related function when compared with non-opioid analgesics and that adverse medication-related events were more common among patients receiving opioid therapy.[54] Gabapentinoids, which have been prescribed as an alternative to opioids, have been shown to be both addictive and ineffective.[55]

Interventional Procedures

Despite a tremendous growth in the number of interventional procedures targeting neuropathic low back pain over the last decade, some of which appear to be associated with short or intermediate pain relief, [56] their ability to improve function and work status in mechanical CLBP is less clear-cut. More importantly, interventional procedures have not resulted in a reduction of opioid intake, a crucial outcome for a population at high risk of OUD.[57] Furthermore, trials have shown a number of interventions to be ineffective for patients whose pain becomes chronic and sustained.[58,59,60,61,62,63]

For example, no evidence shows Spinal Cord Stimulation (SCS) to be effective for patients with mechanical CLBP. The European guidelines on chronic NSLBP[64] state "spinal cord stimulation cannot be recommended for nonspecific CLBP." Similarly, surgery for chronic low back pain represents an irreversible intervention that leaves at least one in five patients with a diagnosis of failed back surgery syndrome.[65] In fact, evidence suggests that surgery performed where chronic back pain is the predominant symptom and radicular lower extremity is not prominent, outcomes are worse.[66,67]

Despite these facts, many patients have historically opted for back surgery, in part because of the poor outcomes of existing nonsurgical therapies. Clinical data suggests that surgical intervention is indicated only for approximately 20% of CLBP patients[68] Therefore, clinicians and patients

routinely resort to either ineffective and risky chronic opioid therapy or poorly indicated spine surgery when CLBP is severe and refractory.

Societal Cost

Back pain is the largest cause of years lived with disability globally, the leading driver of work absenteeism, and a leading reason for chronic opioid use. [69,70,71] The effects of mechanical CLBP can leave many patients disabled and severely restrict their participation in society. Dependence on prescribed medication, alcohol or other drugs, and psychological distress can complicate their presentation significantly.[72] This extracts a large cost from the patients and society related to healthcare and disability support.

In the United Sates, epidemiologic data show that the direct health care costs and indirect costs related to work absenteeism are substantial.[73,74]

Long-term disability is particularly impactful: “recovery after 12 weeks (of low back pain) 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.”[75]

Like many chronic conditions, the costs are driven by the small proportion of the population who have been sick for the longest period – patients with disability >1 year account for 5% of cases but 65% of costs.[76,77] Indeed, CLBP is not only a very common cause of work-related disability but is also the most expensive with respect to workers’ compensation benefits and medical expenses.[78]

ReActiv8 Therapy

Arthrogenic muscle inhibition is the well-known physiological mechanism by which pain in a skeletal joint disrupts the motor control to the muscles that stabilize that joint.[79,80,81] AMI is a presynaptic, ongoing reflex inhibition of musculature surrounding a joint after distension or damage to structures of that joint, and serves as a natural response to protect the joint from further damage.[82] A common example of this is the disruption quadriceps motor control,[83] often observed after knee injury or knee surgery.[84] Persistent AMI may eventually lead to muscle atrophy and weakness.[85]

A similar mechanism can cause motor control disruption of the key lumbar spine-stabilizing muscle – the lumbar multifidus muscle (“multifidus”).[86]

The multifidus is an axial load-bearing endurance muscle, and it is the strongest local stabilizer of the lumbar spine.[87,88] Motor control of the multifidus becomes disrupted following initial injury and often persists after the resolution of acute, first-episode low back pain.[89] Impaired motor control of the multifidus is associated with changes in cortical representation of the multifidus and subsequent inability to exert voluntary control.[90]

Published studies show that targeted multifidus motor control exercises guided by ultrasound biofeedback, that enable a patient to override the normally involuntary motor control system, can lead to improvements in back pain.[91] Clinical researchers studying the impact of repetitive multifidus contraction on low back pain developed the biofeedback method to ensure multifidus contraction. This involves dedicating a physical therapist with expertise in ultrasound imaging to

continuously apply ultrasound imaging during physical therapy sessions to guide individual patients through motor control exercises and to further repeat such a session daily for several weeks or months. The proposed mechanism of action in these studies is the restoration of motor control of the multifidus, thereby leading to improved functional spine stability and reduction in back pain. However, this approach has not been adopted in clinical practice due to inherent practical challenges, economic difficulties, and patient compliance issues.

Electrical stimulation to facilitate motor control restoration by causing muscle contractions is being used successfully with other skeletal muscles. In particular, stimulation via superficial (skin) electrodes over the motor point of the quadriceps can restore neural drive and facilitate rehabilitation of the muscle in patients following total knee arthroplasty[92] or other surgical procedures.[93,94] 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.[95]

Mainstay Medical Limited ("Mainstay") has developed the ReActiv8 neurostimulation system ("ReActiv8" or "the device") to treat mechanical CLBP by incorporating the principles of these prior approaches. ReActiv8 targets restoration of neuromuscular control by delivering electrical stimulation to the medial branch of the dorsal ramus of the spinal nerve to cause episodic contraction of the multifidus muscle, to override the underlying arthrogenic muscle inhibition of the multifidus. Restoration of neuromuscular control of the multifidus is expected to improve functional stability of the spine and reduce mechanical CLBP.[96]

The ReActiv8 System obtained CE Marking on 24 MAY 2016, TGA approval 05 DEC 2019, and FDA PMA approval on 16 JUN 2020.

Conclusions

Thus, current pharmacological, conservative, and interventional therapies do not offer clinically relevant long-term improvement to the refractory mechanical CLBP population that does not get pain relief from physical therapy and non-opioid medications.

As a result, these patients are often prescribed stronger agents such as opioids as well as gabapentinoids in an effort to manage pain, despite evidence that such drugs may cause more harm than benefit. Outcomes from opioid therapy for chronic low back pain are poor,[97,98] and alternatives such as gabapentinoids have also been shown to be ineffective in this population.[99] Given the considerable personal suffering, familial impact, and societal costs, improving treatment effectiveness for patients with intractable mechanical CLBP represents an important public health challenge.

The development of novel, effective, non-opioid therapies for mechanical CLBP addresses a critical unmet clinical need and will greatly contribute to solving the public health crisis of opioid use disorder. Such therapies should demonstrate a multidimensional benefit for mechanical CLBP sufferers, including reduction in pain alongside improvements in physical and social function, overall quality of life, and reduction of opioid intake.

1.1. Overall Synopsis of the Clinical Study

This study is a prospective, randomized study comparing ReActiv8 Therapy to Optimal Medical Management (OMM), where OMM means the patient has been managed according to available guideline-directed treatments[100] (e.g., medication, physical therapy, injections), and are intending to continue with their existing course of care during the study. OMM will follow physician treatment practices per the guidelines such that it will be individualized to meet the patient needs. A synopsis of the study in tabular form is shown in Table 1.

All patients who satisfy the enrollment criteria are randomized (1:1) to receive either ReActiv8 (Treatment group) or OMM (Control group).

After randomization, those in the Treatment group will be implanted, and then all patients will be followed at the following timepoints post-implant: 1.5 months, 3 months, 6 months, 1 year, 18 months, and 2 years. After the 1-year visit, patients in the Control group may elect to be implanted with the ReActiv8 device and, in addition to the visits noted above, will have follow-up visits at 13.5 months and 15 months. Patients in the Control group who are not implanted with a ReActiv8 device after the 1-year visit will be exited from the study at that time.

The primary efficacy endpoint is a comparison of mean change in Oswestry Disability Index (ODI) at 1 year compared to baseline.

Secondary and tertiary endpoints will be assessed at the 1-year visit compared to baseline, including change in Numerical Rating Scale (NRS) Pain score, a composite of change in ODI and change in NRS Pain score, change in EQ-5D Quality of Life, Percent Pain Relief, Subject Global Impression of Change (SGIC), and Treatment Satisfaction.

Related adverse events (AEs) and all serious adverse events (SAEs) will be reported from enrollment through study exit.

Table 1: Synopsis of the Clinical Study

Study Purpose	To compare the effectiveness of ReActiv8 to OMM for the treatment of intractable chronic low back pain (CLBP).
Indications for Use	The ReActiv8 System is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the L3 transverse process as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery.
Study Device	ReActiv8 System
Study Design	Prospective, randomized study comparing ReActiv8 to OMM. See Figure 2 for the study schema.
Treatment Arm	ReActiv8 Therapy
Control Arm	OMM
Randomization	Patients meeting all eligibility criteria will be randomized 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.
Sample Size	A minimum of 204 randomized patients are required to sufficiently power the primary endpoint. To account for attrition, approximately 230 patients will be randomized.
Number of Sites	Up to 30 sites
Primary Endpoint	The primary endpoint is a comparison of 1-year mean change from baseline in ODI between the Treatment and Control groups.
Secondary Endpoints	1. Comparison of 1-year change from baseline in LBP NRS between Treatment and Control 2. Comparison of 1-year change from baseline in EQ-5D between Treatment and Control
Tertiary Endpoints	1. Comparison of Percent Pain Relief at 1 year between Treatment and Control 2. Comparison of Subject Global Impression of Change at 1 year between Treatment and Control 3. Comparison of Treatment Satisfaction at 1 year between Treatment and Control 4. Comparison at 1 year of the percent of patients with a change in ODI ≥ 15 or reduction in NRS ≥ 50% (and no decrease in either measure) between Treatment and Control 5. Comparison at 1 year in the change from baseline in Leg Pain NRS between Treatment and Control
Additional Supporting Analyses	1. Comparison between Treatment and Control in the of responder rate in ODI at 1 year, where a change ≥15 points is considered a responder 2. Comparison between Treatment and Control in the cumulative proportion of responder rate in ODI at 1 year 3. Comparison between Treatment and Control in the of responder rate in NRS at 1 year, where a change ≥50% is considered a responder 4. Comparison between Treatment and Control in the cumulative proportion of responder rate in NRS at 1 year 5. Within group changes in all analyses will be assessed at 2 years 6. Cost-effectiveness assessment including: • Change in work status, work-days missed and ability to do their work at 1 and 2 years compared to baseline • Health care utilization (office visits, hospital visits, emergency room visits, and other therapies such as physical therapy) at 1 and 2 years compared to baseline 7. Activity monitoring, including the number of steps and amount of sleep, will be collected on a subset of patients and assessed through 2 years compared to baseline 8. Additional ad hoc analyses may also be conducted

Adverse Events	Adverse events related to the system, procedure, or therapy, and all serious adverse events will be reported from enrollment through study exit and will be summarized.
Study Duration	Approximately 4 years from first enrollment to the last 2-year visit
Study Schedule	The study visit schedule will vary slightly between the groups to account for the Treatment group bring implanted after the randomization visit. After the 1-year visit, patients in the Control group may elect to be implanted with the ReActiv8 device and will continue to be followed through the 2-year visit. Patients in the Control group who do not receive a device after the 1-year visit will be exited from the study at that time. For the Treatment group, visit timing for all visits will be based on Activation. For the Control group visit timing will be Randomization for visits through the 1-year visit. After those in the Control group are implanted, the remaining visit timing will be based off their Activation visit.

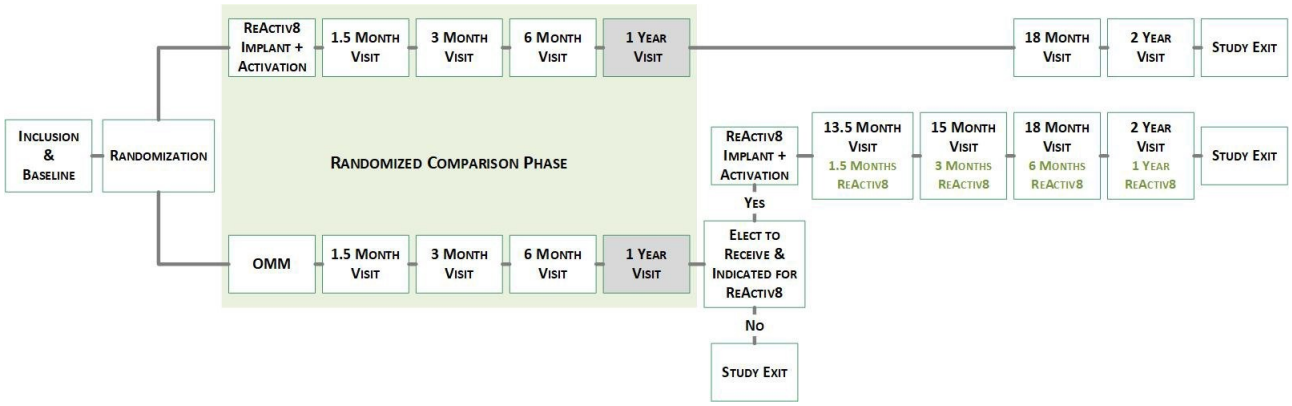


Figure 2: Study Schema

Eligibility Criteria

Inclusion Criteria

1. Indicated for the ReActiv8 System
   - Age ≥21 years
   - Evidence of lumbar multifidus muscle dysfunction
   - Intractable Chronic Low Back Pain that has persisted >6 months prior to enrollment, resulting in pain most of the days in the 12 months prior to enrollment
   - Failed therapy including pain medications and physical therapy
   - Not a candidate for spine surgery
2. Low Back Pain NRS of ≥6 and ≤9
3. Oswestry Disability Index score ≥30 and ≤60
4. Willing and capable of giving Informed Consent
5. Able to comply with this protocol
6. On Optimal Medical Management per the Investigator

Eligibility Criteria

Exclusion Criteria

1. Contraindicated for the ReActiv8 System
   - Unable to operate the ReActiv8 System
   - Unsuitable for ReActiv8 implant surgery
2. BMI > 35
3. 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. An independent MRI assessment identifying a pathology that is likely the cause of the CLBP and is amenable to surgery
4. Leg pain described as being worse than back pain, or radiculopathy (neuropathic pain) below the knee
5. Surgical or other procedures exclusions:
   a. Any previous back surgery (e.g., laminectomy, discectomy, spinal fusion) at or below segmental level T8
   b. Any previous thoracic or lumbar sympathectomy
   c. Any lumbar rhizotomies within the past 12 months
   d. Any lumbar nerve blocks within the past 30 days
   e. Any previous or existing neuromodulation devices (e.g., drug pump, spinal cord stimulation, and/or peripheral nerve stimulation)
6. Other clinical conditions:
   a. Pregnant or planning to be pregnant in the next 12 months
   b. Any condition unrelated to CLBP such as muscle wasting, muscle atrophy, or progressive neurological disease which, in the opinion of the Investigator, could limit physical movement or compliance with the protocol, or interfere with the assessment of efficacy
   c. 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 the Investigator in consultation with a psychologist or psychiatrist as appropriate
   d. An opioid addiction or drug-seeking behavior, as determined by the Investigator
   e. Any active malignant disease
   f. Any active infection in the vicinity of the implant site or any systemic infection
   g. Poorly controlled diabetes (Type I or Type II) determined by HbA1c >8
7. General exclusions:
   a. Current smoker
   b. Current or planned participation in any other clinical trial during the study
   c. A condition currently requiring or likely to require use of MRI or diathermy
   d. Life expectancy less than one year
   e. A pending or approved financial compensation claim (e.g., worker's compensation claim, long term disability claims, injury claim under litigation)

2. ReActiv8 Therapy

2.1. Summary of ReActiv8

ReActiv8 is an implantable electrical stimulation system consisting of the following components:

1. Implantable Pulse Generator (IPG) – (pre-loaded with IPG Firmware Code and packaged with a Torque Wrench to aid in implant procedure)
2. Percutaneous Leads (with Stylet and Suture Sleeves)
3. Application Software
4. Programmer Wand
5. Activator (pre-loaded with Activator Firmware Code)
6. Magnet
7. Tunneler

The ReActiv8 Programmer Wand and Application Software are provided with a commercially available laptop computer and AC adapter. Commercially available surgical tools such as a 7Fr Introducer Kit is used at implant and is not part of ReActiv8.

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 via Application Software stored on a laptop computer. 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 set facing forward and one set facing backwards. The tines are positioned to lie on either side of the intertransversarii lateralis, thus reducing the risk of lead migration by either advancement or retraction. The lead body is a polyurethane tube containing the lead conductor, incorporating a lumen to allow passage of a stylet. Refer to the Implant and Programming Manual (990070-001) for more detail on device specifications and operation.

2.1.1. Implantable Components of ReActiv8

The ReActiv8 IPG, and the two sizes of leads (45 cm and 65 cm) are designed for permanent implant. The implantable components of ReActiv8 are supplied sterile and are intended for single use only.

- Model 5100 ReActv8 Implantable Pulse Generator
- Model 8145 ReActiv8 Percutaneous Lead, 45 cm length
- Model 8165 ReActiv8 Percutaneous Lead, 65 cm length

2.1.2. Non-Implantable Components of ReActiv8

The Torque Wrench and Stylet are provided to facilitate implantation of the IPG and leads. The Application Software and Programmer Wand are used with a laptop computer 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).

The non-implantable components of the ReActiv8 system are:

- Model 7000 ReActiv8 Activator
- Model 4000 ReActiv8 Magnet
- Model 5500 ReActiv8 Torque Wrench
- Version 1.0.1.6 (English) and 1.0.1.9 (Multilanguage) Application Software
- Model 6000 Programmer Wand
- Model TUN1 Tunneler

The ReActiv8 Programmer Wand and Application Software are provided with a commercially available laptop computer and AC adapter.

2.2. Indications for Use

The ReActiv8 System is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery.

2.3. Surgical Implantation and Device Activation

The surgical implantation procedure, device programming, and use by the patient are per the Implant and Programming Manual (990070-001) and the User Manual (990071-001).

2.4. Physician and Health Care Personnel Training

All physicians who will implant any portion of the ReActiv8 system must have participated in product training.

3. Study Design

The ReActiv8 Stimulation Therapy vs Optimal Medical Management: A Randomized Evaluation (RESTORE) study is a prospective, randomized study comparing ReActiv8 therapy to Optimal Medical Management (OMM). Patients meeting all eligibility criteria will be randomized to either the Treatment group (ReActiv8) or the Control group (OMM). Randomization will be performed according to a random permuted block design stratified by clinical site with a 1:1 allocation ratio.

The primary endpoint will be a comparison of the change in Oswestry Disability Index (ODI) at 1 year between the Treatment and Control groups. After 1-year visit, all patients in the Control group may elect to receive a ReActiv8 device and will continue to be followed through the 2-year visit. Patients in the Control group who do not receive a device after the 1-year visit will be exited from the study at that time.

A minimum of 204 evaluable patients is required to sufficiently power the primary endpoint. To allow for attrition, approximately 230 patients will be randomized at up to 30 clinical sites. To account for screen failures prior to randomization approximately 400 patients may be enrolled.

The study visit schedule will vary slightly between the groups to allow for those in the Treatment group to be implanted after the randomization visit. After the 1-year visit, patients in the Control group may elect to be implanted. The study schema is provided in Figure 3.

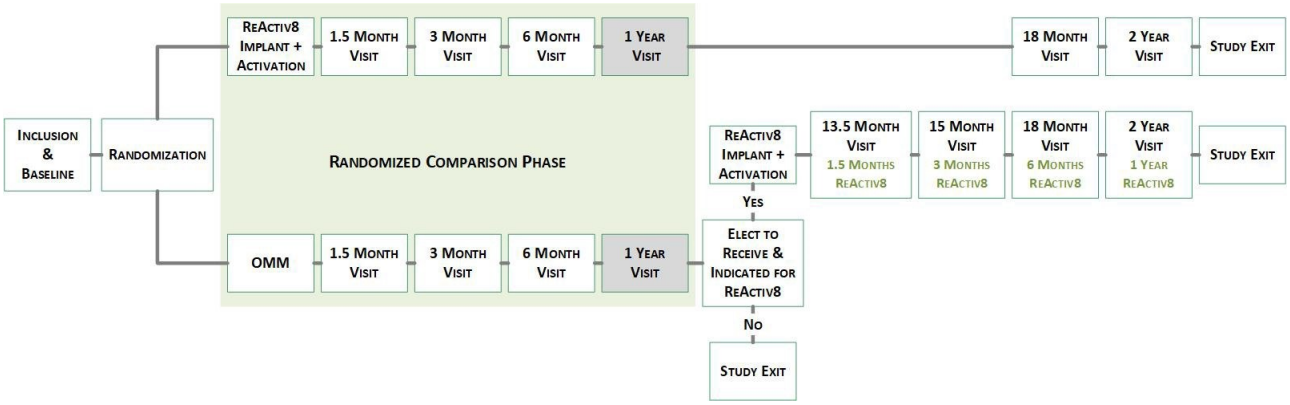


Figure 3: Study Schema

Total study duration is anticipated to be approximately 4 years from first enrollment to the last 2-year visit.

3.1. Endpoints

3.1.1. Primary Efficacy Endpoint

3.1.1.1. 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. Fairbank, et al., suggest a minimally important change is 15 points.[101]

Hypothesis Test

The Primary endpoint is a comparison between the Treatment group and Control group of average change in ODI at 1 year compared to baseline.

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

H_0: $\mu ODI_T - \mu ODI_C \geq 0$
H_A: $\mu ODI_T - \mu ODI_C < 0$

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 1-year visit. These hypotheses will be tested using the 1-year treatment effects contrast obtained from a mixed model for repeated measures (MMRM). The two-sided p-value for the equality null hypothesis will be reported as well as the two-sided adjusted 95% confidence interval for the difference in mean changes. Superiority will only be claimed if $p<0.05$ and the mean change is more negative (greater improvement) for the Treatment group compared to the Control group. This is equivalent to specifying a one-sided test at $\alpha=0.025$.

3.1.1.2. Sample Size Rationale

The sample size for the study is determined under the following assumptions for the primary efficacy endpoint, which are based on a prior study of ReActiv8[102], and approximately the MMRM test by its corresponding unadjusted t-test. All else being equal, this is a conservative estimate of power since control for baseline and inclusion of intermediate time points is not accounted for.

- Minimum power of 80%
- Type I error of 5%
- Assumed mean change in Treatment group: 18.2
- Assumed mean change in Control group: 12.2
- Pooled Standard Deviation: 15

Under the above assumptions, a minimum of 204 evaluable patients is required in order to demonstrate superiority of the ReActiv8 treatment. To account for attrition, approximately 230 patients will be enrolled and randomized.

3.1.2. Secondary Efficacy Endpoints

The same MMRM will be applied to NRS and EQ-5D. To control type 1 error, the p-values for superiority at 1 year will only be interpreted as inferential if the superiority for improvements in Year 1 ODI is demonstrated at 2-sided type 1 error rate of α=0.05 (with hypothesized directionality). The Hochberg method (Hochberg 1988[103]) will be used to control type 1 error among these two secondary endpoints.

3.1.2.1. Low Back Pain NRS

Average Low Back Pain will be measured using the 11-point Numerical Rating Scale for Low Back Pain (Figure 4), as recommended by IMMPACT.[40] Specifically, the NRS scale for "average low back pain in the last 24 hours" will be used.

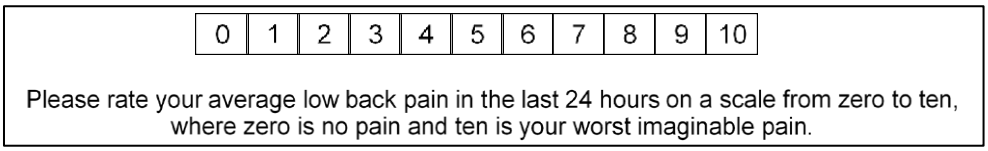


Figure 4: 11-Point Numerical Rating Scale for Low Back Pain

The endpoint will compare change from baseline in NRS between Treatment and Control groups at the 1-year visit.

Hypothesis Test

The NRS objective will be assessed by the following hypotheses:

H_0: $\mu NRS_T - \mu NRS_C \geq 0$
H_A: $\mu NRS_T - \mu NRS_C < 0$,

where μNRS_T is the mean change in NRS from baseline to 1 year in the Treatment group and μNRS_C is the mean change in NRS from baseline to 1 year in the Control group. These hypotheses will be tested using 1-year contrast from an MMRM as described above.

3.1.2.2. EQ-5D

The EQ-5D-5L (referred to as EQ-5D throughout this document) is a quality-of-life questionnaire comprising of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

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. An EQ-5D index score of <0 is possible in some circumstances.

The endpoint will compare change from baseline in EQ-5D between Treatment and Control groups at the 1-year visit.

Hypothesis Test

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

H_0: $\mu EQ5D_T - \mu EQ5D_C \leq 0$
H_A: $\mu EQ5D_T - \mu EQ5D_C > 0$

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. These hypotheses will be tested using 1-year contrast from an MMRM as described above.

3.1.3. Tertiary Endpoints

3.1.3.1. Percent Pain Relief (PPR)

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

The endpoint will compare PPR at the 1-year visit between Treatment and Control groups in descriptive analyses.

3.1.3.2. Subject Global Impression of Change (SGIC)

Subject Global Impression of Change (SGIC) is based on the "Subject Global Impression of Change" as described by Farrar.[65] The patient is presented with a questionnaire with 7 choices, as shown in Figure 5.

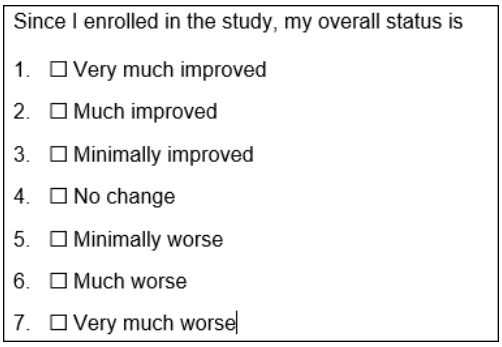


Figure 5: Subject Global Impression of Change (SGIC) Questionnaire

The endpoint will compare SGIC at the 1-year visit between Treatment and Control groups in descriptive analyses.

3.1.3.3. Treatment Satisfaction

Treatment satisfaction will be measured by a single question as shown in Figure 6.

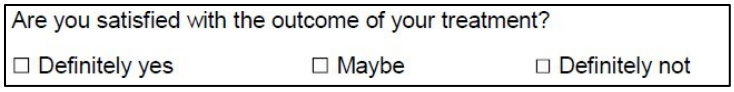


Figure 6: Treatment Satisfaction Question

The endpoint will compare Treatment Satisfaction at the 1-year visit between Treatment and Control groups.

3.1.3.4. ODI and NRS Composite

Patients suffering from CLBP are continuously balancing their activity level with their level of pain. As their condition improves, patients make personal choices on whether to increase their level of activity while tolerating a certain level of pain, or to continue with the same level of activity as earlier but with less discomfort, or somewhere in between. These choices are based on the

patients' individual circumstances and preferences. Therefore, when evaluating a therapy for CLBP, an evaluation of improvements in pain interpreted in conjunction with functional improvements allows for a more comprehensive assessment of the therapy.

This endpoint will compare the percent of patients with a change in ODI ≥ 15 or a reduction in NRS ≥ 50% (and no decrease in either measure) at the 1-year visit between Treatment and Control groups.

3.1.3.5. Leg Pain NRS

Average Leg Pain will be measured using an 11-point Numerical Rating Scale for Leg Pain. The patient will rate his/her average leg pain in the last 24 hours on a scale from zero to ten, where zero is no pain and ten is the worst imaginable pain

The endpoint will compare change from baseline in Leg Pain NRS between Treatment and Control groups at the 1-year visit.

3.1.4. Safety Assessment

Reportable adverse events (AEs) are those related to the device, procedure, stimulation or other therapies utilized to treat LBP, and all serious adverse events (SAEs), whether related or not.

All reportable AEs will be documented and reported from the time of informed consent through the end of the study with summary statistics presented for observed rates. No formal statistical hypotheses will be tested in the safety assessment. The following definitions are used:

Adverse Event (AE):
An AE is defined as any undesirable clinical occurrence that affects the health or safety of the patient.

Serious Adverse Event (SAE):
An SAE is defined as an AE that led to death, or led to serious deterioration in the health of the patient, 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.

Unanticipated Adverse Device Effect (UADE):
A UADE 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 protocol or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Adverse Event Relatedness:

The Investigator must determine whether the event was related to the device, stimulation, procedure, and/or other therapies. The categories used for relatedness are listed in Table 2.

Table 2: Adverse Event Relatedness Categories

Related to Device	Events reasonably anticipated to be related to the physical presence of the device (e.g., lead fracture requiring revision).
Related to Stimulation	Events reasonably anticipated to be related to 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 the implant procedure.
Related to Other Therapies	Events reasonably anticipated to be related to treatments being utilized to treat the patient's LBP (e.g., medications, injections, physical therapy).

AE Notes:

1. AEs that would be reasonably expected to be associated with any surgical procedure and are not specific to the ReActiv8 procedure (e.g., anesthesia associated nausea, transient post-op surgical site pain) will not be collected.
2. If an AE leads to multiple outcomes that sequentially worsen, only the worst AE is reported. For example, a hematoma leading to infection is reported as a single AE for the infection.
3. 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.
4. Removing, suspending or stopping use of ReActiv8 due to pain relieved is not an AE.
5. Planned hospitalization for a procedure required by this protocol is not an AE.
6. Symptoms felt during a programming session are not considered AEs unless they are caused by the final programming parameters and persist after the programming session.
7. 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, it is not considered an AE.
8. Removal or replacement of any part of the device due to malfunction would be considered a device related AE, since it requires the patient to undergo a surgical procedure.
9. Death should not be recorded as a separate AE, but rather as an outcome of the specific SAE which led to the patient's death.

3.1.5. Supporting Analyses

The supporting efficacy analyses will include:

- Comparison between the Treatment and Control groups in the of responder rate in ODI at the 1-year visit, where a change ≥15 points is considered a responder
- Comparison between the Treatment and Control groups in the cumulative proportion of responder rate in ODI at the 1-year visit
- Comparison between the Treatment and Control groups in the of responder rate in NRS at the 1-year visit, where a change ≥50% is considered a responder
- Comparison between the Treatment and Control groups in the cumulative proportion of responder rate in NRS at the 1-year visit
- Within group changes in all analyses will also be assessed at the 2-year visit

- Endpoints will be further analyzed by baseline EQ-5D index score
- Health economic outcome measures at the 1- and 2-year visits will be compared to baseline
- Activity monitoring will be collected on a subset of patients and assessed through the 2-year visit and compared to baseline
- Additional ad hoc analyses may also be conducted

3.1.6. Health Economics

Health economic outcome measures to be recorded will include:

- Work status, work-days missed and ability to do their work the year prior to baseline, and at the 1- and 2-year visits
- Health care utilization (office visits, hospital visits, emergency room visits, and other therapies such as physical therapy) the year prior to baseline and at the 1- and 2-year visits

3.1.7. Activity Data Collection

Activity data will be collected on a subset of patients who:

- have an activity tracker that they have used regularly for at least three months,
- agree to wear the activity tracker for the duration of the study, and
- agree to have activity data transmitted to be saved in the database.

After signing consent and meeting enrollment criteria, activity data from at least 2 weeks prior to enrollment will be downloaded. Activity data will be collected continuously while the patient is wearing the activity tracker and downloaded periodically by the patient. To help ensure complete data are obtained, a download of the data will also occur at each study visit.

The time period from Baseline through Activation will serve as the Baseline assessment of activity, with the following exceptions:

- Patients in the Treatment group would be expected to be moving less during the healing process post-procedure; therefore, activity data will be excluded between the Implant and Activation visits (approximately 2 weeks).
- Patients in the Control group will have the 2-week time period prior to Activation excluded to align with the timeframe excluded for the Treatment group.

Activity data to be collected include:

- Distance and Number of Steps
- Stationary Time
- Sleep Data

3.2. Study Visits and Data Collection Schedule

The study visit schedule is provided in Table 3. The study visit schedule will vary slightly between the groups to account for the Treatment group being implanted after the randomization visit. For the Treatment group, visit timing for all visits will be based on Activation. For the Control group visit timing through the 1-year visit will be based on Randomization. After those in the Control group are implanted, the timing of the remaining visits will be based on the Activation visit.

Table 3: Visit Schedule with Recommended Visit Windows

Visit	Treatment	Control
Informed consent, baseline	✓	✓
Randomization (Approx. 14 days post baseline)	✓	✓
ReActiv8 implant (Approx. 14 days post randomization)	✓	
Activation (Approx. 14 days post implant)	✓	
1.5-month (45 ± 14 days)	✓	✓
3-month (90 ± 30 days)	✓	✓
6-month (180 ± 30 days)	✓	✓
1-year (365 ± 60 days)	✓	✓
ReActiv8 implant (within 60 days of the 1-year visit)		✓
Activation (Approx. 14 days post implant)		✓
13.5-month (410 ± 14 days)		✓
15-month (450 ± 30 days)		✓
18-month (540 ± 30 days)	✓	✓
2-year (730 ± 60 days)	✓	✓

A summary of the data collection schedule is shown for the Treatment group in Table 4 and for the Control group in Table 5.

Table 4: Summary Data Collection Schedule – Treatment Group

	Informed Consent & Baseline	Randomization	ReActiv8 Implant & Activation	1.5 Month Visit	3-Month Visit	6-Month Visit	1-Year Visit	18-Month Visit	2-Year Visit	Unscheduled Visit
Screening Data & Physical Exam	✓									
MRI	✓									
Multifidus Dysfunction Assessment	✓									
$DASS_{21}$	✓									
ODI	✓			✓	✓	✓	✓	✓	✓	
Low Back Pain NRS	✓			✓	✓	✓	✓	✓	✓	
EQ-5D	✓			✓	✓	✓	✓	✓	✓	
Low Back Pain Description	✓			✓	✓	✓	✓	✓	✓	
Leg Pain Description and NRS	✓			✓	✓	✓	✓	✓	✓	
Percent Pain Relief				✓	✓	✓	✓	✓	✓	
SGIC				✓	✓	✓	✓	✓	✓	
Treatment Satisfaction				✓	✓	✓	✓	✓	✓	
Health Care Utilization	✓						✓		✓	
Work Status Evaluation	✓						✓		✓	
Activity Data Download (if applicable)	✓		✓	✓	✓	✓	✓	✓	✓	
Pain Treatments Log	✓			✓	✓	✓	✓	✓	✓	✓
Related AEs & All SAEs			✓	✓	✓	✓	✓	✓	✓	✓
Device Measurements Download			✓	✓	✓	✓	✓	✓	✓	✓

Table 5: Summary Data Collection Schedule – Control Group

	Informed Consent & Baseline	Randomization	1.5 Month Visit	3-Month Visit	6-Month Visit	1-Year Visit	ReActiv8 Implant & Activation	13.5 Month Visit	15-Month Visit	18-Month Visit	2-Year Visit	Unscheduled Visit
Screening Data & Physical Exam	✓											
MRI	✓											
Multifidus Dysfunction Assessment	✓											
$DASS_{21}$	✓											
ODI	✓		✓	✓	✓	✓				✓	✓	
Low Back Pain NRS	✓		✓	✓	✓	✓				✓	✓	
EQ-5D	✓		✓	✓	✓	✓				✓	✓	
Low Back Pain Description	✓		✓	✓	✓	✓				✓	✓	
Leg Pain Description and NRS	✓		✓	✓	✓	✓				✓	✓	
Percent Pain Relief			✓	✓	✓	✓				✓	✓	
SGIC			✓	✓	✓	✓				✓	✓	
Treatment Satisfaction			✓	✓	✓	✓				✓	✓	
Health Care Utilization	✓					✓					✓	
Work Status Evaluation	✓					✓					✓	
Activity Data Download (if applicable)	✓		✓	✓	✓	✓	✓			✓	✓	
Pain Treatments Log	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓
Related AEs & All SAEs			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Device Measurements Download							✓	✓	✓	✓	✓	✓

3.3. Patient Selection

3.3.1. Inclusion Criteria

1. Indicated for the ReActiv8 System
   - Age ≥21 years
   - Evidence of lumbar multifidus muscle dysfunction
   - Intractable Chronic Low Back Pain that has persisted >6 months prior to enrollment, resulting in pain most of the days in the 12 months prior to enrollment
   - Failed therapy including pain medications and physical therapy
   - Not a candidate for spine surgery
2. Low Back Pain NRS of ≥6 and ≤9
3. Oswestry Disability Index score ≥30 and ≤60
4. Willing and capable of giving Informed Consent.
5. Able to comply with this protocol
6. On Optimal Medical Management per the Investigator

3.3.2. Exclusion Criteria

1. Contraindicated for the ReActiv8 System
   - Unable to operate the ReActiv8 System
   - Unsuitable for ReActiv8 implant surgery
2. BMI > 35
3. 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. An independent MRI assessment identifying a pathology that is likely the cause of the CLBP and is amenable to surgery
4. Leg pain described as being worse than back pain, or radiculopathy (neuropathic pain) below the knee
5. Surgical or other procedures exclusions:
   a. Any previous back surgery (e.g., laminectomy, discectomy, spinal fusion) at or below segmental level T8
   b. Any previous thoracic or lumbar sympathectomy
   c. Any lumbar rhizotomies within the past 12 months
   d. Any lumbar nerve blocks within the past 30 days
   e. Any previous or existing neuromodulation devices (e.g., drug pump, spinal cord stimulation, and/or peripheral nerve stimulation)
6. Other clinical conditions:
   a. Pregnant or planning to be pregnant in the next 12 months
   b. Any condition unrelated to CLBP such as muscle wasting, muscle atrophy, or progressive neurological disease which, in the opinion of the Investigator, could limit physical movement or compliance with the protocol, or interfere with the assessment of efficacy

c. 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 the Investigator in consultation with a psychologist or psychiatrist, as appropriate
d. An opioid addiction or drug-seeking behavior, as determined by the Investigator
e. Any active malignant disease
f. Any active infection in the vicinity of the implant site or any systemic infection
g. Poorly controlled diabetes (Type I or Type II) determined by HbA1c >8

7. General exclusions:
   a. Current smoker
   b. Current or planned participation in any other clinical trial during the study
   c. A condition currently requiring or likely to require use of MRI or diathermy
   d. Life expectancy less than one year
   e. A pending or approved financial compensation claim (e.g., worker's compensation claim, long term disability claims, injury claim under litigation)

4. Study Therapies

4.1. ReActiv8 Stimulation

Patients will be instructed to deliver stimulation for 60 minutes per day up to the 1-year visit, 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 1-year visit, patients 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.

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

4.2. Other Therapy During the Study

Other therapy during the study should be managed per the OMM plan developed using the RESTORE Treatment Guidelines document (980016), to the extent possible. Any therapy changes during the study should be managed through the study Investigator. If other therapies (e.g., medications, physical therapy) are being managed by another provider, it will be important for the study Investigator to be in contact with the patient's provider throughout the study.

5. Study Visits

Timing of visits and recommended visit windows are shown in Table 3. The visit windows are intended to provide guidance on timing of visits. A deviation will not be required if the visit is early or late, but will be required if the visit is missed. To avoid introduction of bias, all patient reported endpoint data will be collected before any other intervention or interview during the follow up visit. Programming the ReActiv8 and data collection via the Programmer will be performed by the Sponsor under Investigator direction and guidance.

5.1. Informed Consent, Baseline Data, Inclusion Decision

The process for obtaining informed consent shall comply with the Declaration of Helsinki, Good Clinical Practice (GCP) and IRB requirements. Patients will be provided with the Informed Consent Form which advises that data will be collected for evaluation of eligibility for inclusion in the study. If the patient agrees to inclusion for data collection, the Informed Consent will be signed and recorded in the patient's records. The patient will then be assigned a unique study identifier.

Data to be collected:

- Screening data as required by the enrollment criteria
- Treatment Plan Worksheet per the RESTORE Treatment Guidelines document (980016)
- Medical History (including Physical Exam)
  - Baseline demographics
  - Comorbid conditions
  - Characteristics of the patient's LBP such as diagnosis, duration, and number of episodes of LBP
- Depression Anxiety Stress Scale ($DASS_{21}$)
- ODI
- LBP NRS
- EQ-5D
- Leg pain description and NRS
- Work status evaluation
- Healthcare utilization
- Pain treatments
- Download activity monitoring data (if applicable)

Activities to be performed:

- Answer any questions the patient may have and confirm willingness to proceed if the baseline criteria are verified
- Verify that the enrollment 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 1 year prior to enrollment. If an MRI is being performed for the purposes of this study, please follow the recommended settings (Appendix 1).
- MRI images will be reviewed to assess conditions that may be a possible cause of low back pain and to rule out possible surgical candidates by institutional guidelines
- Multifidus dysfunction assessment (e.g., Prone Instability Test, Lift test)
- Pregnancy test in women of child-bearing potential
- Assessment by the Investigator of the patient's suitability for ReActiv8 implant

5.1.1. Eligibility Assessment

In addition to the Site Principal Investigator (PI) assessment of eligibility, an Independent MRI Assessment, and a Study PI Review will also be completed to determine eligibility.

5.1.1.1. Independent MRI Assessment

If the site determines that the patient is not excluded based on the MRI assessment, the site will upload images for further review. An appropriately trained independent physician will review the patient's MRI to assess any current indication for back surgery according to appropriate evidence as summarized in the MRI Assessment Guidelines document (980017).

5.1.1.2. Study Physician Advisor Review

A Study Physician Advisor will review baseline data for all patients to confirm that the patient meets the eligibility criteria for the study. This review will take place prior to randomization and will be communicated to the Site PI and study staff.

5.2. Randomization

If the patient meets the enrollment criteria, the patient should be randomized approximately 14 days after the baseline data have been collected. For those randomized to the Treatment group, schedule the surgery for the ReActiv8 implant.

5.3. Implant Procedure (Treatment Group)

The implant procedure should take place approximately 14 days following randomization. The implant procedure, including pre- and post-implant care, will follow the ReActiv8 Implant and Programming Manual (990070-001), and institutional guidelines.

Data to be collected:

- Device information (e.g., serial numbers, implant location, procedure duration)
- Related AEs and all SAEs

5.4. Activation (Treatment Group)

Data to be collected:

- Related AEs and all SAEs

Activities to be performed:

- Inspect surgical wound to verify healing and remove sutures (if not previously removed)
- Perform electrode impedance and threshold measurements and program the IPG
- Device download
- Train in use of the Activator and document assessment of patient'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 positioning
- Download activity monitoring data (if applicable)

5.5. 1.5-Month Visit

Data to be collected:

- ODI
- LBP NRS
- EQ-5D
- Percent Pain Relief
- SGIC
- Treatment Satisfaction
- Low back pain description
- Leg Pain Description and NRS
- Pain treatments
- Related AEs and all SAEs
- Download activity monitoring data (if applicable)

For patients in the Treatment group only:

- Remind patient to continue to lie down and activate therapy twice daily
- Device download
- Adjustment of stimulation configuration as appropriate

5.6. 3- and 6-Month Visits

Data to be collected:

- ODI
- LBP NRS
- EQ-5D
- Percent Pain Relief
- SGIC
- Treatment Satisfaction
- Low back pain description
- Leg Pain Description and NRS
- Pain treatments
- Related AEs and all SAEs
- Download activity monitoring data (if applicable)

For patients in the Treatment group only:

- Remind patient to continue to lie down and activate therapy twice daily
- Device download
- Adjustment of stimulation configuration as appropriate

5.7. 1-Year, 18-Month and 2-Year Visits

At the 1-year visit patients in the Control group may elect to receive ReActiv8 therapy. Schedule the surgery for the ReActiv8 implant and discuss with the patient.

Data to be collected:

- ODI
- LBP NRS
- EQ-5D
- Percent Pain Relief
- SGIC
- Treatment Satisfaction
- Low back pain description
- Leg Pain Description and NRS
- Health care utilization (not required at the 18-month visit)
- Work Status Evaluation (not required at the 18-month visit)
- Low Back Pain descriptive characteristics (not required at the 18-month visit)
- Pain treatments
- Related AEs and all SAEs
- Download activity monitoring data (if applicable)

For patients in the Treatment group only:

- Device download
- Adjustment of stimulation configuration as appropriate

5.8. Implant (Control Group)

The implant procedure, including pre- and post-implant care, will follow the ReActiv8 Implant and Programming Manual (990070-001), and institutional guidelines.

Data to be collected:

- Device information (e.g., serial numbers, implant location, procedure duration)
- Related AEs and all SAEs

5.9. Activation (Control Group)

Data to be collected:

- Related AEs and all SAEs

Activities to be performed:

- Inspect surgical wound to verify healing and remove sutures (if not previously removed).
- Perform electrode impedance and threshold measurements and program the IPG
- Device download
- Train in use of the Activator and document assessment of patient'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 positioning
- Download activity monitoring data (if applicable)

5.10. 13.5-Month and 15-Month Visits (Control Group)

Data to be collected:

- Pain treatments
- Related AEs and all SAEs
- Download activity monitoring data (if applicable)

Activities to be performed:

- Remind patient to continue to lie down and activate therapy twice daily.
- Device download
- Adjustment of stimulation configuration as appropriate

5.11. Unscheduled Visits

If an unscheduled visit occurs for any reason, collect all related AEs and all SAEs, update pain treatments, and download device information.

5.12. Revision/Explant Procedure

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

- Device information (e.g., serial numbers, implant location, procedure duration)
- Related AEs and all SAEs

Data to be collected after an explant procedure:

- Related AEs and all SAEs will be collected over the last 30 days prior to exiting the study

6. Anticipated Benefits and Risks

6.1. Anticipated Benefits

Although there are no guaranteed benefits, based on previous studies utilizing ReActiv8 therapy, the benefits from the stimulation to be delivered by the ReActiv8 may include decrease in low back pain, decrease in disability, and improvement in quality of life. As OMM is per standard of care, there are no additional benefits associated with OMM beyond those expected with standard of care.

6.2. Anticipated Risks

All medical device treatments have the potential to cause AEs or side effects. AEs are expected to be similar to other neurostimulation devices for treatment of back pain, such as spinal cord stimulators. Risks associated with OMM are the same as would be expected with standard of care.

Additional information on risks and anticipated AEs may be found in the Implant and Programming Manual (990070-001), which also includes warnings and precautions.

6.3. Risk Minimization

Additional risks may exist. Risks can be minimized through the use of strict compliance with this protocol, and adherence to the guidelines for patient selection, site training, and close monitoring of the patient's physiologic status at follow-up visits. In addition, the product labeling (including the Implant and Programming Manual (990070-001) and the User Manual (990071-001)) details warnings and precautions which must be followed to minimize risk to patients.

6.4. Patient Deaths

A patient death during the study should be reported to the Sponsor as soon as possible. The clinical site's IRB must be notified of any deaths in accordance with that clinical site's IRB policies and procedures.

7. Data Management

The Sponsor will be responsible for collection of the data required for this study in accordance with Health Insurance Portability Accountability Act (HIPAA) and GCP. The Sponsor will use an electronic database which shall have written procedures and document requirements. Security, reliability, consistency of the data will be maintained throughout the study. Only those staff at each site that are identified and designated by the Investigator and trained will be allowed access to the database. Any questionnaires completed by the patient will be done electronically or on paper CRFs then transferred to the database by the designated study site personnel.

7.1. Adverse Event Reporting

The Investigator will monitor the occurrence of related AEs and all SAEs for each enrolled patient and will report them on the AE form. If a patient undergoes an explant procedure, the patient should remain in the study for at least 30 days post-explant to ensure that any AEs resulting from the procedure may be reported and addressed.

All Related AEs, all SAEs, and all UADEs will be reported to all Investigators and IRBs participating in the study per their reporting requirements. Interim reports and a final study report prepared by the Sponsor will provide this information.

7.2. Reporting of Device Deficiencies

Device deficiencies will be reported through the Complaint Handling system.

7.3. Management of Protocol Deviations

An Investigator is required to conduct this study in accordance with this protocol and any IRB conditions of approval. All deviations from the protocol must be reported to the Sponsor together with the reason for the deviation and possible corrective actions for the deviations. In some circumstances, the clinical site may be required to notify the clinical site's IRB.

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 patients, prior IRB approval is required.

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

7.4. Informed Consent

Informed Consent is required from all patients (or their legal representatives) prior to the patient's participation in the study. The process of obtaining Informed Consent shall comply with the Declaration of Helsinki, GCP, and IRB requirements.

The process of obtaining informed consent shall:

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

7.5. Patient 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 patient shall be preserved in reports and any publication of the results. Only authorized personnel and their designees will have access to these confidential files. Patient data may be made available to regulatory agencies, under strict confidentiality condition. Source documents should be maintained at the clinical site. The clinical sites shall ensure that data (e.g., worksheets, programmer printouts, medical records, digital images, activity monitoring data) forwarded to the Sponsor do not contain any patient identifying data (such as name and birth date) other than the patient ID.

All patients' health information will be kept confidential in accordance with all applicable laws and regulations. Patients' 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. Patient personal information received during the study will not be used to market to patients; patient names will not be placed on any mailing lists or sold to anyone for marketing purposes.

7.6. Record Keeping

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

- All correspondence with another Investigator, an IRB, the Sponsor, or a monitor, including required reports
- The signed protocol with any amendments
- The approved template of the patient informed consent form
- IRB approval of the protocol and any amendments and renewals
- The Investigators' agreement and the study agreement (separate or combined)
- The Implant and Programming Manual (990070-001) User Manual (990071-001) and any other documentation provided with the device
- Current curriculum vitae for the PI and all Sub-investigators
- Monitoring letters (if applicable)
- Interim/final reports
- Study initiation forms
- Study closure documents

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

- Signed informed consent forms
- Records of any related AE or any SAE, including supporting documentation
- Records pertaining to patient deaths during the study
- Relevant source data
- Any other records required by the Sponsor

8. Study Management

8.1. Procedures to Amend the Protocol

All amendments to the protocol 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 protocol, the local rules for approval of modifications shall be followed, including by way of example a submission to the IRB (either in full or to the Chairman), and modifications to the clinical study contract with the institution if applicable.

8.2. Data Monitoring Plan

It is the responsibility of the Sponsor to ensure proper monitoring of the study per GCP. Appropriately trained Sponsor personnel or delegates appointed by the Sponsor will perform study monitoring at the clinical site to ensure that the study is conducted in accordance with the protocol, the signed Clinical Study Agreement, and any IRB requirements. The Sponsor must therefore be allowed access to the patients' clinic and hospital records when so requested as per the consent form, Privacy Authorization and Clinical Study Agreement. A separate Monitoring Plan will detail levels of source verification for this study.

8.3. 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 study.

It is the responsibility of the Sponsor to ensure proper monitoring of the study and to see that all clinical requirements are met.

Participation in the study will be limited to Sponsor personnel who are appropriately qualified and trained on the clinical study and on appropriate clinical study regulations and guidelines for medical device studies. It is the responsibility of the Sponsor to ensure appropriate training of all individuals involved in the clinical study. This includes Investigators and other health care professionals at the clinical sites, Sponsor personnel, and contractors, if applicable.

8.4. Role of the Sponsor Representatives

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

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 protocol, and interact with the patient 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
- Observing testing or medical procedures to provide information relevant to protocol 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 patient the patient's diagnosis or recommend treatment
- Enter data into the database

8.5. Clinical Investigators

The Investigator is responsible for conducting the study in accordance with the protocol, the Declaration of Helsinki, the signed Investigator Agreement and other agreements, and any IRB conditions of approval. By agreeing to this protocol, the Investigators and their institutions accept

to allow monitoring and IRB review 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 patient consent and patient data confidentiality.

The Investigator is responsible for protecting the rights, safety, and welfare of patients under the Investigator's care. The Investigator is also responsible for ensuring that informed consent is obtained in accordance with this protocol, GCPs, and IRB requirements.

8.6. Investigator Selection

The PI shall be:

- Qualified by education, training and experience to assume responsibility for the proper conduct of the clinical study; evidence of such qualifications of the PI and key members of the clinical site team shall be provided to the Sponsor through up-to-date CVs, current GCP certification or other relevant documentation
- Experienced in the field of application and trained in the use of the study device
- Knowledgeable with the method of obtaining informed consent.

A PI and any Sub-investigator(s) must be experienced in and responsible for the following:

- Patient well-being
- Strict adherence to the protocol, which includes all testing requirements to provide for optimal safe and efficacious use of the study device
- Return of explanted devices, if applicable
- Providing the patient with comprehensive information about the study and documenting patient consent and data during the study
- Addressing medical questions which might be asked, either by the Sponsor or by the IRB, during or after the study
- Ensuring that any related AE or any SAE is reported according to Section 7.1
- Notifying the Sponsor of any deviation from the Protocol with an explanation for the deviation according to Section 7.3
- Reporting patient deaths according to Section 6.4

It is acceptable for the PI to delegate one or more of the above functions to an associate or Sub-investigator. However, the PI remains responsible for proper conduct of the study. The study is not transferable to other locations attended by the Investigator unless prior approval is obtained from the appropriate reviewing IRB and the Sponsor.

8.7. Publication Policy

Authorship of publications shall follow the recommendations of the International Committee of Medical Journal Editors[1], which may result in employees of the Sponsor being included as authors.

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

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.

8.8. Payments and Costs to Patient

The patient will not be charged for tests or procedures required only for the study, including the device and implant procedure. This includes the device and procedure for the Control group after the 1-year timepoint if they elect to receive the device at that time. The Sponsor will reimburse the clinical site and/or Investigator for their fair costs for the tests and procedures required for the study.

The Sponsor will not pay the patient or anyone else for any other medical costs (e.g., prescriptions, other therapies) related to the patient's participation in the study.

Patients will be reimbursed for reasonable transportation costs according to local institutional guidelines of up to $550 in any calendar year.

8.9. Maintaining Compliance

The study will be conducted according to GCP and the Declaration of Helsinki.

8.9.1. Study Monitoring

Monitoring will be performed during the study to ensure that compliance with the protocol and IRB requirements, and 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 the Sponsor.

8.9.2. Review of Submitted Data

In addition to the site monitoring visits the data submitted by the clinical site will be reviewed for completeness and accuracy. The clinical site personnel will be contacted regarding any missing or unclear data.

8.10. Study Completion

The Sponsor will notify each Investigator of the completion or termination of the study 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 of their data.

8.11. Suspension or Premature Termination of the Study

The procedure to be followed as a result of suspension or premature termination of the study shall be in compliance with the Sponsor's SOPs.

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 PI and Sponsor shall keep each other informed of any communication received from the IRB.

If the Sponsor decides to discontinue the study for any reason, the Sponsor will promptly inform all Investigators and IRBs along with detailed information on how enrolled patients should be managed thereafter. All patients enrolled in the study will continue to be followed according to the protocol unless the Sponsor notifies the clinical sites 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

If suspension or premature termination occurs, the Sponsor shall remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the patients enrolled in the clinical study, and the PI or authorized designee shall promptly inform the enrolled patients at his/her clinical site, if appropriate.

9. Administrative Data

9.1. Name and Address of the Sponsor

MML US Inc.
2159 India Street, Suite 200
San Diego, CA 92101

MML US Inc. is a subsidiary of

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

Sponsor's Contact:
Mainstay Medical Clinical Management

9.2. Investigators

Each clinical site shall have a Site PI. Subject to Sponsor approval, a Site PI shall delegate some or all of the patient interaction and data collection to one or more Sub-investigators or Study Coordinators.

9.3. Statements of Compliance

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

The clinical study shall not begin until the required approval or favorable opinion from the IRB.

Any additional requirements imposed by the IRB shall be followed.

Appendix 1: MRI Recommended Protocol

If an MRI is being performed for the purposes of this study, please make every effort to follow the recommended settings as noted below.

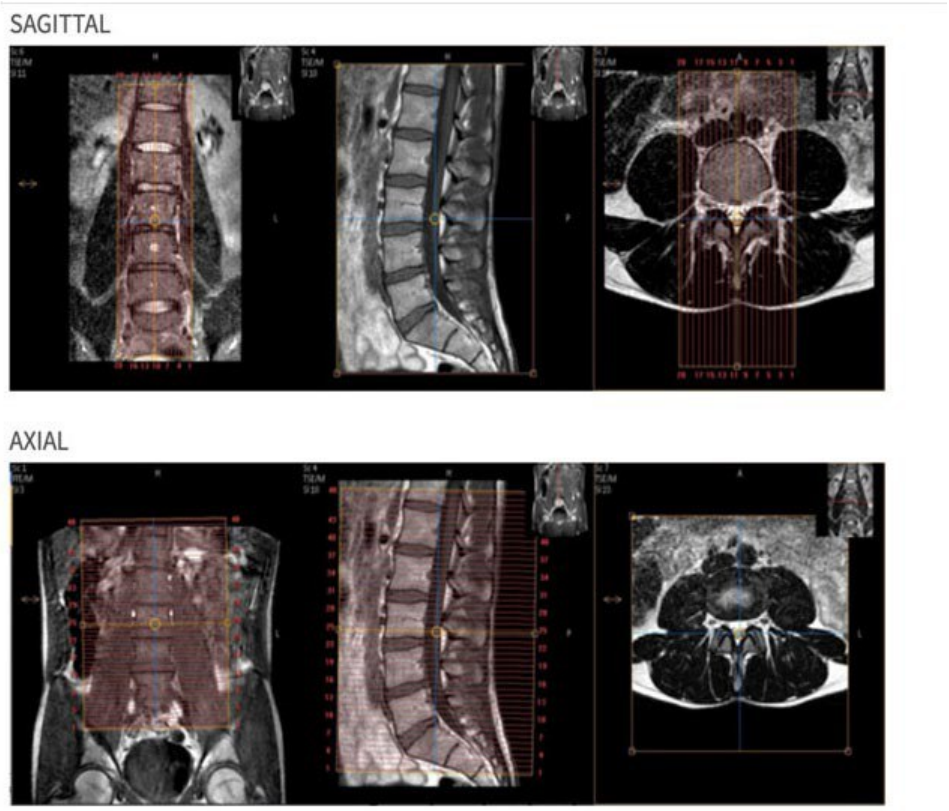
General:

- Sagittal imaging must extend through the facet joints into distal transverse processes.
- All axial imaging should be contained within one sequence. If the images need to be angled, please angle within a single axial set of images as opposed to generating multiple axial sets with different angles, preferrable perpendicular to spinal canal at L4.
- Scanner preference is standard configuration 1.5T or 3T (Preferred), **not open MRI.**
- **Axial 3D T2 is preferred (SPACE, VISTA, CUBE) with isotropic 1.0mm^3 voxels, otherwise 2D axial slices.**

Coverage:

- Sagittal images from T11-T12 through S2-S3.
- Axial imaging should cover at a minimum L1 to S1, out to the iliac crests, and posterior adipose tissues to obtain all paraspinal muscles in the image.

Plane	Weighting	Slice	Gap	Fat Sat	Notes
SAG	T2	5mm	1mm	None	Through to distal transverse processes, T12-S2 min
Axial 3D	T2	1mm^3 ISOTROPIC		None	Through to Iliac to cover paraspinal muscles, cover L1-L5 disc spaces, posterior to adipose tissue, continuous slices, perpendicular to canal at L4 if necessary. 3D T2 preferred at 1.0mm^2 (SPACE, VISTA, CUBE, etc).
Axial 2D **(only if 3D not available)**	T2	4mm	0.5mm	None	Through to Iliac to cover paraspinal muscles, cover L1-L5 disc spaces, posterior to adipose tissue, continuous slices, perpendicular to canal at L4 if necessary.
SAG	T1	5mm	1mm	None	Through to distal transverse processes, T12-S2 min
SAG	STIR	5mm	1mm	STIR	Through to distal transverse processes, T12-S2 min



MRI Order Notes:

- Standard configuration 1.5T or 3T (Preferred) scanner, **not open MRI.**
- If the images need to be angled, please angle within a single axial set of images as opposed to generating multiple axial sets with different angles, preferrable perpendicular to spinal canal at L4.

Image Sets:

- T2 SAG, 5mm Slice 1mm gap, FOV through to distal transverse processes, T12-S2 min
- T2 Axial 3D (SPACE, VISTA, CUBE, etc), $1mm^3$ ISOTROPIC, FOV through to Iliac, L1-S1 minimum, posterior to adipose tissue to cover paraspinal muscles, perpendicular to canal at L4 if necessary.
- IF NO 3D: T2 Axial 2D, 4mm Slice 0.5mm Gap. Continuous slices. FOV through to Iliac, L1-S1 minimum, posterior to adipose tissue to cover paraspinal muscles, perpendicular to canal at L4 if necessary.
- T1 SAG, 5mm Slice 1mm gap, FOV through to distal transverse processes, T12-S2 min
- STIR SAG, 5mm Slice 1mm gap, FOV through to distal transverse processes, T12-S2 min

Appendix 2: Acronyms

ACP	American College of Physicians
AE	Adverse Event
AMI	Arthrogenic Muscle Inhibition
APS	American Pain Society
BMI	Body Mass Index
CLBP	Chronic Low Back Pain
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum vitae
DASS	Depression Anxiety and Stress Scale
EQ-5D	European Quality of Life Assessment
FBSS	Failed Back Surgery Syndrome
FDA	Food and Drug Administration
FOV	Field of View
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability Accountability Act
ICMJE	International Committee of Medical Journal Editors
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
LBP	Low Back Pain
MCID	Minimal Clinical Important Difference
MIC	Minimally Important Change
MRI	Magnetic Resonance Imaging
NICE	The National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NSLBP	Non-Specific Low Back Pain
ODI	Oswestry Disability Index
OMM	Optimal Medical Management
OUD	Opioid Use Disorder
PI	Principal Investigator
PMA	Pre-Market Approval
PPR	Percent Pain Relief
QOL	Quality of Life
SAE	Serious Adverse Event
SAG	Sagittal
SCS	Spinal Cord Stimulation
SGIC	Subject Global Impression of Change
STIR	Short-IT Inversion Recovery
TENS	Transcutaneous Electrical Nerve Stimulation
UADE	Unanticipated Adverse Device Effect
US	United States

Appendix 3: Bibliography

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