ReActiv8
Post Market Surveillance Registry
(ReActiv8-C)

for the
ReActiv8 Implantable Neurostimulation System
for Chronic Low Back Pain

Sponsor

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Revision History

Rev	DCR#	Change Description	Effective Date
01	DCR-01227	Initial Release	29-OCT-2015
A	DCR-01520	Updated with performance measures, visit schedule, and system definitions from CE review with Notified Body along with other minor changes	13-APR-2016
B	DCR-01562	Updated to include the Pain Detect Questionnaire at baseline and corrected the AE's language to be consistent throughout the document. Other minor changes.	16-MAY-2016
C	DCR-01596	Updated to correct reference to SADEs on page 12 (should say AEs) and to correct error in Table 3 (Medical History not taken at 1 year – only required at baseline).	26-MAY-2016
D	DCR-01629	Updated to include a 3-month visit and to allow for enrollment of subjects before or after implant to allow for performance of the system to be collected.	07-JUN-2016
E	DCR-01710	Updated to include age restriction in the inclusion criteria	13-JUL-2016
F	DCR-02331	Revised to add the Model 8145/8165 leads to the ReActiv8 product family.	16-FEB-2017
G	DCR-04322	Allow telehealth annual follow-up visits and mailing of study questionnaires for subjects at the annual visits.	27-MAY-2020

Investigator Signature Page

Investigator Acknowledgement Signature:

I have received and reviewed this Post-Market Surveillance Registry. I will conduct the Registry as described.

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

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1. Registry Summary

Registry Purpose	To gather data on the long-term safety of ReActiv8 and identify any residual risks by reporting all Serious Adverse Device Effects as well as performance and health care utilization through two years post-implant.
Indications For Use	ReActiv8 is an adjunct to medical management of Chronic Low Back Pain for relief of pain in adults who have attempted at least medical management and physical therapy.
Registry Device	ReActiv8
Registry Design	The ReActiv8 Registry is an international, multi-center, data collection registry in Subjects who meet the CE Mark indications and are not contraindicated for ReActiv8. A minimum of 50 Subjects will be implanted at up to 25 sites. Subjects will be followed for two years post-implant, at which point they will be exited from the Registry.
Population	A minimum of 50 Subjects will be implanted at up to 25 sites.
Enrolment Criteria	Inclusion Criteria • Meet the Indications for ReActiv8 • Willing to sign the Informed Consent for the ReActiv8-C Post-Market Surveillance Registry • Age ≥ 18 years Exclusion Criteria • Contraindicated for ReActiv8
Safety, Performance, Health Utilization Measures	Safety • Assessment of all Serious Adverse Device Effects that occur through two years post-implant. Performance • Change in average low back pain from baseline to follow-up visits (NRS) • Change in Oswestry Disability Index from baseline to follow-up visits (ODI) • Change in EQ-5D from baseline to follow-up visits (EQ-5D) • Assessment of Percent Pain Relief at follow-up visits (PPR) • Assessment of Subject Global Impression of Change at follow-up visits (SGIC) • Assessment of Patient Treatment Satisfaction at follow-up visits (TSQ) Health Care Utilization • Change in work status from baseline to follow-up visits • Change in use of opioids from baseline to follow-up visits • Assessment of Health Care Utilization (office visits, hospital visits, imaging and diagnostics and other pain management treatments) at follow-up visits
Study Visit Schedule	• Visit 1: Baseline visit • Visit 2: Activation visit: Approximately 14 days post-surgery • Visit 3: 3 month visit: 90±30 days post-activation • Visit 4: 6 month visit: 180±30 days post-activation • Visit 5: 1 year visit: 1 year±60 days post-activation • Visit 6: 2 year visit: 2 year±60 days post-activation

2. Background

Mainstay Medical 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 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 (MF). The leads are coupled to a battery powered implantable pulse generator (IPG) which is activated by an external Activator and is programmed using Application Software provided on a laptop computer. 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]

ReActiv8 was investigated under an ongoing clinical trial at nine sites in Australia and Europe (ReActiv8-A). The data from the first 47 Subjects implanted with ReActiv8 in this trial served as the basis for CE Marking on 24-May-2016. A summary of the ReActiv8-A Trial can be found at http://clinicaltrials.gov/show/NCT01985230.

2.1. Chronic Low Back Pain

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] There are many publications on the epidemiology[6] of back pain including prevalence,[7,8,9] 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.[10] 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."[11] 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.[12,13]

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.[14] 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).[15] US guidelines for acute and chronic low back pain are similar to the European guidelines.[16]

Exercise therapy is frequently prescribed for NSLBP, but the effectiveness of exercise therapy for *acute* back pain is negligible.[17] Systematic reviews of the literature[18,19] 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 therapies have been tried with modest or no success, and several reviews are available.[20] Therapies include lumbar extensor strengthening exercises;[21] watchful waiting (i.e., no therapy),[22] traction therapy,[23] the McKenzie Method of exercise therapy,[24] various types of energy application including ultrasound, TENS,[25] osteopathic therapy,[26] and thermotherapy,[27] and lumbar stabilization exercises.[28]

“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)[29] 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[30] and delayed reflex response of the MF to perturbations.[31] Pain alters the magnitude of activation of deep MF during certain types of activity.[32] Ultrasound imaging evidence of reduced neural drive in back pain patients includes diminished cross sectional area with contraction,[33] reduced ability to cause a muscle thickness change on command,[34] and altered contraction patterns with changes in posture.[35]

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[36] or other surgical procedures.[37,38] 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.[39]

ReActiv8 has been designed to incorporate the principles of these prior approaches. Electrical stimulation of the medial branch of the dorsal ramus nerve that innervates the lumbar multifidus is delivered episodically (in a stimulation session of 10 seconds on 20 seconds off, for 30 minutes, twice per day).

3. ReActiv8 Therapy

3.1. Summary of ReActiv8

ReActiv8 is a CE Marked 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 for more detail on device specifications and operation.

3.1.1. Implantable Components of ReActiv8

The ReActiv8 IPG, and the two sizes of leads (45 cm and 65 cm), 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 ReActv8 Implantable Pulse Generator (“IPG”) pre-loaded with Firmware Code
- Model 8000-45 ReActiv8 Percutaneous Lead, 45 cm length (“Lead”)
- Model 8000-65 ReActiv8 Percutaneous Lead, 65 cm length (“Lead”)
- Model 8145 ReActiv8 Percutaneous Lead, 45 cm length (“Lead”)
- Model 8165 ReActiv8 Percutaneous Lead, 65 cm length (“Lead”)

3.1.2. 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 ("Activator") with Firmware Code
- Model 4000 ReActiv8 Magnet ("Magnet")
- Model 5500 Torque Wrench ("Torque Wrench")
- Version 1.0.1.6 (English) and 1.0.1.9 (Multilanguage) Application Software
- Model 6000 Programmer Wand ("Wand")
- Model TUN1 Mainstay Tunneler ("Tunneler")

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

3.2. Indications for Use

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

3.3. Contraindications

ReActiv8 is contraindicated for patients who are:

- Unable to operate the system
- Unsuitable for ReActiv8 implant surgery

3.4. Surgical Implantation and Device Activation

The surgical implantation procedure, device programming, and use by the Subject are per 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 a duty cycle of 10 seconds on and 20 seconds off, delivered for a Session of 30 minutes.

To start a Session, it is recommended that 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).

3.5. Physician and Health Care Personnel Training

All physicians who will implant any portion of the ReActiv8 system in the ReActiv8 Registry must have participated in product training. The Sponsor will document completion of training for each implanting physician.

All physicians and other health care personnel who will interact with the programming system will receive training from the Sponsor, which includes lectures and use of a programming system with a simulator. This training will also include interaction with the Activator and Magnet handled by the Subject.

4. Registry Design

4.1. Objective

To gather data on the long-term safety of ReActiv8 and identify any residual risks by reporting all Serious Adverse Device Effects as well as performance and health care utilization through two years post-implant.

4.2. Overview

The ReActiv8 Registry is an international, multi-center, data collection registry in Subjects who meet the CE Mark indications and are not contraindicated for ReActiv8. A minimum of 50 Subjects will be implanted at up to 25 sites. Subjects will be followed for two years post-implant, at which time they will be exited from the Registry. Subjects may decide to be enrolled in the registry before or after implant so that information on the performance of the system can be collected.

4.3. Enrolment Criteria

4.3.1. Inclusion Criteria

In order to be included in this Registry, Subjects must meet the following inclusion criteria:

1. Meet the Indications for ReActiv8
2. Willing to sign the Informed Consent for the ReActiv8-C Post-Market Surveillance Registry
3. Age ≥ 18 years

4.3.2. Exclusion Criteria

Subjects will be excluded from the Registry if they are contraindicated for ReActiv8.

4.4. Safety Reporting

4.4.1. Adverse Events

All adverse events will be collected during this registry. Safety definitions used during this Registry will be per the definitions in ISO 14155 and are provided in Table 1 and Table 2.

Table 1: Safety Reporting Definitions

Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device NOTE For users or other persons, this definition is restricted to events related to the study device.
Adverse Device Effect	Adverse event related to the use of the study device NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use,

	deployment, implantation, installation, or operation, or any malfunction of the study device. NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the study device.
Serious Adverse Event	Adverse event that a) led to death, b) 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, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
Serious Adverse Device Effect	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious 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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE Device deficiencies include malfunctions, use errors, and inadequate labelling.

For all AEs the Investigator must determine whether the event was related to the device and/or procedure. 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 2.

Table 2: Adverse Event Relatedness Categories

Related to Device	
Related to Device Hardware	Events reasonably anticipated to be related to the physical presence of the device, e.g. erosion, or a device malfunction, e.g. 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	
Related to Procedure	Events reasonably anticipated to be related to procedures described in the labeling.

4.4.2. Unavoidable Events

Adverse Events that would be reasonably expected to be associated with any surgical procedure will not be categorized as procedure or device related in the 30 days after a surgical procedure (e.g.: device implant, explant, or revision). These may include the following:

- Anesthesia related nausea/vomiting within 24 hours
- Low-grade fever within 48 hours
- Incisional pain within 72 hours
- Mild to moderate bruising/ecchymosis of surgical sites within 72 hours
- Sleep problems within 72 hours
- Muscle pain related to lying on table within 72 hours
- Mild swelling and/or drainage from incision within 48 hours
- Numbness medial to incisions that occur immediately post-procedure
- Pain/irritation/minor bleeding during removal of sutures
- Urinary retention immediately post-procedure with removal of the Foley catheter
- Constipation and/or dehydration that may occur within 72 hours

4.4.3. Reporting by the Investigator

The Investigator shall report to the Sponsor all AEs The sites are obliged to forward as soon as possible, in a follow-up report, any AE-related information (e.g. outcome) that may have been missing at the time of the initial report as the event is recorded at the site.

4.4.4. Reporting by the Sponsor

All SADEs reported in the Registry will be reported to the Notified Body on an annual basis.

SADEs that meet the criteria of an Incident per MEDDEV 2.12/1 (Revision 8) shall be reported as part of Vigilance reporting to the relevant competent authority and to the Notified Body. Vigilance reportable events will be reviewed for reporting requirements in other applicable geographies outside of the European Union.

4.5. Performance Measures

Documentation of performance of ReActiv8 is by reporting on the measures summarized below.

4.5.1. Low Back Pain – NRS

Average Low Back Pain will be measured using the 11-point Numerical Rating Scale for Low Back Pain (Figure 1), as recommended by IMMPACT.[40] Specifically, the NRS scale for “average low back pain in the last 24 hours” will be used.

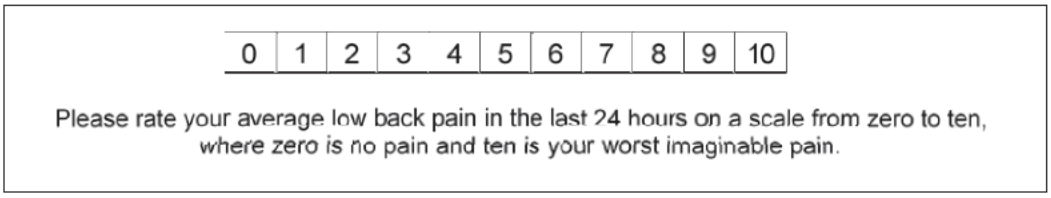

Figure 1: 11 Point Numerical Rating Scale for Low Back Pain

4.5.2. Disability – ODI

Disability is measured using the Oswestry Disability Index (ODI). ODI is a disease specific assessment of the disabling effects of back pain utilizing a questionnaire consisting of 10 sections: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life (if applicable), social life, and travelling. Each section consists of six statements correlating to scores of 0 through 5, with the Subject choosing the statement that matches his or her ability. The statement correlating with a score of 0 indicates the least disability, and the statement correlating to 5 represents the greatest disability. Scores from 0% to 20% indicate minimal disability; 21% to 40%, moderate disability; 41% to 60%, severe disability; 61% to 80%, crippled; and 81% to 100%, bedbound or exaggerating.

4.5.3. Quality of Life – EQ-5D

EQ-5D is the acronym for the European Quality of Life Score on Five Dimensions. Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. The EQ-5D Index is scored on a scale from -0.59 to 1.00, with a score of 1.00 indicating full health.

4.5.4. Percent Pain Relief (PPR)

Percent Pain Relief (PPR) is a question regarding that Subject's perception of how much better the Subject's back pain is compared to the time of baseline in the Registry, where 0% is no improvement, and 100% is no low back pain.

4.5.5. Subject Global Impression of Change (SGIC)

The SGIC is a question regarding the Subject's impression of how their condition has changed since baseline on a scale of 1 (much better) to 7 (much worse). Therefore, a decreased score on this measurement indicates an improvement.

4.5.6. Treatment Satisfaction Questionnaire (TSQ)

The TSQ is a questionnaire used to find out if a Subject is satisfied with the treatment based on a yes/no question. Therefore, a higher percent indicates that more Subjects in the Study are satisfied with the treatment. In addition, Subjects who indicate that they are satisfied with the treatment are asked if they are "satisfied" or "very satisfied".

4.6. Health Care Utilization

Cost-effectiveness data will be collected for ReActiv8 at baseline and the annual visits post-activation, to be extrapolated to the lifetime of the device. The key economic outcome measures to be recorded will be:

1. Work status
2. Use of Opioids
3. Health Care Utilization (office visits, hospital visits and other therapies such as physical therapy)

4.7. Data Collection Schedule

The data for the registry will be collected according to the following schedule:

Visit 1: Baseline visit

Visit 2: Activation visit (approximately 14 days post-surgery)

Visit 3: 90±30 days Post-Activation

Visit 4: 180±30 days Post-Activation

Visit 5: 1 year±60 days Post-Activation

Visit 6: 2 years ±60 days Post Activation

The above mentioned visits are part of the standard of care for patients with this type of treatment. The given time windows are advisable and data collection outside these windows will not be seen as a protocol deviation.

Any unscheduled visits will be recorded as stated in Table 3 and in section 4.7.6.

Note that data collection of all performance measures shall be done as the first thing in the follow up visit, prior to any other procedures.

Note that once a Subject has consented to participate in the Registry Adverse Events will be collected at each visit.

4.7.1. Visit 1: Baseline Visit

The process for obtaining informed consent shall be in compliance with ISO 14155.

If the subject agrees to participate in the registry 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 Registry identifier and will be asked to complete the baseline questionnaires.

Data will be collected according to the data collection schedule (Table 3).

4.7.2. Visit 2: Activation Visit (≈ 14 days Post Implant)

Activation of the therapy shall be about 14 days from the date of implant surgery.

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 activation visit, then the activation visit may be postponed to allow the issue to resolve. This will not be considered a deviation.

Activities to be performed:

- Perform electrode impedance and threshold measurements and record results
- Program IPG
- Train the Subject in use of the Activator, and document assessment of Subject's ability to self-administer therapy. Instruct Subject on timetable of therapy delivery (i.e.: twice a day starting the next day).
- Train the Subject in the procedure to deliver stimulation, including time of day and Subject positioning.

Data will be collected according to the data collection schedule (Table 3).

4.7.3. Visits 3 and 4: 90 ± 30 Days and 180 ± 30 Days Post Activation

During this visit data will be collected according to the data collection schedule (Table 3) and the following activities will be performed:

Device activities (if applicable):

- Electrode impedance and threshold measurements
- Readout from IPG of therapy delivery times and duration
- Adjustment of stimulation configuration and amplitude as appropriate

If a subject is unable to return to the clinic for an annual office visit, the clinical site may send the questionnaires to the subject for completion and a telehealth visit may be completed by the investigator and study coordinator.

Device interrogation and programming will be done at a later date when the subject is able to return for a visit.

If programming is completed it will be entered on the annual visit form. It will not be a deviation when the interrogation and programming of the system is required at a later date.

4.7.4. Visit 5: 1 year ± 60 Days Post Activation

During this visit data will be collected according to the data collection schedule (Table 3) and the following activities will be performed:

Device activities (if applicable):

- Electrode impedance and threshold measurements
- Readout from IPG of therapy delivery times and duration
- Adjustment of stimulation configuration and amplitude as appropriate

If a subject is unable to return to the clinic for an annual office visit, the clinical site may send the questionnaires to the subject for completion and a telehealth visit may be completed by the investigator and study coordinator.

Device interrogation and programming will be done at a later date when the subject is able to return for a visit.

If programming is completed it will be entered on the annual visit form. It will not be a deviation when the interrogation and programming of the system is required at a later date.

4.7.5. Visit 6: 2 years ± 60 Days Post Activation

During this visit, data will be collected according to the data collection schedule (Table 3) and the following activities will be performed:

Device activities (if applicable):

- Electrode impedance and threshold measurements
- Readout from IPG of therapy delivery times and duration
- Adjustment of stimulation configuration and amplitude as appropriate

If a subject is unable to return to the clinic for an annual office visit, the clinical site may send the questionnaires to the subject for completion and a telehealth visit may be completed by the investigator and study coordinator.

Device interrogation and programming will be done at a later date when the subject is able to return for a visit.

If programming is completed it will be entered on the annual visit form. It will not be a deviation when the interrogation and programming of the system is required at a later date.

4.7.6. Unscheduled Visits

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

- Low Back Pain NRS (average low back pain in the last 24 hours)
- Report Adverse Events (if applicable)
- Complete and document device activities if applicable

Data will be collected according to the data collection schedule (Table 3).

Table 3: Data Collection Schedule

	1: Baseline Visit	2: Activation Visit about 14 Days Post-Surgery	3: 90±30 Days Post Activation	4: 180±30 Days Post Activation	5: 1 Year ±60 Days Post Activation	6: 2 Year ±60 Days Post Activation	Unscheduled Visit
Medical History including Pain Detect Questionnaire	✓						
Low Back Pain (NRS)	✓	✓	✓	✓	✓	✓	✓
ODI	✓		✓	✓	✓	✓	
EQ-5D	✓		✓	✓	✓	✓	
Percent Pain Relief (PPR)			✓	✓	✓	✓	
Subject Global Impression of Change (SGIC)			✓	✓	✓	✓	
Treatment Satisfaction Questionnaire (TSQ)			✓	✓	✓	✓	
Work Status Evaluation	✓		✓	✓	✓	✓	
Medications: Opioids	✓		✓	✓	✓	✓	
Health Care Utilization	✓				✓	✓	
Device Measurements & Stimulation Thresholds*		✓	✓	✓	✓	✓	✓
Adverse Events (AE's)		✓	✓	✓	✓	✓	✓

*Device information will be collected at the implant procedure.

4.8 Sample Size Rationale

The sample size was based on the desire to gain a sufficient amount of representative data with the device in the market-released setting. In order to more fully characterize the experience with the system and detect rare events, the sample size of 50 Subjects provides 80% power to observe the incidence of at least one rare event for any events occurring at a population rate as low as 3.2%.

4.9 Informed Consent

4.9.1 Obtaining Informed Consent

Informed Consent is required from all Subjects (or their legal representatives) prior to the Subject's participation in the Registry. The process of obtaining Informed Consent shall comply with the Declaration of Helsinki 2004 (amendment Fortaleza, Brazil, October 2013), ISO 14155 and applicable national regulations, 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 health personnel as required by the Ethics Committee.

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

4.9.2 Requirements for Informed Consent

The Sponsor will provide the recommended Subject Informed Consent Form template. The Ethics Committee (EC) may alter or amend the text as appropriate, but the EC and the Sponsor must approve the final text of the informed consent before Subject enrolment can begin. After the information contained in the informed consent document has been reviewed with each Subject, the Subject and the investigator (or appointed designee) must sign and date the Informed Consent Form. A signed informed consent indicates the Subject's willingness to participate in the Registry prior to the subject's participation in the Registry.

4.10 Subject Data Confidentiality

Throughout the Registry, 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 and taking into account the applicable data protection laws. The sites shall ensure that data (e.g. worksheets, laptop computer 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.

Source documents as per ISO 14155 are printed, optical or electronic documents including the information in original records and necessary for the reconstruction and evaluation of the data. Original source data should remain at the site.

Any changes of the reported data should be reported to the Sponsor. A participating Investigator shall provide direct access to source data and documents for Registry-related monitoring, audits, Ethics Committee review, and regulatory inspection.

Subjects' health information will be kept confidential in accordance with applicable laws and regulations. Subjects' health information may be used to conduct this Registry, 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. Information received during the Registry will not be used to market to Subjects.

5 Risks and Benefits

All risks and benefits are identical to the CE Marked product. These are listed in the Implant and Programming Manual (990002-001), the User Manual (990003-001) and in the subject information (consent form).

6 Registry Management

6.1 Procedures to Amend the Registry Protocol

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

In all cases of changes to the Registry Protocol, the local rules for approval of modifications shall be followed, including by way of example a submission to the Ethics Committee (either in full or to the Chairman), and modifications to the Registry Agreement with the institution if applicable.

6.2 Sponsor Responsibilities

Mainstay Medical Limited is the Sponsor of the ReActiv8-C Registry. It is the responsibility of the Sponsor to ensure proper monitoring of the Registry and to see that all clinical requirements are met. In addition, Sponsor representatives may participate in the conduct of the Registry to the extent described in the following section on the role of the Sponsor representatives. Participation in the Registry will be limited to Sponsor personnel who are appropriately qualified and trained.

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

6.3 Role of the Sponsor Representatives

Sponsor representatives can provide technical support to the Investigator and other health care personnel (collectively HCP) as needed during implant, and testing. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of equipment supplied by Mainstay Medical (including laptop computers and other support equipment) or the data related to the Registry.

At the request of the Investigator and while under the Investigator's supervision, Sponsor representatives may operate equipment during implant or follow-up visits, assist with the conduct of testing, 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 laptop computer 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 Registry data from laptop computers and other equipment
- Entering data on Registry worksheets as long as the responsible Registry Investigator verifies and signs the completed worksheet
- Observing testing or medical procedures to provide information relevant to the Registry
- Reviewing collected data and Registry documentation for completeness and accuracy

At no point shall Sponsor representatives:

- Practice medicine;
- Discuss with the Subject the Subject's diagnosis or recommend treatment;
- Enter data onto the CRF; or
- Discuss the Study with the Subject.

6.4 Investigators

The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care. The Investigator is also responsible for ensuring that informed consent is obtained in accordance with this Registry, applicable regulatory requirements, and Ethics Committee requirements. The Investigator or co-Investigator may request the presence of Sponsor representatives at device-related procedures.

6.4.1 Record Keeping

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

- All correspondence with another Investigator or Ethics Committee, Mainstay Medical, a monitor, including required reports
- The signed Registry Protocol with any and all amendments
- The approved template of the Subject informed consent form
- Ethics Committee approval of the Registry Protocol and any amendments and renewals
- The Registry Agreement
- The Implant and Programming Manual and any other documents provided with the device
- Current curriculum vitae for the principal Investigator and all sub-investigators
- Monitoring letters (if applicable)
- Interim/final reports
- Registry initiation forms
- Registry closure documents

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

- Signed informed consent forms
- Source documents used for recording data (e.g., telephone visit documentation, device characteristics at implant and follow-up)
- All AEs
- Records of any SADE, including supporting documentation
- Records pertaining to Subject deaths during the Registry
- Relevant source data
- Any other records required by the Sponsor

6.5 Publications

Should a 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*, which may result in employees of the Sponsor being included as authors.

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

6.6 Registry Monitoring

Monitoring will be performed at least annually at each site during the Registry to ensure that compliance with applicable regulations are maintained. Monitors are individuals who are designated to oversee the progress of a Registry. These individuals are appropriately trained and qualified to monitor the progress of a Registry. Monitors will be selected and assigned by Mainstay Medical.

At times throughout the study, remote monitoring may be required. If performed, it will be done in compliance with the country, EC and clinical site requirements.

6.7 Registry Completion

The Sponsor will notify each Investigator of the completion or termination of the Registry or of the Investigator's participation in the Registry.

6.8 Suspension or Premature Termination of the Registry

If suspicion of an unacceptable risk to Subjects arises during the Registry, or when so instructed by the Ethics Committee, or regulatory authorities, the Sponsor shall suspend the Registry while the risk is assessed. The Sponsor shall terminate the Registry if an unacceptable risk is confirmed.

If the Sponsor makes a decision to discontinue the Registry for any reason (e.g., significant change in risk/benefit due to unanticipated adverse device effect, or other scenario), then the Sponsor will promptly inform all Investigators, Ethics Committees, and relevant regulatory bodies.

6.9 Name and Address of the Sponsor

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

Sponsor’s Contact:

Clinical Affairs
Mainstay Medical
Phone: 877 702-8488
Email: clinical@mainstaymedical.com

6.10 Statements of Compliance

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

The Registry shall not begin until the required approval or favorable opinion from the Ethics Committee and any other regulatory body as appropriate and necessary. Any additional requirements imposed by the Ethics Committee shall be followed, if appropriate.

Appendix 1: Acronyms and Definitions

ADE	Adverse Device Effect - adverse event related to the use of the study device
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
CLBP	Chronic Low Back Pain
CRF	Case Report Form(s) - set of documents for each Subject on which information to be reported to the Sponsor is recorded
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
EC	Ethics Committee - independent body whose responsibility it is to review the registry in order to protect the rights, safety and well-being of human subjects participating in the Registry
EMG	Electromyogram
HCP	Health Care Personnel
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IPG	Implantable Pulse Generator
MF	Multifidus muscle of the lumbar spine
NSLBP	Non-Specific Low Back Pain
PI	Principal Investigator. A qualified physician who takes overall responsibility for conduct of the Registry according to the protocol and regulations.
SADE	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SAE	Serious Adverse Event. An adverse event that a) led to death, b) 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, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. NOTE This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
TENS	Transcutaneous Electrical Nerve Stimulation
USADE	Unanticipated serious adverse device effect

Appendix 2: Bibliography

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