Leicestershire Partnership NHS
NHS Trust

PATIENT INFORMATION SHEET

RESTORE-LIFE

Study Code LNN800

A Global PRospective, Multi-cEnter, ObServational post-marketT Study tO assess shoRt, mid and long-term Effectiveness and efficiency of VNS Therapy® as adjunctive therapy in reaL-world patIents with diFficult to treat dEpression.

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This Informed Consent Form has two parts:

- Information Sheet (to share information about the study with you)
- Informed Consent Form (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

INTRODUCTION

Dear Madam, Dear Sir,

Your doctor has invited you to participate in a clinical study called RESTORE-LIFE. Your doctor has determined that you are a possible candidate for this study because you have been diagnosed with difficult to treat depression and have been referred for treatment with the VNS Therapy® system.

The purpose of this study is to collect information about subjects with difficult to treat depression (e.g., treatment resistant depression) who are referred for treatment with VNS Therapy. Data will be collected on their responses to treatments, their quality of life, their productivity, and their use of healthcare services. Your participation in this registry will consist of evaluations by a participating study doctor or his/her designee, who will review your past and current medical and psychiatric histories and complete several questionnaires now and during several follow-up visits over time. These questionnaires will

include questions about your depression and how it affects your quality of life and your use of health care services. This study is sponsored by LivaNova.

Your agreement to participate in this registry and to permit your health information to be used is voluntary (your choice).

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family, friends, or your regular doctor before making your decision. Your doctor will answer any questions you may have about participation in this study.

1. What is the aim of the study?

Study Overview:

A large group (roughly 30%) of patients with depression does not have success treating their depression after their first round of treatment. Many of these same patients fail to find success following their second, third, or additional anti-depression treatments. These patients are considered to have difficult to treat depression also called Treatment Resistant Depression (TRD).

Subjects who have difficult to treat depression referred for treatment with VNS Therapy will participate in this study. All qualifying participants will continue to receive their currently prescribed anti-depressant treatment for depression, treatment in addition to VNS Therapy from the study psychiatrist or other health professional. Bipolar patients will continue on their prescribed mood stabilizer in addition to VNS Therapy during the study.

This registry is a prospective, observational, multi-site, global post-market study using VNS Therapy as an adjunctive therapy and intended to assess short, mid, and long-term effectiveness and efficiency outcomes in "real-world" settings among patients with difficult to treat depression.

VNS Therapy was originally approved as adjunctive treatment for patients with partial onset epilepsy. To-date, over 100,000 and 4,000 patients have received a VNS Therapy implant for epilepsy and depression, respectively. VNS Therapy was approved for the adjunctive treatment of depression in 2001 in Europe and Canada, and in 2005 in the US.

A minimum of 500 subjects at nearly 80 study sites world-wide will participate in this study, and each subject will be seen for at least 3 years but no more than 5 years.

If you agree to participate in this study, you will be asked detailed questions about your depression, medical history, treatments for your depression, your quality of life, your productivity, and your use of healthcare services. You also agree to attend all of the scheduled study visits, and you agree to complete the required study questionnaires.
Some of the questions may upset you, but your honest responses to these questions will be recorded by the research staff and compared to responses from other subjects in this registry to see how well the treatment works and what mixture of treatments makes patients feel better or worse overall.

If your depression significantly worsens or if you express serious suicidal thoughts or plans, your study doctor or study staff will contact your treating physician so that you can obtain immediate treatment. If you think the device is not working properly, you should tell your doctor or study staff as soon as possible.

Why have I been selected to participate in this study?

You have been selected as a potential subject for this study because you have treatment resistant or difficult to treat depression and have been referred for treatment with VNS Therapy. The questions you answer will determine if VNS Therapy improves and sustains clinical and economical health outcomes of patients with difficult to treat depression.

2. Study Design

Enrollment

If you agree to participate in this study, you will be asked to complete several questionnaires at a baseline visit. This visit will occur within 6 weeks to 1 week prior to VNS Therapy implant.

The questionnaires to be completed include but are not limited to questions on:

- The symptoms and severity of your depression
- Your quality of life
- Your daily functioning

In addition, information on your medical history, previous and current use of anti-depressant treatments and your use of additional healthcare services will be collected via a study doctor and/or study staff interview.

Some sites will participate in a substudy and, in that case, you may also be asked to answer questions on the presence of manic symptoms or the presence of feelings of anxiety. In addition, you might be asked to perform a test called "THINC-it" that evaluates changes in cognition.

Implantation with VNS Therapy

Your doctor should have explained VNS Therapy to you in detail. In brief, the VNS Therapy System consists of an implantable generator (a small metallic device), a small thin insulated wire called "lead" (connecting the generator to the left Vagus nerve), and an external programming system which includes a programming wand, programming software and a compatible computer that allows programming of the implanted generator to send varied electrical signals to the left Vagus nerve via the lead.
The electrode is placed around the left Vagus nerve on the left side of the neck. The generator is placed under the skin under the left chest wall. The electrode is connected to the generator under the skin. Surgery takes about 45 minutes in an outpatient setting under local, regional, or general anesthesia. Your surgeon and anesthesiologist will decide which anesthesia will be used during the surgery.

You may be required to stay overnight in the hospital and, if so, you will need a companion to take you home from the hospital.

Post implantation you will visit a physician or nurse to have the device switched on and titrated to clinical efficacy. The rate of titration varies by patient and will be adjusted based on your response or sensitivity to the stimulation.

The implantation procedure itself and the titration visits, are not part of this study; however, data available from the implant procedure and any follow-up visits will be collected, which may include information on the performance of the device, device settings, your general health (including any hospitalizations you may have had, any complaints related to the device), and any changes to the adjunctive anti-depressant treatments you are having.

Study Duration

Mandatory clinic visits occur every 3 months for the first 18 months ±45 days for a total of 6 mandatory visits. You will have a physician's and/or study staff interview, and you will be asked to complete the same questionnaires as described above.

Following the 18 month visit, mandatory clinic visits occur every 6 months ±45 days until minimum 3 years or maximum 5 years post-implant. The study end will be determined and communicated by the sponsor; the study may end when the last patient enrolled in the study has reached the 3-years follow-up visit. All subjects will be expected to attend a minimum of 9 and maximum of 13 mandatory study visits post-implant. More visits are possible immediately following implant to achieve a stable VNS Therapy dosage; these visits will be scheduled according to standard care.

3. What are the possible disadvantages and risks of taking part?

If you decide to participate in this study, you may experience unpleasant emotions associated with answering study questionnaires. You may also experience inconveniences such as more frequent visits to your study doctor, including time and travel commitments.

There is no anticipated increased risk related to the implant and titration of VNS Therapy when you decide to participate in this study as all procedures are considered standard of care.

4. What are the possible risks associated to VNS Therapy?

With any medical device, adverse events are common. The statistically significant adverse events (occurring in ≥ 5% of subjects), associated with surgery or stimulation, reported during the pre-clinical studies include but are not limited to:

- Increased cough
- Device site pain
- Device site reaction
- Dysphagia (difficulty swallowing)
- Dyspnea (shortness of breath)
- Headache
- Hypesthesia (impaired sense of touch)
- Incision pain
- Incision site reaction
- Laryngismus (throat, larynx spasms)
- Nausea
- Neck pain
- Pain
- Paresthesia (prickling of the skin)
- Pharyngitis (inflammation of the pharynx, throat)
- Voice alteration (hoarseness)

Some of these events might lead to a surgical or non-surgical treatment or removal of the device.
Ask your study doctor to refer to the local VNS Therapy Physician's Manual for a detail of the most current list of anticipated adverse device effects, risks, contraindications, warnings, and precautions related to the use of VNS Therapy.

Surgery and treatment with VNS Therapy have possible risks, complications, and side effects. Most of these are known from previous clinical studies; however, there may be side effects from surgery and stimulation by the VNS Therapy System that are unknown at this time. There may also be other risks we cannot predict. If any new information about the VNS Therapy System that may affect your willingness to stay in the study becomes available, you will be told about it promptly.

The VNS Therapy System should not be used (and is contraindicated) in people who have had the left Vagus nerve cut to treat another disorder.
Inform anyone treating you that you CANNOT have any short-wave diathermy, microwave diathermy, therapeutic ultrasound diathermy (hereafter referred to as "diathermy"), or MRI using body coil for transmission anywhere on your body because you have an implanted VNS Therapy System. Diagnostic ultrasound can be used. Your doctor will discuss these in detail with you.

5. What are the possible benefits of taking part?

If you agree to take part in this study, there may or may not be a direct benefit to you. You may benefit from more frequent visits to the clinic.

The data learned from this study may help other patients with depression and/or VNS Therapy in the future. Additionally, the study may also demonstrate an economical benefit associated to VNS Therapy for difficult to treat depression.

6. Do I have to take part?

Your participation in this registry is voluntary. You may choose not to participate. If you do not want to participate, tell your doctor. If you decide not to participate in this registry, your medical care or treatment will not be affected in any way. No penalties will occur if you choose to start the study, change your mind, and decide to drop out. You may leave the study at any time.

Once you withdraw from the study, you will not be able to continue in the study. You will no longer be required to complete the study questionnaires, and no new data will be added to the database once you withdraw. All data collected prior to your withdrawal may still be used as part of the study. Your withdrawal will not affect your regular medical care or treatment that you would have received had you not started the registry.

Your participation in this study in no way limits your rights under any applicable laws or the authority of a doctor to provide you with emergency medical care. If you need medical treatment for any reason while participating in this study, you should contact your doctor.

At the discretion of your doctor or the sponsor, you may be removed from the study at any time, without your consent, due to unanticipated circumstances. You may be withdrawn from the study for one or more of the following reasons: if your doctor determines that continued participation in the study might harm you; if you need treatment not permitted by the study; if the study is cancelled; or for other administrative reasons.

7. What if new information is discovered?

Your doctor will inform you of any significant new information discovered during this study that might change your decision to continue taking part in this study. You may be asked to sign a new consent form if this occurs.

8. Are there any costs or reimbursement associated with this study?

You will not incur additional medical costs as a result of participating. If visits to the hospital fall outside the scope of the care you would normally receive, you are able to claim reasonable travel expenses. These will be paid at a rate of 45 pence per mile if driving to the hospital (the return journey to and from your home address to the hospital) or reimbursement of the taxi, bus or rail fare on production of receipts. There will be a maximum reimbursement set. If you require any further details, please discuss this with your Study Doctor.

9. Am I insured during the clinical study?

The sponsor has entered into a "Clinical Trial Liability" insurance which covers compensations for damages unintentionally caused to you in connection with the study, provided these charges have not been reimbursed by your medical insurance or other third party.

10. Will my participating in this study be confidential?

LivaNova Belgium NV (referred to as "LivaNova" below) is the sponsor for this study based in Belgium. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. LivaNova will keep identifiable information about you for 15 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting DataProtection@LivaNova.com.

The NHS organisation will collect information from you and your medical records for this research study in accordance with our instructions.

The NHS organisation will keep your name, NHS number and contact details confidential and will not pass this information to LivaNova. The NHS

organisation will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from LivaNova and regulatory organisations may look at your medical and research records to check the accuracy of the research study. LivaNova will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details

The NHS organisation will keep identifiable information about you from this study for 15 years after the study has finished.

LivaNova will collect information about you for research from the data collected in this study. The data collected will not provide any identifying information about you to LivaNova. We will use this information to do future analysis for improvements to the device used in this study. The pseudonymized data may be used to develop new therapies for conditions like yours, or used for medical meetings, training of physicians, and other medical personnel. Additionally, it may be used for reimbursement advocacy purposes which shows how effective the technology is to help make decisions on whether insurance companies will pay for the use of these devices.

The pseudonymized data may be given to regulatory agencies, so the sponsor can receive marketing approval for the products used in this study in other countries. The pseudonymized data may also be used to meet the reporting requirements of governmental agencies.

Pseudonymized data may be used for purposes of establishing information regarding the cost of treatment over the study time period. The results of this study may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed in any publications.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

In recording the results of the study, you will be referred to by an identification code, consisting of letters and/or numbers.

By consenting, you will allow your General Practitioner to be informed of your participation, unless you tell the study doctor not to do so. If you allow your General Practitioner to be informed of your participation, there may be an exchange of data between the General Practitioner and the study doctor.

Optional data collection

In addition to already described data collection, and where possible, your national records may also be used to collect objective information to analyse the use of depression-related healthcare resources (such number as depression-related Accident & Emergency (A&E) visits, GP visits, hospital admissions). To achieve this, your personal information (such as your patient identification number, date of birth and gender) may need to be shared by your Study Doctor with a licensed third party who will collect this information from the NHS Digital (national provider of information, data and IT systems for commissioners, analysts and clinicians in health and social care), in accordance with local laws, ensuring your confidentiality is maintained. The applicable agency will, under an approved protocol, provide anonymised data for the purpose of said analysis to LivaNova and ensure your confidentiality is maintained. Without your consent, your Study Doctor will not contact the applicable agency and LivaNova will not be permitted to collect this additional information. Furthermore, you may choose to not allow this data to be collected by not signing this optional section on the Consent Form and you may also withdraw consent for this separately, without withdrawing your consent from the main study.

*** End of optional data collection ***

The personal data collected in this study will be transferred to countries outside the European Economic Area, such as USA, where the level of data protection may not be as strict as in your own country and for instance the security authorities may inspect the study data. Please note your data will be pseudonimized making it more difficult for third person to identify you.

At the end of the study, the results will be analysed and could be published in medical journals, but your identity will not be revealed. As it will take time for all patients participating to complete the study, the data may not be available for some time after you finish your participation. If you are interested in reading any subsequent results please ask your doctor.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

To the extent provided by the General Data Protection Regulation, you may request access to, rectification of or erasure of your personal data, restriction of processing concerning your personal data, object to processing your personal data as well as receipt of the personal data provided to LivaNova.

In such case, please contact the RESTORE-LIFE Study Manager, LivaNova Belgium N.V., Ikaroslaan 83, 1930 Zaventem, Belgium. In particular for queries, you may also contact the data protection officer (DataProtection@LivaNova.com).

In case of a data breach you may lodge a complaint with the local supervisory authority at Information Commissioner's Office ("ICO") (https://ico.org.uk/).

LivaNova will take all necessary steps to protect your privacy.

11. Who is organizing and funding the study?

The study is organized and funded by LivaNova:

LivaNova Belgium NV
Ikaroslaan 83
1930 Zaventem
Belgium

The sponsor has representatives that may be present during visits with your study doctor to provide technical device support. The sponsor may be present during the implant of VNS Therapy system and during follow-up clinic visits. The sponsor representative will be available as necessary to provide technical support and/or system programming under the supervision of the study doctor or hospital staff.

12. Who has reviewed the study?

This study has been reviewed and approved by the London-Riverside Research Ethics Committee which is a committee whose task it is to make sure that research participants are protected from harm. If you have any questions about your rights as a subject or have questions about the study, please contact the EC at London-Riverside Research Ethics Committee Level 3 Block B, Whitefriars, Lewins Mead, Bristol, phone number: 02071048204. The REC reference of this study is: 18/LO/1001 and IRAS Identification number is 246304.

13. Whom can I contact if I have questions?

If you have any questions regarding this clinical study, involved risks, benefits, adverse events, or alternative treatments, if you want additional information about your rights as a participant in this study, please do not hesitate to ask your doctor or the study staff working on this study. In the event of injury, please contact your doctor. Contact information can be found on the first page of this document.