Research Protocol
(including Statistical Analysis Plan)
version 2.0

A Randomised, Single-blind, Sham-controlled, Crossover Pilot Study Assessing the Effect of Non-invasive Vagus Nerve Stimulation (nVNS) on Autonomic Symptoms and Pain Management in Patients With Chronic Musculoskeletal Pain and Autonomic Dysfunction

Reducing sympathetic tone with nVNS for MSK pain relief

(RESTORE-MSK)

Norah Almutairi, Darren C Greenwood, Manoj Sivan

NCT number:

UNIVERSITY OF LEEDS

Leeds Institute of Rheumatic and Musculoskeletal Medicine

Academic Department of Rehabilitation Medicine

Research Protocol

Version 2.0

Date: 14-01-2026

Study Short Title: RESTORE-MSK: Reducing Sympathetic Tone with nVNS for MSK Pain Relief

Study Full Title: A randomised, single-blind, sham-controlled, crossover pilot study assessing the effect of non-invasive vagus nerve stimulation (nVNS) on autonomic symptoms and pain management in patients with chronic musculoskeletal pain and autonomic dysfunction.

Sponsor Name: University of Leeds

Sponsor Number: 2025-NCT57

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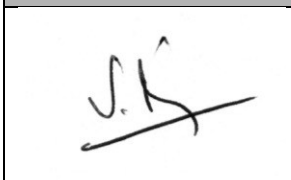
INVESTIGATOR DECLARATION AND SIGNATURE(S)

RESTORE-MSK Study, Protocol Version 3, Date: 24/11/2025

DECLARATION OF PROTOCOL ACCEPTANCE

I confirm that I am fully informed and aware of the requirements of the protocol and agree to conduct the study as set out in this protocol.

	
Chief Investigator	Date 4/12/2025

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ANS	Autonomic Nervous System
AD	Autonomic Dysfunction
BPI-SF	Brief Pain Inventory - Short Form
CI	Chief Investigator
CMP	Chronic Musculoskeletal Pain (CMP)
COMPASS-31	Composite Autonomic Symptom Score-31
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
MHRA	Medicines And Healthcare Products Regulatory Agency
MSK	Musculoskeletal
NSAID	Nonsteroidal Anti-Inflammatory Drug
nVNS	Non-invasive Vagus Nerve Stimulation
TFA	Theoretical Framework of Acceptability
QA	Quality Assurance
REC	Research Ethics Committee
RCT	Randomized Controlled Trial
RUSAEs	Related and unexpected serious adverse events
SAE	Serious Adverse Event
SD	Standard Deviation

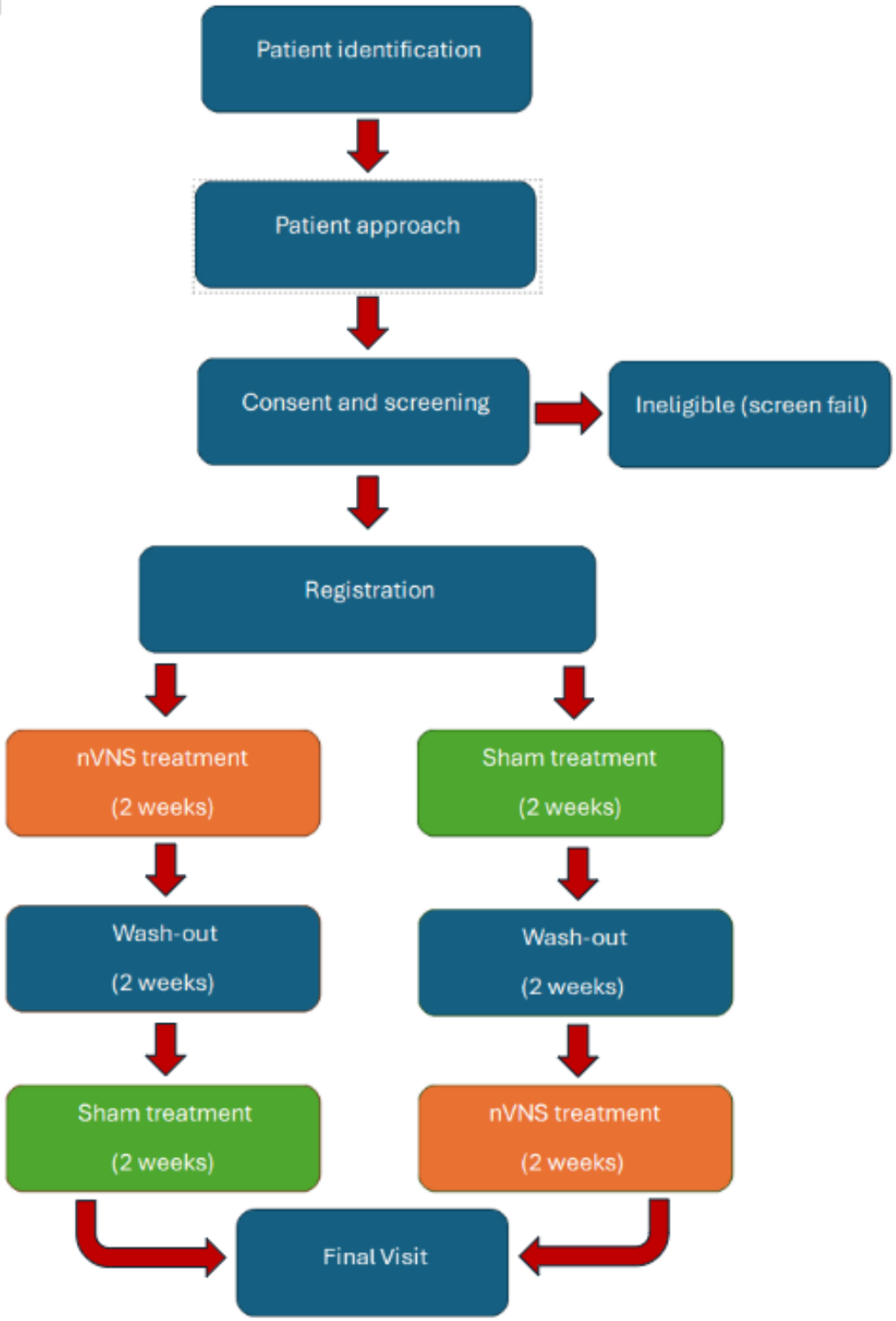
PROTOCOL SYNOPSIS

GENERAL INFORMATION	
Short Title	**RESTORE-MSK: Reducing Sympathetic Tone with nVNS for MSK Pain Relief**
Full Title	A randomised, single-blind, sham-controlled, crossover pilot study assessing the effect of non-invasive vagus nerve stimulation (nVNS) on autonomic symptoms severity in patients with chronic musculoskeletal pain (CMP) with autonomic dysfunction (AD).
Sponsor	University of Leeds, Leeds, UK
Sponsor ID	2025-NCT57
MREC No.	
Chief Investigator	Professor Manoj Sivan
Co-ordinating Centre	Chapel Allerton Hospital
National / International	National
STUDY INFORMATION	
Phase	Pilot
Indication	chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD)
Design	a randomised, single-blind, sham-controlled, crossover pilot study
Number of sites	1 site
Primary Objective	• Effect of non-invasive vagus nerve stimulation (nVNS) using the GammaCore device on autonomic function in patients with chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD).
Secondary Objective(s)	• Effect of non-invasive vagus nerve stimulation (nVNS) using the GammaCore device on pain characteristics in patients with chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD). • Effect of non-invasive vagus nerve stimulation (nVNS) using the GammaCore device on specific AD-related physiological responses, individual's quality of life, anxiety, depression, and quality of life. • Participants' response rate to invitation to participate. • Acceptability of the intervention.
Primary Endpoint	• Severity of autonomic symptoms measured by the Composite Autonomic Symptom Score-31 (COMPASS-31).

	•
Secondary Endpoint(s)	• Physiological response to the lean test, an objective measure of autonomic dysfunction (scored positive/negative response). • Pain severity measured by the Brief Pain Inventory - Short Form (BPI-SF). • Impact of pain on an individual's life, measured by the BPI-SF. • Depression and anxiety measured by the Hospital Anxiety and Depression Scale (HADS). • Quality of life measured by the EQ-5D-5L. • Acceptability of the intervention measured by Theoretical Framework of Acceptability (TFA) based questionnaire (Participant Feedback Questionnaire). • Response rate to invitation to participate measured by number of people consenting divided by the number of people invited.
STUDY TIMELINES	
Expected start date	02/01/2026
Subject enrolment phase	02/01/2026-31/07/2026
Follow-up duration	6 weeks
End of Study Definition	Last visit of the last participant.
Expected completion date	31/7/2026
STUDY SUBJECT INFORMATION	
Number of study subjects	12
Age group of study subjects	18 years or older
Inclusion criteria	a. Individuals diagnosed with musculoskeletal (MSK) conditions and currently experiencing MSK pain lasting for 12 weeks or longer. b. Identified as having autonomic dysfunction (AD) if scoring 17 or more on COMPASS-31 c. Ability to understand and willingness to sign a written informed consent document.

	d. Stated willingness to comply with all study procedures and be available for the entire duration of the study. e. Ability to read and understand English.
Exclusion criteria	a. Pregnancy. b. Advanced Heart Disease such severe heart failure, recent myocardial infarction or ongoing investigations for arrhythmias. c. Use of another active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device. d. Use of another muscle stimulating device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device. e. Inability to provide informed consent.

SCHEMATIC DIAGRAM



1. INTRODUCTION

1.1. Background

Musculoskeletal pain, often presenting as a chronic condition, affects an estimated 20–33% of the global population, according to the World Health Organization (WHO, 2022). This equates to approximately 1.75 billion individuals worldwide, with the prevalence continuing to increase. In the United Kingdom alone, chronic pain is reported in at least 28 million individuals (Fayaz et al., 2016). Chronic musculoskeletal pain (CMP) may arise from various etiological factors, including physical injury, muscular overuse, inflammatory processes, or degenerative changes. Additionally, CMP is frequently associated with a spectrum of comorbid health conditions, such as fibromyalgia, back pain, osteoarthritis, and rheumatoid arthritis (Woolf and Pfleger, 2003; Ayis and Dieppe, 2009).

A growing body of research has highlighted the significant impact of chronic pain as a key predictor of functional impairment on a global scale (Rundell et al., 2019; Welsh et al., 2020). Moreover, chronic pain constitutes the leading cause of rehabilitation needs worldwide (Cieza et al., 2020). According to the Global Burden of Disease Study 2019, several chronic pain conditions, including fibromyalgia, neck pain, migraine, osteoarthritis, and other musculoskeletal disorders, are among the most significant contributors to years lived with disability (YLDs). Among these, chronic low back pain was identified as the single greatest cause of YLDs globally (Rice et al., 2016; Anon, 2018).

Chronic musculoskeletal (MSK) pain is characterised by complex pathophysiology involving not only nociceptive and neuropathic mechanisms, but also potential dysregulation of the autonomic nervous system (ANS) known as autonomic dysfunction (AD). Emerging evidence suggests that autonomic dysfunction (AD), described as altered sympathetic nervous system reactivity (either exaggerated or blunted responses to stimuli) has been implicated in the pathogenesis of muscle pain (Kalezic, 2006; Yater et al., 2021), linking autonomic dysregulation directly to chronic pain. Characterised by symptoms such as orthostatic intolerance, palpitations, gastrointestinal dysmotility, and fatigue, autonomic dysfunction may co-occur in a significant proportion of patients with chronic MSK pain, further exacerbating symptom burden and reducing quality of life (Raj et al., 2000; Furlan et al., 2005; Sjors et al., 2009). Given limited evidence on the positive effects of conventional pharmacological treatments on managing chronic MSK pain management in patients with autonomic dysfunction (Koechlin et al., 2019), non-pharmacological interventions targeting central mechanisms of pain modulation are gaining increasing attention. One such modality is non-invasive transcutaneous vagus nerve stimulation (nVNS), a form of neuromodulation, which has been studied for its analgesic properties based on the electrical stimulation of the vagus nerve to modulate autonomic tone and central pain processing.

Non-invasive vagus nerve stimulation (nVNS) offers a non-pharmacological means to influence autonomic tone and central pain processing. With the new development of implantable and non-invasive vagus nerve stimulators, recent studies have demonstrated the

analgesic effect of vagal nerve stimulation (VNS) across a range of chronic pain conditions including trigeminal allodynia, fibromyalgia, chronic pelvic pain, cluster headache, and migraines, with preliminary data indicating potential benefits for alleviating chronic pain and associated dysautonomia (Multon and Schoenen, 2005; Chakravarthy et al., 2015; Napadow et al., 2012; Garcia et al., 2017). Although the exact mechanism by which VNS modulates chronic pain has not yet been clearly established, emerging evidence suggests that its effects may be mediated through anti-inflammatory pathways, in combination with modulation of both central and peripheral pain processing mechanisms (Shao et al., 2023; Liu et al., 2024). These findings have contributed to the growing interest in the therapeutic potential of non-invasive vagus nerve stimulation (nVNS) leading to the development and commercialization of several medical devices in this domain.

The GammaCore® device (electroCore LLC, Basking Ridge, NJ, USA) is a non-invasive vagus nerve stimulator (nVNS) designed to deliver low-voltage electrical stimulation to the cervical branch of the vagus nerve. Initially approved in Europe with Conformité Européenne (CE) marks for the treatment of primary headaches, GammaCore received FDA clearance in the United States for the acute treatment of episodic cluster headache in 2017 and for acute migraine in 2018 (Mwamburi et al., 2018). In the UK, the National Institute for Health and Care Excellence (NICE) evaluated GammaCore's clinical effectiveness and cost impact as a handheld, patient-controlled device for both the treatment and prevention of cluster headache, supporting its use within the NHS for selected patients (O'Connell et al., 2021).

The efficacy of GammaCore device in managing migraine has been demonstrated in several clinical trials. The PRESTO randomized controlled trial (RCT) found that GammaCore significantly improved pain-free response rates compared to sham stimulation at 30- and 60-minutes post-treatment (Tassorelli et al., 2018). In one of the largest randomized sham-controlled studies for acute cluster headache treatment, nVNS provided significant, clinically meaningful, rapid, and sustained benefits for episodic cluster headache (Silberstein et al., 2016). Additional open-label studies support its analgesic benefit, demonstrating rapid pain relief and improved quality-of-life outcomes in both acute and preventive settings (Barbanti et al., 2015; Goadsby et al., 2018). Across trials, GammaCore was consistently reported safe and well tolerated, with adverse events being mild and involving local discomfort, skin irritation, transient muscle stiffness, and pain responsive to the nonsteroidal anti-inflammatory drug (NSAID) treatment (Chakravarthy et al., 2015; Mwamburi et al., 2018).

Despite encouraging results in headache and related conditions, the therapeutic potential of nVNS in individuals with chronic MSK pain and autonomic dysfunction remains underexplored. The aim of this trial is to generate important insights into the potential of nVNS as a non-pharmacological treatment option targeting both autonomic and pain-related mechanisms. In the proposed study, we hypothesized that a non-invasive vagus nerve stimulator (nVNS) with the use of the GammaCore medical device could be effective as a

treatment to alleviate pain and improve quality of life in patients with chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD).

Consequently, the primary objective of this study is to evaluate the effect of non-invasive vagus nerve stimulation (nVNS) using the GammaCore® device on autonomic function in individuals with chronic musculoskeletal (MSK) pain and autonomic dysfunction (AD). Secondary objectives include assessing the impact of nVNS on pain characteristics, specific AD-related physiological responses, quality of life, anxiety, and depression. Additionally, the study aims to determine the response rate to the invitation to participate and evaluate the acceptability of the intervention.

1.2. Rationale for the proposed study

Autonomic dysfunction (AD) is increasingly recognised as a contributing factor in chronic musculoskeletal pain (CMP), yet its role remains poorly understood and largely overlooked in current treatment approaches. Conventional therapies for CMP often fail to address the autonomic component, limiting their effectiveness in patients with coexisting AD. Non-invasive vagus nerve stimulation (nVNS), delivered via the GammaCore device offers a transformative approach based on a novel, dual-target intervention with the potential to modulate both autonomic and pain pathways. Investigating this approach may uncover a promising therapeutic strategy for a complex and underserved patient population.

2. STUDY AIM AND OBJECTIVES

2.1. Study aim

To evaluate the effect of non-invasive vagus nerve stimulation (nVNS), delivered via the GammaCore device, on pain and symptoms of dysautonomia in population of patients with chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD), in view of establishing feasibility and proof of concept for a larger randomised controlled trial.

2.2. Primary objective

To investigate the effect of non-invasive vagus nerve stimulation (nVNS) on autonomic function in patients with chronic musculoskeletal (MSK) pain with autonomic dysfunction (AD).

This objective will be achieved through using an adaptive Composite Autonomic Symptom Score-31 (COMPASS-31) to assess the severity of autonomic symptoms before and after nVNS.

2.3. Secondary objective(s)

2.3.1. To investigate the physiological response to nVNS in patients with chronic musculoskeletal (MSK) pain and autonomic dysfunction (AD)

This objective will be achieved through using the following methods:

(1) physiological response to NASA lean test, an objective measure of autonomic dysfunction (scored positive/negative response)

2.3.2. Study the impact of Reducing Enduring Sympathetic Tone with nVNS on pain characteristics, anxiety and depression level, and quality of life in patients with chronic musculoskeletal (MSK) pain and autonomic dysfunction (AD).

This objective will be achieved through using the following methods:

(1a) pain severity measured by the Brief Pain Inventory - short form (BPI-SF),

(1b) impact of pain on an individual's life, measured by the BPI-SF,

(2a) anxiety measured by the Hospital Anxiety and Depression Scale (HADS),

(2b) depression measured by Hospital Anxiety and Depression Scale (HADS),

(3) quality of life measured by the EQ-5D-5L.

2.3.3. Participants' response rate to invitation to participate

This objective will be measured by number of people consenting divided by the number of people invited.

2.3.4. Acceptability of the intervention

This objective will be measured by the Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire, which has been developed as a generic questionnaire that can be adapted to assess acceptability of any healthcare intervention.

3. STUDY VARIABLES

3.1. Standard variables

- COMPASS 31 score
- Physiological response to NASA Lean Test
- Pain severity measured by BPI-SF

- Impact of pain on individual's life measured by BPI-SF
- Anxiety measured by HADS
- Depression measured by HADS
- Quality of life measured by the EQ-5D-5L
- Participants' response rate measured by number of people consenting divided by the number of people invited
- Acceptability of the intervention measured by adapted Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire
- Patient demographics which include (age group, gender, pre-existing conditions and comorbidities, medical diagnosis, disease duration, and medication history)

4. STUDY DESIGN

4.1. Study description

This study is an investigator-initiated, randomised, single-blind, sham-controlled, crossover clinical trial assessing the effect of nVNS for pain treatment in patients with chronic musculoskeletal (MSK) disease with autonomic dysfunction (AD). The study will be conducted at Chapel Allerton Hospital, Leeds from 2nd January 2026 to 31 of July 2026. As active nVNS treatment, an FDA approved medical device (GammaCore-S, ElectroCore LLC, Basking Ridge, New Jersey, USA) will be used, and the sham devices were identical in appearance (ElectroCore LLC, Basking Ridge, New Jersey, USA).

4.2. Study duration

The time frame of the study starts from recruiting the participants from the Leeds Teaching Hospitals to the final clinic visit of the last recruited participant to apply the Lean Test.

4.3. Rationale for the study design

This study is a randomised, single-blind, sham-controlled, crossover pilot trial designed to evaluate the feasibility and preliminary efficacy of non-invasive vagus nerve stimulation (nVNS) using the GammaCore device in individuals with chronic musculoskeletal pain (CMP) and co-existing autonomic dysfunction (AD). Autonomic dysregulation has been implicated in the pathophysiology of chronic pain, with studies showing altered sympathetic and parasympathetic activity, particularly in conditions like fibromyalgia and chronic fatigue syndrome (Chakravarthy et al., 2015). Vagus nerve stimulation has been shown to modulate autonomic output, reduce inflammation, and influence central pain pathways (Chakravarthy et al., 2015; Muthulingam et al., 2023).

A randomised, sham-controlled design will help to determine the specific effects of nVNS beyond placebo and natural symptom fluctuation. The crossover format will allow each

participant to serve as their own control, enhancing statistical efficiency and reducing between-subject variability—particularly important in small feasibility studies. With the adequate washout period, this design aims to minimise carryover effects and is well-suited for early-phase investigations. Finally, blinding of participants will minimise expectation bias.

As a pilot trial, this study aims to assess the feasibility of recruitment and randomisation, the acceptability of the intervention in this population and setting, and the completeness of outcome data. The study will also explore potential signals of benefit, including changes in autonomic symptoms and pain, to determine whether larger-scale evaluation is warranted.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Target population

Individuals with chronic musculoskeletal pain who have a diagnosed autonomic dysfunction (dysautonomia).

5.2. Estimated number of eligible participants

We plan to enrol 12 participants in this feasibility study, all of whom have experienced musculoskeletal pain on most days for at least 12 weeks, in line with the ICD-11 criteria for Chronic Pain (WHO; Treede et al., 2015). Eligible patients must also score ⩾ 17 on the COMPASS-31 questionnaire to be classified as having autonomic dysfunction (AD).

5.3. Eligibility *criteria*

5.3.1. Inclusion criteria

A. Individuals diagnosed with musculoskeletal (MSK) conditions and currently experiencing MSK pain lasting for 12 weeks or longer.
B. Identified as having autonomic dysfunction (AD) based on COMPASS 31 score (17 or more
C. Ability to understand and willingness to sign a written informed consent document.
D. Stated willingness to comply with all study procedures and be available for the entire duration of the study.
E. Ability to read and understand English.

5.3.2. Exclusion criteria

A. Pregnancy.
B. People diagnosed with Advanced Heart Disease such severe heart failure, recent myocardial infarction or ongoing investigations for arrhythmias.
C. Unable to provide informed consent.

D. Patients who have an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device.
E. Are using another device at the same time (e.g., TENS Unit, muscle stimulator) or any portable electronic device.

5.3.3. Exclusions for general safety

None further to the defined exclusion criteria above.

5.4. Withdrawal criteria

Participants have the choice to withdraw from the study at any time, without any negative impact on their current or future treatment. If they choose to do so, any data already provided will be used in the study. No additional data will be collected, and there will be no further research procedures carried out on or in relation to the participant.

6. RECRUITMENT, CONSENT AND RANDOMISATION

6.1. Recruitment

The Leeds Institute of Rheumatic and Musculoskeletal Medicine will be contacted to provide access to their facility and clinics for identification of potential participants. After the approval and clinics allocation, summary of the study purpose will be sent to the direct care team in each clinic via email, an invitation letter from the research team, the PIS and the consent form will be attached to the same email.

If the participant is identified through a clinic list as a potential participant by clinical colleagues based at the site, the clinical team will perform a face-to-face approach in the clinic. In the first contact the patient will be provided with a brief explanation of the study. This will include detailed information about the rationale, design and personal implications of the study. Having been provided with the PIS and verbal information regarding the study procedures, patients will have at least 24 hours to consider participation before they will be approached by authorised clinician to obtain consent.

Patients will be contacted by the study team at least 24 hours following the initial approach to confirm their interest in the study. If a potential participant expresses interest, they will be invited to the clinic, where informed consent will be obtained. On the same visit, the potential participant will complete the COMPASS-31 questionnaire, which will be used to assess autonomic symptom severity and determine eligibility by categorising participants into high or low dysautonomia groups. Eligible participants will then either proceed on the same day or be invited for a subsequent visit to complete the study surveys (BPI-SF, HADS, and EQ-5D-5L) and undergo the NASA Lean Test. They will also receive training on how to use the GammaCore device and they will be provided with the device and a stimulation diary.

6.2. Consent

Informed consent will be obtained prior to the participant undergoing any study specific procedures. The right of potential participants to refuse consent with or without reason will be respected. Consent will be obtained by an authorised clinician who has signed the study delegation log. Once consent is obtained, a copy of the consent form will be given to the participant, one filed in the study files, and one in the hospital notes.

6.3. Patients who withdraw consent

The right of participants to refuse participation without giving reasons will be respected. Further, participants will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

The investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either at the eligibility assessment or arising during the study)
- Significant protocol deviation
- Consent withdrawn
- Death

If participants withdraw from the study, any data already collected will be retained and be used in the study. No further data would be collected, or any other research procedures carried out on or in relation to the participant.

6.4. Randomisation process

This is a randomised, sham-controlled, crossover pilot study. Each participant will receive both the active and sham interventions in a randomly allocated order. Participants will be randomly assigned to one of two treatment sequences:

- **Sequence A**: Active stimulation followed by sham stimulation.
- **Sequence B**: Sham stimulation followed by active stimulation

A washout period of 2 weeks will be included between treatment periods to minimise carryover effects.

Randomisation will follow a restricted approach with stratification to ensure balanced allocation across sequences, and simple randomisation applied within each stratum. Stratification will be based on baseline COMPASS-31 autonomic profile score, split into high and low dysautonomia group at <40/40+, the median of eligible participants identified in our previous study of autonomic dysfunction in people living with chronic MSK pain. The randomisation schedule will be generated in advance by the trial statistician using a computer-based algorithm and implemented via REDCap, a secure web-based data capture system.

Following eligibility confirmation and informed consent, participants will be randomised by the enrolling research team member using simple randomisation within strata, with strata defined by baseline COMPASS-31 score <40 vs 40+, which is the median identified in participants meeting the eligibility criteria in our previous study. The randomisation list will be generated in Stata. The randomisation list will be concealed from investigators in contact with participants and implemented through appropriate software such as the REDCap randomisation module. Allocation will remain concealed from the study team until randomisation is triggered.

Metadata related to randomisation (assigned sequence, treatment received) will be collected to evaluate feasibility and inform the design of a future definitive trial.

6.5. Study blinding

This is a single-blind study, where participants involved in the intervention delivery will be blinded to the treatment allocation.

Blinding will be maintained by Norah Almutairi at clinic visits 1 and 3 by adjusting the device's stimulation amplitude to produce a low-frequency signal. This signal will be perceptible on the skin but will not activate the vagus nerve or cause the muscle contractions typically associated with higher-intensity active stimulation. Previous studies comparing nVNS treatment with a sham device—where the sham was identical in appearance but delivered no active signal—have demonstrated that this approach provides an adequate control for blinding (Silberstein et al., 2016; Tassorelli et al., 2018).

To mitigate the risk of unblinding, as participants may notice reduced muscle contraction, a blinding assessment will be built into the study. At study completion, participants will be asked to indicate whether they believe they received active or sham treatment in each stage of the intervention.

Any incidents of unblinding, intentional or accidental, will be documented and reported.

To evaluate the success of blinding, participants will be asked to indicate which treatment (active or sham) they believe they received. This blinding poll will be completed on the final day of treatment and documented in the follow-up CRF.

6.6. Managing/replacing participants who withdraw early

Participants who withdraw from the trial early will not be replaced.

6.7. Definition of the end of the trial

Study completion will be defined as the time at which the last data item has been locked for the last recruited participant.

7. PATIENT ADVISORY GROUP

A Patient Advisory Group was established, comprising patients diagnosed with chronic musculoskeletal (MSK) conditions and autonomic dysfunction (AD), identified through Chapel Allerton Hospital, the Institute of Rheumatic and Musculoskeletal Medicine, and the outpatient clinic. The group reviewed the patient-facing documents (Participant Information Sheet and Consent Form), and amendments were made based on their feedback.

8. DEVICE IMPLEMENTATION AND PARTICIPANT USE

8.1. Device training and distribution

Following informed consent, eligible participants will either proceed on the same day or be invited for a subsequent visit to receive training on how to use the GammaCore device and they will be provided with the device and a stimulation diary for home use.

8.2. Vagus nerve stimulation

Participants will self-administer the GammaCore® device using a small amount of conduction gel applied to the stimulation surfaces. The device is positioned bilaterally under the angle of the mandible, guided by the carotid pulse. Each stimulation consists of a two-minute application per side. Participants will complete two stimulations per day—morning and evening—for two weeks. Afterward, they will have a two-week break. This will be followed by additional two weeks of daily use of the device as per the initial schedule. Stimulation is painless and may produce a mild buzzing sensation. The stimulation schedule is identical across study arms.

8.3. Vagus nerve stimulation diary

Participants will be asked to record their compliance to the intervention schedule using a stimulation diary. They will indicate their compliance to each stimulation sequence . Diaries will be collected after the first 2 weeks and again following the final stimulation sequence, with the data transcribed onto the Follow-up CRF.

9. METHODS OF ASSESSMENT

9.1. Subjective assessment variables (Patient Reported Outcomes)

9.1.1. Composite Autonomic Symptom Score (COMPASS-31)

The COMPASS-31 self-administered instrument which commonly employed for evaluating and measuring the intensity of autonomic dysfunction symptoms in patients (Sletten et al., 2012). It consists of 31 items that are categorized into six categories, each indicating a specific element of autonomic function. These domains include orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor symptoms. The questionnaire assigns a score to each item based on its severity and frequency, resulting in a total score that ranges from 0 to 100. Greater scores suggest a higher degree of autonomic dysfunction (Puri & Lee, 2022). It will be used in this study to have an insight into the prevalence and impact of autonomic symptoms in various populations.

9.1.2. Brief Pain Inventory – Short Form (BPI-SF)

The Brief Pain Inventory–Short Form (BPI-SF) is a shortened version of the BPI that requires no more than five minutes to complete. It is an essential instrument for evaluating the intensity and impact of pain on daily activities. This brief survey requires participants to assess their pain level on a scale from 0 (no pain) to 10 (most extreme pain). it captures pain at its worst, least, average, and at the moment of completing the survey. In addition to assessing pain severity, the BPI-SF evaluates the impact of pain on many aspects of the individual's life such as general activity, mood, walking, work, social interactions, sleep, and enjoyment of life, using the same 0 to 10 scale. The average of the four pain severity ratings provides a pain severity score, and similarly, the average of the seven pain interference ratings offers a pain interference score. These averaged scores offer a detailed perspective on the impact of pain on an individual's life, assisting healthcare providers in developing customized pain treatment strategies.

9.1.3. The Hospital Anxiety and Depression Scale (HADS)

The HADS is a reliable instrument for identifying depression and anxiety in a general medical population of patients (Zigmond & Snaith, 1983). It’s an effective tool that contains only 7 questions that take roughly 2–5 minutes to complete. Bjelland et al. (2002) conducted a review and concluded that HADS enables healthcare professionals to categorize the intensity of symptoms related to anxiety and depression in the general population and patients with different medical conditions. Individuals scoring below 7 on HADS are known as non-cases, while those scoring between 8 and 10 are classified as mild, 11–14 as moderate, and 15–21 as severe (Bjelland et al., 2002).

9.1.4. EuroQol EQ-5D-5L Quality of Life Questionnaire

The EuroQol EQ-5D-5L is a widely validated, standardised instrument developed by the EuroQol Group to measure generic health status in clinical and economic evaluations (Herdman et al., 2011). The instrument includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated by the participant on five levels of severity: no problems, slight problems, moderate problems, severe problems, and extreme problems. Participants select one level per domain to describe their current health state. Responses are summarised descriptively, with the distribution of responses within each domain reported. In addition, domain scores are combined into a five-digit code representing the participant's overall health profile (e.g. 12345), which is converted into a single index value using the UK EQ-5D-5L value set (Devlin et al., 2018).

9.2. Objective assessment tests

9.2.1. NASA 10 Minute lean test

The lean test is a clinical test performed to evaluate Autonomic Nervous System (ANS) dysfunction, specifically in the context of diagnosing conditions like Postural Orthostatic Tachycardia Syndrome (POTS) or other forms of orthostatic intolerance (Lee et al., 2020). The test begins with the participant lying on the exam table or bed. The participant heart rate and blood pressure are measured in this position to establish baseline values. Following that, the participant asked to stand up without support and remain still. The heart rate and blood pressure are reassessed periodically, usually at 2, 5, and 10-minute intervals. Then, the participant is instructed to lean against a wall while keeping heels about 6 inches away from it. The back and elbows are allowed to touch the wall. This posture minimizes the muscular effort required for standing, which can help isolate the autonomic contribution to standing. While leaning, heart rate and blood pressure are continuously monitored. The positive sign during the Lean Test is a significant increase in heart rate upon standing, which doesn't decrease upon leaning. For a POTS diagnosis, an increase of more than 30 beats per minute (or more than 40 beats per minute in adolescents) without a substantial drop in blood pressure is generally considered significant. If heart rate increases significantly upon standing but decreases or normalizes upon leaning, it may suggest that orthostatic tachycardia is related more to other non-autonomic factors.

9.2.2. Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire

The acceptability of the medical device intervention will be measured using an adapted version of the Theoretical Framework of Acceptability (TFA) questionnaire developed by Sekhon et al. (2022). The TFA is a validated, theory-informed model that defines acceptability as a multifaceted construct comprising seven components: affective attitude, burden,

ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. This framework enables assessment of both prospective and retrospective acceptability from the perspective of intervention recipients and providers across different stages of intervention delivery. A generic TFA-based questionnaire was developed and pre-validated using a systematic 5-step method, including item generation, discriminant content validation, and stakeholder feedback. For this study, the questionnaire will be tailored to reflect participant experience of the use of GammaCore medical device. Each construct will be assessed using a single-item measure alongside a general acceptability item, using a 5-point Likert scale. This approach offers a structured yet flexible method to identify potential barriers and inform future optimisation of the intervention (Sekhon et al., 2022).

10. STUDY PROCEDURES BY VISIT

10.1. Summary schedule of study assessments

Specific Activity	**Duration (Minutes)**	**Undertaken by**	Day -x	Day 0	Days 1-14	Day 15 (+/- 2 days)	Days 15-28	Day 28 (+/- 2 days)	Days 29-42	Day 43
			Screen	**Baseline/ Visit 1**		**Visit 2**		**Visit 3**		**Final Visit**
Identification of chronic pain participants		Local Outpatient Staff	✓							
Approach of potential participants		Local Outpatient Staff	✓							
Check eligibility		Research Team	✓							
Trial consent	30	Research Team	✓							
COMPASS-31 questionnaire	5	Research Team + participant	✓			✓		✓		✓
Study survey (BPI-SF, HADS, EQ-5D-5L)	15	Research Team + participant		✓		✓		✓		✓
NASA lean test	10	Research Team + participant		✓		✓		✓		✓
Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire	10	Research Team + participant								✓
Device training	20	Research Team		✓						
Device distribution	-	Research Team		✓						

Randomly assigned intervention (GammaCore vagus nerve stimulation / sham vagus nerve stimulation)	2	Participant			✓				✓	
Stimulation diary	2	Participant			✓				✓	
Wash-out period – 2 weeks	-	Participant					✓			

10.2. Screening visit (Day -x to Day 0) – in person at CAH

During the screening visit, potential participants will be identified as either chronic pain patients with dysautonomia or chronic pain patients without dysautonomia. Written informed consent will be obtained. Participants will complete Composite Autonomic Symptom Score (COMPASS-31) questionnaire. Eligibility will be assessed and confirmed. Identification procedures and consent will not be included in the CRF, as they are not intended for data analysis; however, the score of COMPASS-31 questionnaire and the eligibility assessment will be recorded in the CRF.

10.3. Baseline (Day 0 / Visit 1) - in person at CAH

At baseline, participants will complete the study survey, which consists of:

- Brief Pain Inventory – Short Form (BPI-SF)
- Hospital Anxiety and Depression Scale (HADS)
- EuroQol EQ-5D-5L Quality of Life Questionnaire

They will also undergo the NASA Lean Test. These assessments will be recorded in the CRF and used for data analysis. Device training and distribution will take place during this visit; however, these are procedural activities only and will not be recorded in the CRF.

10.4. Randomly assigned intervention: GammaCore vagus nerve stimulation / sham vagus nerve stimulation (Days 1 – 14)

Participants will perform twice daily vagus nerve stimulation using the GammaCore device and will record their use in a stimulation diary. Both activities will be captured in the CRF and included in the data analysis.

10.5. Visit 2 (Day 15, ±2 days) in clinic or remotely (via Teams) in-person or remotely via Microsoft Teams

At this visit, participants will complete the COMPASS-31 questionnaire and the study surveys (BPI-SF, HADS, and EuroQol EQ-5D-5L).

For in-person visits: Questionnaires can be completed online via REDCap before the appointment or on paper at the clinic. The NASA Lean Test will be performed at the clinic under researcher supervision.

For remote visits: Participants will receive a secure REDCap link to complete the questionnaires online prior to the Microsoft Teams appointment. Participants will perform the NASA Lean Test at home using the blood pressure monitor provided at baseline, guided by the researcher via video call.

All assessments will be recorded in the CRF for data analysis.

10.6. Wash-out Period (Day 15–28)

A two-week wash-out period will follow, during which no study interventions will be undertaken. This period is procedural only and will not be recorded in the CRF.

10.7. Visit 3 (Day 28, ±2 days) - in person at CAH

At this visit, participants will complete the COMPASS-31 questionnaire and the study surveys (BPI-SF, HADS, and EuroQol EQ-5D-5L). Questionnaires can be completed online via REDCap before the appointment or on paper at the clinic. Participants will also repeat the NASA Lean Test at the clinic under researcher supervision.

The GammaCore device will be adjusted by the researcher to the alternate setting (active or sham) for the second treatment phase to maintain blinding. This visit must be conducted in person at Chapel Allerton Hospital to allow for device adjustment.

All assessments will be recorded in the CRF for data analysis..

10.8. Randomly assigned intervention: GammaCore vagus nerve stimulation / sham vagus nerve stimulation (Day 29-42)

Participants will perform twice daily sham vagus nerve stimulation and record usage in a stimulation diary. All procedures will be documented in the CRF and included in the analysis.

10.9. Final visit (Day 43, ±2 days in-person or remotely via Microsoft Teams

At the final visit, participants will complete the COMPASS-31 questionnaire and the study surveys (BPI-SF, HADS, and EuroQol EQ-5D-5L). In addition, they will complete the Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire and a blinding assessment questionnaire.

For in-person visits: Questionnaires can be completed online via REDCap before the appointment or on paper at the clinic. The NASA Lean Test will be performed at the clinic under researcher supervision.

For remote visits: Participants will receive a secure REDCap link to complete the questionnaires online prior to the Microsoft Teams appointment. Participants will perform the NASA Lean Test at home using the blood pressure monitor provided at baseline, guided by the researcher via video call.

All assessments will be recorded in the CRF for data analysis.

10.10. Withdrawal

In the event of withdrawal, participants will be asked to complete the same assessments scheduled for the completion visit, that is COMPASS-31 questionnaire, study survey (BPI-SF, HADS, EuroQol EQ-5D-5L), the NASA Lean Test, and the Theoretical Framework of Acceptability (TFA) / Participant Feedback Questionnaire. Data from these assessments will be recorded in the CRF and included in the analysis.

11. SAFETY ISSUES

11.1. RISK ASSESSMENT

Risk	Likelihood	Severity	Mitigation strategy
Device-related adverse events (tingling, skin redness, headache, dizziness)	Moderate	Low	• Comprehensive device training at baseline • Written instructions provided • Daily diary to monitor symptoms • Contact details provided for concerns
Incorrect device use	Low	Low	• Face-to-face training with demonstration • Written instructions • Practice session at baseline • Follow-up at Visit 2 to check technique
NASA Lean Test - dizziness or fainting	Low	Low	• Test performed under supervision at baseline • Participants can stop at any time • For home tests: participants instructed to

			have support nearby • Clear stopping criteria provided
Distress from questionnaires (HADS - mental health questions)	Low	Low	• Participants informed in PIS about questionnaire content • Can decline to answer any question • Can withdraw at any time • Contact details provided for concerns

11.2. Defining adverse events (AEs) and serious adverse events (SAEs)

An adverse event (AE) refers to any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the research procedure.

A serious adverse event (SAE) is an adverse event which is defined as serious, i.e. that it:

- Results in death. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the patient's final research clinic appointment must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
- Is life-threatening.
- Requires inpatient (overnight) hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the Investigator requires reporting.

11.3. AEs of special interest

Only relevant adverse events (AEs) will be recorded in the (e)CRF. The following are examples of AEs that are NOT considered relevant and will NOT be recorded:

- Pre-existing condition that does not worsen.
- Planned hospitalisations for pre-existing conditions.
- Events that happen before a participant gives informed consent.
- Medical events related to the chronic MSK condition that do not put the patient at risk (e.g., severe back pain).
- Any abnormal lab results related to co-morbidities the participant has.

11.4. Pregnancy

As pregnancy is an exclusion criterion for this study, participants who become pregnant during the trial will be withdrawn immediately. All pregnancies will be followed up until birth. Should there be a congenital anomaly or birth defect, this will be reported as an SAE to the main REC and Sponsor if, in the opinion of the chief investigator, the congenital anomaly or birth defect is related to the research treatment or procedure.

11.5. Defining related and unexpected serious adverse events (RUSAEs)

A serious adverse event suspected to have a reasonable causal relationship to the study treatment or procedure which is unexpected i.e. where the nature or severity is inconsistent with the available information relating to the treatment or procedure or is not listed in this protocol as an expected occurrence is subject to expedited reporting.

11.5.1. Recording and reporting of (RU)SAEs

Relevant adverse events (AEs) will be collected and recorded on the eCRF from the signing of the informed consent form until 30 days after the final study appointment. AEs will be assessed and recorded at every study visit.

Determination of SAEs should be based on signs or symptoms detected during physical examination and clinical evaluation of the participant. Signs and symptoms must be recorded using standard medical terminology. Participants considered incapable of giving consent will not be included in this study.

SAEs will be collected from the signing of the informed consent form until 30 days after the final study appointment. The Investigator must instruct participants to report all AEs and SAEs during this time period. Participants will be required to promptly report any suspected serious adverse events (SAEs) to an investigator via telephone. In the event of a suspected SAE, the participant will be requested to return to the study site for further clinical evaluation and appropriate management.

During the time period specified above, the investigator will:

- Record all AEs and SAEs on source documents
- Record all AEs and SAEs in the eCRF for participants who are not screen failures
- Report all RUSAEs on a 'Serious Adverse Event report form for non-CTIMPs', available from the NRES website, and send to the main REC for the trial

All SAEs and RUSAEs will be reviewed by the Chief Investigator within 24 hours.

The following will be collected and reported to the Sponsor office (governance-ethics@leeds.ac.uk) within 1 working day of the research team becoming aware of the event:

- Full details in medical terms
- Event duration (start and end dates, if applicable)

- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to research investigation), in the opinion of the investigator whether the event would be considered expected.

The Sponsor will maintain detailed records of the SAEs reported by an investigator in accordance with good clinical practice and applicable local regulations.

The Investigator will follow up on all SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized. SAEs that are (or develop into) chronic conditions will be followed up until it is established that the condition is chronic at which point no further follow-ups will be made since the condition will unlikely resolve.

11.5.2. RUSAE reporting requirements

All SAEs identified by the local Investigator as both likely to be related to protocol-treatment and unexpected will be reviewed by the Chief Investigator (CI). The CI, local PI or other qualified and delegated individual may declare an SAE a RUSAE. This may be downgraded in discussion with the CI but if no agreement can be made or in the absence of the CI the event should be reported as a RUSAE. A RUSAE once reported can be downgraded at a later date upon the receipt of new information.

Identifiable patient data, other than linked anonymised data required by the NRES non-CTIMP SAE form, must not be included when reporting RUSAEs.

The CI will then inform the Research Ethics Committee (REC) that gave the favourable opinion for the study of RUSAEs within the required expedited reporting timescales. RUSAEs must be reported to the REC within 15 calendar days of the CI (or their research team) being informed of the event.

RUSAEs will be reported in accordance with the principles of GCP and the UK Policy Framework for Health and Social Care Research 2017. They will all be signed off by the Principal Investigator or, in their absence, by a delegated individual.

12. URGENT SAFETY MEASURES

If the research team becomes aware of information affecting the risk/benefit balance of the trial, they may take immediate action to ensure patient safety. Urgent safety measures deemed necessary must be reported immediately or within 1 working day of research team awareness to the Sponsor (governance-ethics@leeds.ac.uk). The principle Investigator must also notify the main Research Ethics Committee (REC) within 3 days of implementing any

urgent safety measures, providing details of the measures taken and the reasons for taking them.

12.1. Serious breaches of protocol

A **serious breach** is a breach which is likely to effect to a significant degree either:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Serious breaches of GCP will be reported to the Sponsor (governance-ethics@leeds.ac.uk) within 24 hours (same day, except weekends) from the time the research team becomes aware of the incident.

13. STUDY MANAGEMENT AND ADMINISTRATION

13.1. Good clinical practice (GCP)

This clinical trial will be run in accordance with the Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

13.2. Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor and the REC in writing regarding the type of emergency and the course of action taken.

13.3. Monitoring and audit

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the study contract or agreement. A site may be audited by DRMD or an independent contractor working for DRMD, and the Investigator should allow direct access to trial documentation.

13.4. Study management

13.4.1. Definition of source data

Source documents are original records in which raw data are first recorded. These may include, e.g. hospital/clinic/general practitioner records, charts, diaries, laboratory results, printouts, care records, ECG or other printouts, completed scales, or Quality of Life Questionnaires. Source documents should be kept in a secure, limited access area.

Some data will be recorded directly in the CRF and will not appear in a source document as defined in the Source Data Verification form.

13.4.2. Source data verification

Source data verification ensures accuracy and credibility of the data obtained. The Investigator will review the reported data to ensure they are accurate, complete, and verifiable from source documents (e.g. subject files, recordings from automated instruments, ECG tracings, x-ray films, laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in section 13.4.1. Data Verification and will be carried out by the Investigator(s) and members of the study team who will check the case report forms for completeness and clarity, and crosscheck them with source documents.

13.4.3. Study oversight

This study is part of a PhD and will be regularly reviewed with the supervisors.

13.5. Data handling

13.5.1. CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports. Any change or correction to the CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted. Screen failure data will not be entered in the (e)CRF. The Investigator should maintain a list of personnel authorized to enter data into the eCRF. Detailed instructions will be provided in the CRF Instructions.

13.5.2. Database entry and reconciliation

All clinical and participant-reported data will be recorded and managed on Leeds Teaching Hospitals NHS Trust (LTHT) systems, specifically the REDCap database, up to and including the point of data lock. Identifiable data, including participant contact details and the code link document, will be stored separately in a locked filing cabinet at Leeds Institute of Rheumatic and Musculoskeletal Disease (LIRMM), with access restricted to authorised personnel only. Clinical and research data will be stored in anonymised form on the REDCap database, linked only by the unique study ID code. Identifiable data will be stored separately from clinical and research data to ensure participant confidentiality. Once data collection is complete and the database has been locked, an export of the anonymised research dataset will be securely transferred to the University of Leeds's nominated statistician for analysis. A copy of this final dataset, alongside all outputs, tables, and code from statistical analyses, will be stored securely on University of Leeds server space managed by LIRMM for the duration of the required retention period. Data will only be shared between the clinical site (Chapel Allerton Hospital) and the Sponsor site (University of Leeds LIRMM Department, located within the same building at Chapel Allerton Hospital). No identifiable data will be transferred electronically or physically outside of these premises, minimising any risk of confidentiality breaches. Regular backups of electronic data will be performed.

13.5.3. Screening and enrolment logs

Subject's Screening will be recorded in the Subject Screening Log.

The Investigator will keep a list containing all subjects enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date informed consent signed, date of screening, and the hospital number or National Health Security number, if applicable.

The subject's consent and enrolment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.6. Archiving and data retention

Although not required by law for non-CTIMPs, in line with the principles of GCP essential study documents will be retained for a minimum of 5 years following the completion of the study. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.

Essential documents include (this list is not exhaustive):

- Signed informed consent documents for all subjects.
- Subject identification code list, screening log (if applicable) and enrolment log.
- Record of all communications between the Investigator, the REC and the Sponsor.
- Composition of the REC, and the Sponsor (or other applicable statement as described in section 14.5.
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and documentation of corrections for all subjects.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

13.7. Study suspension, termination and completion

Suspension or termination of the study may occur at any time for any reason, following discussion between the Investigator and the Sponsor. Upon study completion, the Investigator will provide the Sponsor with final reports and summaries as required by regulations and will be responsible for completing a premature end of study report to the Research Ethics Committee (REC) within 15 days.

Study completion will be defined as the time at which the last data item has been locked for the last recruited participant.

14. DATA EVALUATION

14.1. Responsibilities

Norah Almutairi will be responsible for data evaluation under the supervision of Dr. Darren Greenwood and Professor Manoj Sivan. Data analysis will be performed collaboratively, with oversight provided by the supervisors. The final reports will be written by Norah Almutairi, with input, review, and approval from Dr. Darren and Professor Manoj.

14.2. General statistical considerations

In general, summary statistics [n (number of available measurements), arithmetic mean and standard deviation, median and interquartile range] for quantitative variables and absolute and relative frequency tables for qualitative data will be presented, as appropriate.

Estimates will be presented with 95% confidence intervals and two-tailed tests used throughout. Results will be taken to be statistically significant at two-tailed $P<0.05$.

No adjustment will be made for the stratifying factor as the treatment comparison is within-person. No corrections for multiple comparisons are planned.

Wherever possible the trial will be reported in accordance with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement, including CONSORT recommendations for presentation of crossover trials.

14.3. Planned analyses

Statistical analysis will be performed in Stata (StataCorp 2023, Release 18 or higher, Texas, United States).

Exploration of the effect of the intervention on daily the primary outcome (COMPASS-31 score) and continuous secondary outcomes (BPI-SF pain severity, BPI-SF, impact of pain, HADS depression and anxiety scores, EQ-5D-5L quality of life, TFA-based Participant Feedback Questionnaire) will be evaluated using the pkcross package in Stata, to implement the appropriate ANOVA model. The secondary outcome of physiological response to the lean test

(scored positive/negative response) will be evaluated using the equivalent mixed-effects logistic regression model.

The models will take sequence, period and intervention (active or sham) as covariates.

Response rate to invitation to participate will be summarised as above using descriptive statistics.

14.4. Safety analyses

Line listings of all SAEs will be provided in the end of trial report. The frequency of all SAEs recorded during the study period will be presented. The data will be displayed as number of subjects experiencing the SAEs, percentage of subjects, and number of SAEs. Data will also be corrected for exposure by 100 patient-years.14.5. Handling of dropouts and missing data

Based on our previous work with the COMPASS-31 questionnaire and the NASA lean test in the same population, we do not anticipate substantial losses to follow-up. The primary analysis will therefore be on a complete case basis. However, were necessary, we will use linear mixed-effects models rather than ANOVA, as they handle missing data more effectively.

14.5. Determination of sample size

Sample size determination is based on Senn (2002). Based on our previous study of autonomic function in people living with chronic MSK pain, we assume a standard deviation of the COMPASS-31 score is approximately 20. A minimal clinically important difference (MCID) has not been established for COMPASS-31 in people living with chronic MSK pain, so we assume an MCID of 0.5 standard deviations, i.e. 10 points on the COMPASS-31 score. In addition, based on previous literature, the intraclass correlation for COMPASS-31 across a range of populations and conditions is consistently between 0.8 and 0.9 (Tresister et al., 2015; Drulovic et al., 2017; Ahn et al., 2021; Is et al., 2021), so we assume the intraclass correlation is 0.85. This indicates how similar the repeated compass-31 measures are across the time periods.

Based on these figures, to achieve 80% power to detect a difference in COMPASS-31 scores between tVNS and sham of 10 points, at two-tailed $P<0.05$, needs complete data on n=12 participants in total, receiving both interventions in random order.

While we expect dropout to be minimal in this study, it is sensible to plan for some uncertainty. To provide flexibility, we may recruit up to 16 participants, ensuring that complete data are available for at least 12.

15. ETHICS AND REGULATORY REQUIREMENTS

15.1. Good Clinical Practice

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the Good Clinical Practice (GCP) and the recommendations guiding ethical

research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. The Research Ethics Committee (REC) must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the REC-approved informed consent form. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (REC) and the appropriate regulatory authorities prior to entering patients into the study.

15.2. Delegation of Investigator duties

The Investigator should ensure that all persons assisting with the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial related duties and functions.

The Investigator should maintain a delegation log of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

15.3. Subject information and informed consent

Before being enrolled in the study, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document (Patient Information Leaflet) that includes both information about the study and the consent form will be prepared and given to the subject at least 24 hours prior to the screening visit. This document will contain all the elements required by the Good Clinical Practice and any additional elements required by local regulations.

At the screening visit, patients will be given the opportunity to ask questions, and the nature and objectives of the study will be explained by the study doctor responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions, the study doctor.

The original signed consent document will be retained in the study files. Other copies of the consent form are required:

- One copy of the informed consent document will be kept in the patient’s clinical notes.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

15.4. Subject confidentiality

Only the subject number will be recorded in the case report form, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to anyone outside the clinical care team. The subjects will be informed that representatives of the Sponsor, Research Ethics Committee (REC) or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence.

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically.

The study will comply with all aspects of the Data Protection Act 2018.

15.5. Approval of clinical study protocol and amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC and the Sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the NHS, the Sponsor Research and Development department and the REC.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised, thus all protocol amendments and administrative changes must first be discussed with and approved by the Sponsor before being submitted to the REC, in accordance with legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised.

The Investigator must keep a record of all communication with the REC and the Sponsor.

15.6. Protocol amendments

Requests for any amendments to the study must be sent to the Sponsor by the Chief Investigator. The Sponsor will determine whether said amendments are substantial or non substantial prior to their submission to the appropriate bodies for approval. Patients should

be reconsented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Patients should only be re-consented AFTER an amendment has been fully approved.

15.7. Ongoing information for Research Ethics Committee

Unless otherwise instructed by the REC and the Sponsor, the Investigator must submit to the REC and the Sponsor:

- Information on serious adverse events that are unexpected and related to study procedures (RUSAEs) from the Investigator's site, within 15 calendar days of the research team becoming aware of them.
- Expedited safety reports, as soon as possible.
- The NRES Declaration of End of Study form.

16. FINANCE AND INSURANCE

16.1. Indemnity and insurance

The University when acting as sponsor, has insurance cover in force, which meets claims arising from death or injury, which are brought against the University and where those claims arise from the Universities own negligence in its role and activities relating to the study (and which is subject to the terms, conditions and exceptions of the relevant policy). Clinical negligence indemnification will rest with the participating NHS Trust under standard NHS arrangements.

16.2. Financial disclosure

None of the Investigators or members of the research team have any financial involvement with the sponsorship or funding bodies or will receive personal benefits, incentives or payment over and above normal salary.

17. PUBLICATION

The results of this study will be disseminated through: Peer reviewed scientific journals, internal report, conference presentation, publication on website, thesis and others.

The personal data gathered will be anonymised as soon as it is practical to do so (right after the experiment is completed by the participant). This means that all identifiable data will be destroyed. When publishing occurs, all data will be anonymous and be non-identifiable.

Participants will be given the option of receiving a summary of the results obtained from the research. If they are interested in receiving this information, they will be requested to provide contact details (email or postal address) that will not be linked in any way to the data they

have provided in the study. Once the data is analysed and results are obtained from the study a lay summary of the conclusions will be sent to the contact details provided by participants.

18. REFERENCES

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