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Differential target multiplexed spinal cord stimulation in patients with Persistent Spinal Pain Syndrome Type II: a study protocol for a 12-month multicentre cohort study (DETECT)

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ABSTRACT

Introduction Differential target multiplexed spinal cord stimulation (DTM SCS) is a new stimulation paradigm for chronic pain management with the aim of modulating glial cells and neurons in order to rebalance their interactions. Animal studies revealed positive effects of this type of stimulation; however, studies in humans are still scarce, pointing towards the need for an evaluation of the effectiveness and safety of DTM SCS in clinical settings. Furthermore, the differential target multiplexed (DTM) algorithm consists of a combination of several programmes, which will presumably consume more energy from the spinal cord stimulation (SCS) battery. Therefore, the objective of DETECT is to investigate the feasibility, effectiveness and safety of DTM SCS in patients with Persistent Spinal Pain Syndrome Type II through a longitudinal cohort study.

Methods and analysis DETECT is a prospective multicentre cohort study (n≥250) with a follow-up until 12 months after receiving DTM SCS. The study initiated in October 2021 and is currently still recruiting patients. Self-reporting outcome variables were evaluated at baseline (before SCS) and at 1, 6 and 12 months of DTM SCS. The primary effectiveness endpoint is overall pain intensity, measured with the visual analogue scale. Secondary effectiveness outcome measures are back pain intensity, leg pain intensity, disability, health-related quality of life, pain medication use, functional disability, clinical holistic responder status, self-management, impression of change, work status, pain catastrophising, symptoms of central sensitisation, anxiety, depression and healthcare utilisation. Time spent in different body postures and SCS stimulation parameters will be read out from the pulse generator. The prevalence of technical issues, recharge frequency, (serious) adverse events and the proportion of successful DTM trials will be collected as well. Longitudinal mixed models will be calculated to evaluate the effectiveness of DTM SCS over time.

Ethics and dissemination The study protocol was approved by the central Ethics Committee of the Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (B.U.N.1432021000563) and the Ethics Committees of each participating centre. Research findings will be disseminated to key stakeholders through peer-reviewed publications in scientific journals and presentations to clinical audiences.

Trial registration number NCT05068011.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will reflect the effectiveness of differential target multiplexed spinal cord stimulation in standard clinical practice on different treatment outcomes in patients with Persistent Spinal Pain Syndrome Type II to provide complementary evidence to the available RCT data.
⇒ A broad range of outcome variables will be investigated with a rigorous follow-up until 12 months after implantation, even after reprogramming to another modality.
⇒ The results of this study will be collected in Belgium, potentially limiting the generalisability of the results towards other parts of the world.

INTRODUCTION

Spinal cord stimulation (SCS) is a well-established pain management technique with beneficial effects on different domains of life, among which disability and health-related quality of life.[1 2] Specifically for patients with Persisting Spinal Pain Syndrome Type II, that is, chronic pain that is persisting after spine surgery, SCS is considered an efficient treatment option.[3] Standard or so-called 'conventional' SCS typically involves electrical pulses delivered at a frequency of 50–60 Hz[4] generating paraesthesias in the painful area which underpin the mechanism for pain reduction in this type of SCS. To optimise pain control and to minimise the side effects of conventional SCS (eg, uncomfortable SCS-induced paraesthesia, discomfort due to paraesthesia variability by postural changes),[5 6] newer SCS

algorithms have been introduced of which differential target multiplexed (DTM) stimulation is one of the latest developed stimulation paradigm.[7]

Based on the hypothesis that different patterns of SCS activate unique pain-relieving mechanisms,[8] potential 'distinctive therapies' may be offered that provide more choices for patients, offer improved pain relief with extended programming possibilities or target a specific mechanism underlying a pain syndrome. One option involves multiple electrical signals that can be different from each other in several aspects such as frequencies, pulse width and amplitudes, whereby electrical fields could differentially target neurons versus glial cells in the spinal cord.[9] In a preclinical study with rats, multiplexed charge–balanced pulsed signals with frequencies ranging from 20 Hz to 1200 Hz and a maximum pulse width of 500 µS have shown significantly better results than stimulation at 50 Hz (150 µs pulse width) or stimulation at 1200 Hz (50 µs pulse width) for mechanical hypersensitivity using the spared nerve injury model of neuropathic pain.[9] Moreover, gene expression levels of cell-specific transcriptomes were compared between different multiplexed signals, low frequencies and high frequencies versus no SCS versus healthy animals to further elucidate the specific targeting of neurons and glial cells.[10] Differential target multiplexed programming yielded significant correlations to expression levels found in the healthy animals across every evaluated cell-specific transcriptome (ie, microglia, astrocyte, oligodendrocyte and neuron). High rate programming only yielded a strong correlation for the microglia-specific transcriptome, and low rate programming did not yield strong correlations with these cell types.[10] In another experiment to exclusively evaluate microglia-specific activation transcriptomes, multiplexed stimulation revealed higher correlation values with expression levels found in healthy animals, higher than those found with low frequency and high frequency stimulation.[11] Based on these animal studies, it is proposed that DTM stimulation uses multiple electrical signals with the aim of modulating glial cells and neurons in order to rebalance their interactions.[12]

Studies with DTM SCS in humans are still scarce.[13] Up until now, only a couple of studies are available in which the effect of DTM and conventional SCS was explored in patients with chronic intractable pain,[14–16] besides a number of ongoing studies among which the ones of Tanei *et al*.[17 18] Both SCS types were able to significantly reduce back pain intensity. However, a significantly stronger pain reduction was obtained with DTM compared with conventional SCS,[14] suggesting superiority of DTM SCS compared with standard SCS.[15] Moreover, in patients suffering from axial low back pain with or without leg pain and who are ineligible for spinal surgery, DTM SCS proved to be superior to conventional medical management.[19] Additionally, in this population of patients who are non-surgical candidates, DTM SCS also proved to be superior to conventional SCS.[16]

Objectives

Despite the promising results of animal studies and the initial positive experiences from clinical practice, there still is a need for expanding the evidence on the benefits and safety profile of DTM SCS. Additionally, since DTM consists of interleaving of several programmes, the long-term impact of which on battery utilisation and patient acceptance has yet to be evaluated. DTM SCS includes therapy with a low rate (<200 Hz) and high rate (200–1200 Hz) waveform applied at two targets, with and without cycling. Presumably combining several programmes will consume more energy from the SCS battery, which may necessitate the use of rechargeable implantable pulse generators (IPG). However, depending on the specific parameters of the SCS programmes, energy consumption can be variable. The various combinations of DTM SCS that are currently used in clinical practice (ie, various frequencies combined with various configurations) need to be documented. Additionally, safety outcomes of this modality will be evaluated as well. Therefore, the objective of DETECT is to investigate the feasibility, effectiveness and safety of DTM SCS in patients with Persistent Spinal Pain Syndrome Type II (PSPS-T2) through a longitudinal cohort study up to 12 months after receiving DTM SCS. It is our hypothesis that DTM SCS is a safe and feasible pain management option for this patient population.

METHODS AND ANALYSIS

Study design

This prospective multicentre cohort study is being conducted to evaluate DTM SCS for patients with PSPS-T2. Recruitment is ongoing in 14 centres in Belgium (both academic and regional hospitals), all with ample SCS experience, high standards of care and sufficient volume of PSPS-T2 patients for participation in DETECT. Details on study sites can be found at ClinicalTrials.gov with Identifier: NCT05068011, 5th of October, 2021.

Recruitment has started in October 2021 and will be ongoing until 250 patients are included in the study. Randomisation and blinding are not applicable because all patients in this study will receive DTM SCS as part of Good Clinical Practice.

Eligibility criteria

This study is focusing on patients with chronic back and leg pain (due to PSPS-T2) who previously underwent spinal surgery and are scheduled for SCS implantation. In total, 250 patients will be enrolled in this study. This sample size should be sufficient to explore the feasibility, safety and effectiveness of DTM SCS. No formal sample size calculation has been conducted. A trial failure rate of 11.3% is expected.[20] Inclusion criteria are:

- Being diagnosed with PSPS-T2 (defined as the surgical end stage after one or several operative interventions

on the lumbar neuroaxis, indicated to relieve lower back pain, radicular pain or the combination of both without positive effect[21]) with chronic back and leg pain and refractory to best medical treatment.
- Having chronic pain as a result of PSPS-T2 that exists for at least 6 months with a pain intensity of 5 or higher measured on numeric rating scale, a tool mentioned in the Belgian legislation for reimbursement,[22] for the dominant pain location.
- Being offered treatment with DTM SCS as primary treatment option (ie, scheduled for SCS implantation with DTM stimulation).
- Being at least 18 years old.

Exclusion criteria are:
- Expected inability of patients to properly operate the SCS system.
- History of coagulation disorders, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis or Morbus Bechterew.
- Active malignancy.
- Addiction to drugs, alcohol (more than 5 units/day) and/or medication.
- Evidence of an active disruptive psychiatric disorder or other known condition significant enough to impact perception of pain, compliance to intervention and/or ability to complete questionnaires, as determined by the investigator.
- Immune deficiency (eg, HIV positive, immunosuppressive).
- Life expectancy<1 year.
- Local infection or other skin disorder at site of incision.
- Pregnancy.
- Other implanted active medical devices.

Interventions

The treating neurosurgeon or anaesthesiologist (local principal investigator or his/her designee) informs eligible patients of the project. Patients who wish to explore participation in the project are being screened for in- and exclusion criteria. Patients who are eligible for participation and are willing to participate receive detailed oral and written information about the study and have the opportunity to ask questions. Subsequently, they are asked to provide written informed consent before participation.

After the baseline visit, patients undergo an SCS trial period (21 days in Belgium), followed by IPG implantation in case of a successful trial period (50% pain reduction and 50% reduction in pain medication use, according to the current Belgium reimbursement rules). All IPGs are allowed, as long as they are able to apply DTM settings. More concrete, the following types are used: Medtronic Inceptiv implantable neurostimulator or Intellis implantable neurostimulator with AdaptiveStim technology. With respect to the leads, both percutaneous (Vectris SureScan MRI 1×8 Compact lead) and surgical (Specify 5-6-5 SureScan MRI) leads are used. In humans, the DTM algorithm consists of two principles. Principle 1 is called 'multiplexed frequencies'. A low-rate programme or 'base' is a programme with a frequency that varies between 20 Hz and 200 Hz. This base programme is combined with a high-rate component or 'prime', with a rate varying between 200 Hz and 1200 Hz. Principle 2 is called 'multiple targets' or the different configurations on the lead. The base and prime programmes use different cathode and anode configurations. So, DTM SCS includes therapy with a low-rate (200 Hz) and high-rate (200–1200 Hz) waveform applied at two targets, with and without cycling. Intensities are set according to a DTM SCS algorithm, starting at a percentage below the perception threshold and working them up at regular intervals until reaching therapeutic levels (merely subperception threshold). Patients can adjust intensity, and selected DTM SCS options are based on optimal pain relief.[15]

Patients who after an adequate trial period prefer to discontinue DTM SCS can be programmed with another SCS modality. The reasons for changes in the therapeutic regime will be documented, and follow-up will take place according to the protocol, even if a different stimulation paradigm is provided.

Outcomes

Effectiveness outcomes

The primary effectiveness outcome measure is overall pain during the last 7 days, defined as a combination of back and leg pain, but not pain from other body parts, measured with the visual analogue scale (VAS). The VAS (100 mm) pain score is believed to be reliable, valid and sensitive to change.[23 24] The primary endpoint is the difference in pain intensity scores over time from baseline up to 12 months of DTM SCS.

Several secondary effectiveness outcome measures are being collected (randomised order):
- Pain intensity for the lower back and leg pain component is assessed separately with the VAS. In line with the primary effectiveness outcome, pain intensity for the last 7 days will be assessed on a 10-cm line.
- Medication use, which entails the type of medication, dosage and frequency, is being recorded systematically at each visit. Medication will be converted to one score with the Medication Quantification Scale III (MQS III).
- The Oswestry disability index (ODI) is used to measure functional disability due to abnormalities of the spine.[25 26]
- Health-related quality of life is assessed with the EuroQol with five dimensions and five levels (EQ-5D-5L).[27] The EQ-5D-5L index scores range from 0 to 1, with 0 and 1 corresponding respectively to death and full health, based on preference-weighted health state classification algorithms.[28]
- The impression of change after DTM SCS is evaluated through the Patient Global Impression of Change Scale (PGIC). The PGIC consists of a 7-point Likert scale asking the respondent to rate the overall level

of improvement since start of the treatment as 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse' and 'very much worse'.[29]

- The clinical holistic responder status[30] will be determined after data collection and serves as composite measure for success, based on a combination of pain intensity, medication use, disability, quality of life and impression of change measurements.
- Patient Activation Measure-13 (PAM-13) is a 13-item instrument to determine self-reported behaviour, knowledge and confidence for self-management of one's health. PAM-13 has proven to be a reliable instrument to measure patient activation and self-management.[31 32]
- A self-designed questionnaire is being used to evaluate return to work after spinal surgery.[33 34] At baseline, current work status, job type, job description and work regime (eg, full time, part time) are asked. At the follow-up visits, patients fill in whether they already resumed professional activities, and if yes, since when and to what extent. Additionally, patients receive the opportunity to indicate whether a job change was needed or whether their job content needed to be changed to enable effective work resumption.
- The Pain Catastrophizing Scale (PCS) is used to measure the level of pain catastrophising. The internal consistency, test-retest reliability and validity are acceptable for chronic pain patients.[35 36]
- The Central Sensitization Inventory (CSI) consists of 25 symptom-related opinions that require a score on a 5-point Likert scale to evaluate the presence of central sensitisation–associated symptoms.[37] The clinometric properties of the CSI are good in chronic pain patients.[37 38]
- The Hospital Anxiety and Depression Scale (HADS) measures symptoms of anxiety and depression and consists of 14 items: seven items for the anxiety subscale (HADS Anxiety) and seven for the depression subscale (HADS Depression). The HADS was found to perform well in assessing the symptom severity of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population.[39]
- Postoperative healthcare expenditure is investigated by self-reporting methods. Hence, postoperative healthcare expenditure includes the number of days spent in hospital following surgery, medical tests related to postoperative surgery and any kind of post-surgical treatments (eg, pain killers, physiotherapy, psychotherapy, programming sessions).
- Based on the AdaptiveStim technology, the time spent in seven body postures can be recorded from the IPG. If this feature is activated, the data are being extracted from SCS implantation up to 1 month of SCS, from 1 month of SCS up to 6 months and from 6 months up to 12 months.

Safety-related outcome

The primary safety outcome variables are the number of serious adverse events (SAEs) and adverse events (AEs). Any adverse change in health or the appearance or worsening of any undesirable sign, symptom or medical condition occurring after enrolment into the trial is documented as AE (whether or not it is considered to be related to the intervention). Afterwards, AEs will be categorised according to severity and relationship to device and procedure.

An SAE is considered any untoward medical occurrence (whether considered to be related to the investigational intervention or not) that is fatal or life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity, constitutes a congenital anomaly or birth defect, requires intervention to prevent permanent impairment or damage, or is an important medical event. An unexpected SAE is an AE of which the nature or severity is not consistent with the expected side effects or risks of the intervention (suspected unexpected adverse reaction, SUSAR). Hospitalisations which are the result of elective or previously scheduled surgery for pre-existing conditions which have not worsened after initiation of treatment will not be classed as SAEs.

SAEs and SUSARs will be reported to relevant Competent Authorities and to the Ethics Committee, in accordance with the European Union Clinical Trial Directive. The investigator is responsible for the evaluation and report of these events during the study. AEs are recorded in the AE form in Qualtrics; however, SAEs require reporting to the sponsor and principal investigator within 24 hours.

Feasibility-related outcome

Feasibility is being evaluated by determining the proportion of successful DTM trials. As a technical feasibility, the prevalence of technical issues with regard to DTM SCS and battery consumption/recharge frequency is questioned and programming parameters for the different programmes that are provided within DTM SCS are recorded. Identification of clinical effective parameters concerning frequency, pulse duration and amplitude occurs at each visit after implantation.

Table 1 provides an overview of the outcome measurements at each visit.

At baseline, demographic data are recorded. All effectiveness outcomes are being evaluated, except for impression of change, postoperative healthcare utilisation and the time spent in body postures. One month after IPG implantation, the second assessment takes place during which all outcome measures are being evaluated except for work status. Six months and 12 months after IPG implantation, all outcomes are evaluated. Unscheduled visits can be conducted according to daily clinical routines of the participating centres and will be documented through healthcare expenditures. The project flowchart is presented in figure 1.

Table 1 Overview of the outcome measurements at each study visit for DETECT

Outcome measurements	Evaluation tool	Baseline screening	DTM SCS		
		V0	V1 (1 month)	V2 (6 months)	V3 (12 months)
Overall pain	VAS	X	X	X	X
Leg pain intensity	VAS	X	X	X	X
Back pain intensity	VAS	X	X	X	X
Disability	ODI	X	X	X	X
Medication use	MQS III	X	X	X	X
Quality of life	EQ-5D-5L	X	X	X	X
Impression of change	PGIC		X	X	X
Patient activation	PAM-13	X	X	X	X
Holistic responder status	Composite measure		X	X	X
Pain catastrophising	PCS	X	X	X	X
Symptoms of central sensitisation	CSI	X	X	X	X
Anxiety and depression	HADS	X	X	X	X
Work status	Self-developed questionnaire	X		X	X
Patient expectations	Open question	X			
Healthcare utilisation	Patient reporting		X	X	X
Time spent in body postures	IPG output		X	X	X
(Serious) adverse events	Physician reporting		X	X	X
Proportion of successful DTM trials			X		
DTM stimulation parameters	IPG output		X	X	X
Battery consumption/recharge frequency	Patient reporting		X	X	X
Prevalence of technical issues with DTM programming	Physician reporting		X	X	X

CSI, Central Sensitization Inventory; DTM, differential target multiplexed; EQ-5D-5L, EuroQol with five dimensions and five levels; HADS, Hospital Anxiety and Depression Scale; IPG, implantable pulse generators; MQS III, Medication Quantification Scale III; MQS ODI, Oswestry disability index; PAM-13, Patient Activation Measure-13; PCS, Pain Catastrophizing Scale; PGIC, Patient Global Impression of Change Scale; SCS, spinal cord stimulation; V, visit; VAS, visual analogue scale.

In case a patient is lost to follow-up at the outpatient clinic, attempts are made to contact the patient by phone to perform any possible assessments, if the patient agrees.

Patient and public involvement

The selection of questionnaires was performed after identifying goalsetting in patients before SCS implantation through qualitative interviews with independent researchers[40] and exploring factors that chronic pain patients aim to achieve.[41] Patient support groups (not including study participants) will be offered opportunity to discuss the findings on completion of the study. The outcomes of the study will help in enhancing patient and public involvement.

Data management

A web-based data collection tool called Qualtrics is being used for this study to store data from all participants. Patients can complete the self-reported outcome measurements through accessing the URL towards Qualtrics or by scanning the QR code which will direct them immediately towards the data collection tool. The physician can complete the safety and feasibility-related outcome measures through the same system. Each patient is uniquely identified in the trial by the centre identification and the patient number assigned by the investigator. Patient numbers start with number 001, and subsequent patients are assigned consecutive numbers.

The following source data are being generated:

- Medical history of the participants from their patient's medical file to evaluate eligibility.
- Informed consent forms (paper format).
- Questionnaire results (Qualtrics, exported as .csv files).
- Personal data concerning health status (Qualtrics, exported as .csv files).
- Safety reporting and SCS parameters (Qualtrics, exported as .csv files).

The source documents are to be completed at the time of the participant's visit. The participating sites will keep

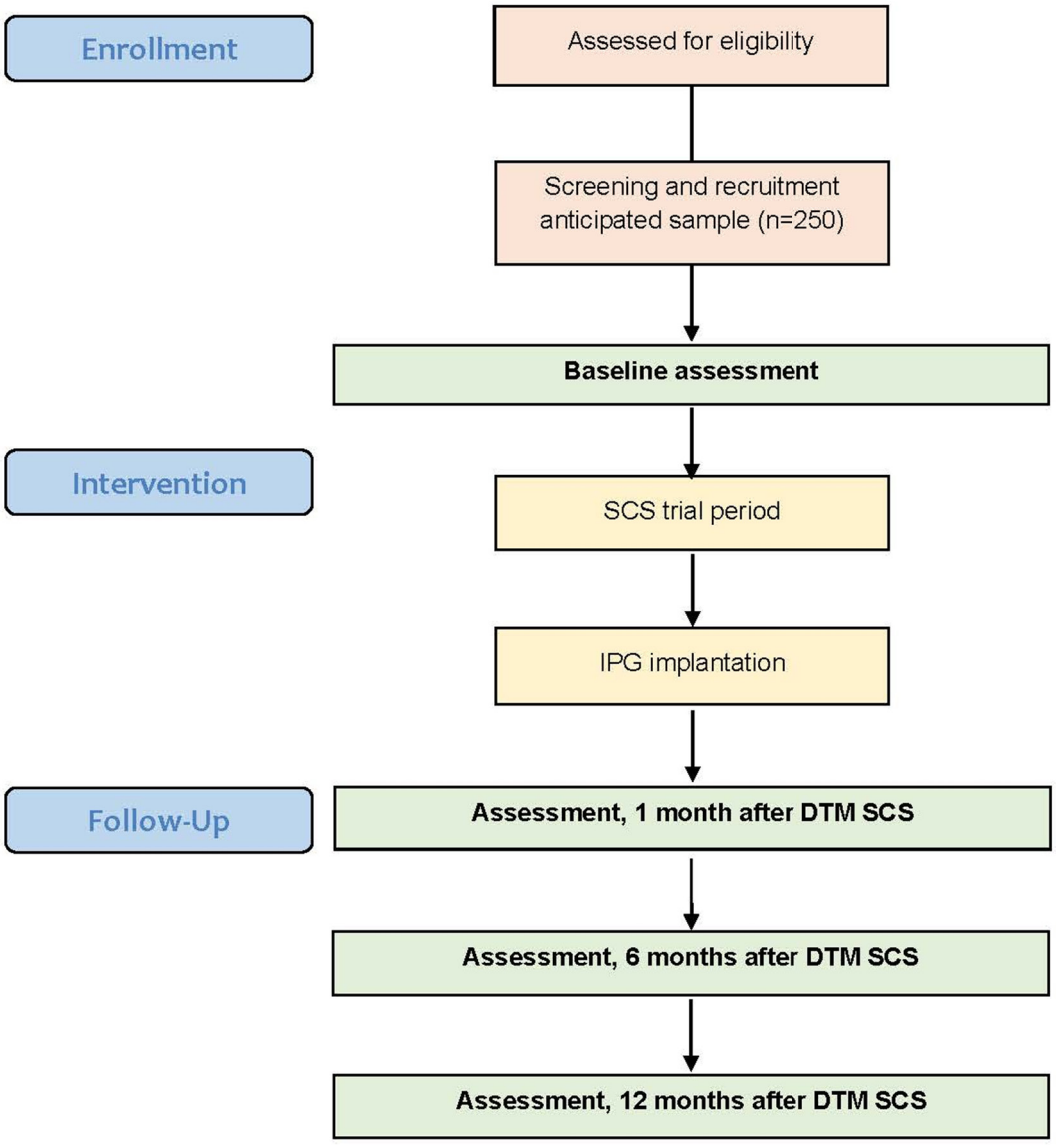

Figure 1 Patient flow chart. DTM, differential target multiplexed; IPG, implantable pulse generator; n, number; SCS, spinal cord stimulation.

copies of relevant documents, as well as essential centre-specific documents in their Investigator Site File.

The investigator is archiving all study related documents and trial data in a safe and secure location according to Good Clinical Practice guidelines and takes measures to prevent accidental or premature destruction of these documents. No trial data should be destroyed without the sponsor's agreement. Any source data are archived according to the archiving regulations of the investigational sites following national regulations. The investigator is required to arrange for the retention of the patient identification codes for at least 25 years after the completion or discontinuation of the trial. The investigator will permit trial-related monitoring, audits from the sponsor, Ethics Committee (EC) review and regulatory inspection(s), providing direct access to source data/documents.

Data analysis plan

Data processing and statistical analyses will be performed on pseudonymised data. The analyses will be performed after last patient completed the study, after monitoring and cleaning of data gathered from all patients. Analysis will be performed by the biostatistician involved in this project, using statistical software packages R studio and SAS 9.2 (or later versions). The flow of participants will be illustrated in a flow diagram. A description will be given of key patient characteristics recorded at the baseline visit.

To respect the design of this study, the longitudinal aspect will be taken into account in all analyses. Therefore, the inferential statistical analysis for the primary outcome, namely an expected reduction in overall pain up to 12 months, will be evaluated with longitudinal mixed models.[42]

In case a statistical significant effect is found for the primary outcome measurement, secondary outcome measurements can be evaluated as well with claims of statistical significance. In case of a non-significant effect for the primary outcome measure, no claims of statistical inference will be made about the secondary outcome measurements. Secondary outcome variables will be evaluated with longitudinal mixed models, Tweedie generalised linear models (in case of a discrete mass at zero[43]) or generalised mixed model to determine differences in scores over time. Analyses will be performed on the data as observed. Sensitivity analyses regarding missing data policy will be performed to evaluate robustness of the obtained results.

In addition to the mixed-effect modelling, which takes into account within-individual correlations for longitudinal data, latent class trajectory modelling (LCTM) will be applied.[44 45] LCTM simplifies heterogeneous populations into more homogeneous clusters, with respect to an unobserved latent variable.[46] One can include random effects to allow for individual variation within these clusters.[47] As such, this data-driven technique will allow to create trajectories to identify clusters in this patient sample based on shared parameters, rather than a priori determination of categories based on patient or clinical characteristics.

Based on the EQ-5D-5L index scores, patient-level quality-adjusted life-years (QALYs) will be calculated. QALYs are estimated by applying the area under the curve method, by summing the areas of the geometrical shapes obtained by linearly interpolating between utility scores over the study period.[48] The same calculation will be performed with a baseline index value that is extrapolated up to 12 months.[34] This value is representing the QALY of a patient who is not receiving an additional treatment. The incremental QALY is calculated by subtracting the QALY without additional treatment from the QALY during DTM SCS, over a period of 12 months.

Data monitoring and oversight

The trial management group (MM, LG and ADS) is the main decision-making and steering body of the project. The trial management group organised a kick-off meeting at the start of the project to establish common working procedures. The main tasks of the trial management group are: (1) agree on common working procedures and management policies, (2) monitor overall progress and follow-up of deliverables, (3) decisions on major changes to the work programme, (4) conflict handling and (5) budget decisions. The Steering Board is assembling meetings at least every year. Additional teleconferences can be organised ad hoc in case of urgent issues. The trial management group is responsible for assuring the quality of the workflow and project implementation, considering the available resources. The principal investigators in the recruiting centres are responsible for patient recruitment and data collection in their own centre. The study coordinator at Vrije Universiteit Brussel will regularly monitor data that are entered in Qualtrics in the participating centres. The study is also monitored by the Clinical Trials Center of UZ Brussel, Vrije Universiteit Brussel. The trial management group is also responsible for scientific communication, dissemination of data and results exploitation. The trial management group will closely interact with all partners involved and will review the scientific and organisational suggestions from the Scientific Advisory Board. The Scientific Advisory Board represents key opinion leaders in the field of neuromodulation research. The composition of this board assembling renowned independent experts will guarantee a sound methodological approach. Ad hoc meetings with the Scientific Advisory Board are organised based on the needs of the project. During the design of the study, the Scientific Advisory Board was asked for advice on the selection of specific questionnaires to avoid questionnaires that are partly evaluating a similar underlying concept.

ETHICS AND DISSEMINATION

Ethics considerations

The study protocol was approved by the central Ethics Committee of the Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel (B.U.N.1432021000563) and the Ethics Committees of each participating centre (AZ Sint-Lucas Brugge, UZ KULeuven, AZ Delta, AZ Turnhout, Vitaz, Jessa Ziekenhuis, CHR La Citadelle, AZ Sint-Maarten, ZNA Antwerpen, GZA Antwerpen, Heilig Hart Lier, AZ Sint-Jan Brugge and AZ Groeninge). The trial will be conducted according to:

- The current version of the principles laid down in the Declaration of Helsinki.
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
- The 'Note for guidance on Good Clinical Practice' (CPMP/ICH/135/95 of 17 January 1997).
- The current version of the Good Clinical Practice regulation.

Confidentiality

All data are handled, and all records are kept in accordance with the European Union General Data Protection Regulation (EU GDPR) applicable from 25 May 2018 (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation)). The EU GDPR was designed to harmonise data privacy laws across Europe, to protect and empower all citizens of the EU data privacy and to reshape the way organisations across the region approach data privacy.

Participant identification codes are being used to link data to patients. On screening forms, digital or other documents submitted to the coordinating centre, sponsor or principal investigator, patients are only identified by the code number. The file containing the link between participant numbers and personal data (ie, key) is managed by the researchers at each site individually and is being locked for access by others. The name and any other identifying details are not included in the study database.

Dissemination plan

Regular updates concerning the study are provided to all stakeholders to keep everyone informed, involved and motivated for this project. Further, we will communicate findings of this project via the publication of scientific manuscripts and presentations on national and international symposia, as well as through social media. The results of the trial will be reported to the Belgian regulatory authorities and Ethics Committee. Publication of the main study results and any information derived from the study or study data will be in accordance with the accepted scientific practice, academic standards and customs. Publication will be on behalf of the DETECT consortium, whereby the investigators of each participating site will be included in the DETECT consortium. DETECT consortium will be included as an author on publications, whereby individual investigators will be named (a) in acknowledgements and (b) as collaborators, depending on the Journal guidelines. Authorship on publication(s) will be according to the scientific guidelines for which guidelines of the International Committee of Medical Journal Editors will be followed.

After finalising the project, access restrictions will be applied to the pseudonymised data and will be specified in a data use agreement containing the following elements: evaluation of the re-use request by ethical committee, non-disclosure agreement and warranties for safely storage of data.

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Contributors MM, LG and ADS conceived the study. LG, ADS, SE, PR, MB, MR, DETECT consortium and MM contributed to the design of the study. LG and MM developed the methodology of DETECT. LG wrote the first draft version of the manuscript with critical input from ADS, SE, PR, MB, MR, DETECT consortium and MM. LG, ADS, SE, PR, MB, MR, DETECT consortium and MM read and approved the final version of the manuscript.

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