Peripheral Nerve Field Stimulation for Chronic Back Pain: Therapy outcome predictive factors

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Running title: Predictive factors for PNFS response

ABSTRACT

Objective: Identify variables that influence pain reduction following peripheral nerve field stimulation (PNFS) in order to identify a potential responder profile.

Methods: Exploratory univariate and multivariate (Random forest) analyses were performed separately on two randomized controlled trials and a registry; all included patients with chronic back pain (CBP), mainly failed back surgery syndrome (FBSS). An international expert panel judged the clinical relevance of variables to identify responders by consensus.

Results: Variables identified that may help predict PNFS success in patients with back pain include patient and pain characteristics (age, time since: onset of pain and spinal surgery, pain medication history, position and size of pain area, pain severity, mixed nociceptive/neuropathic pain, health-related quality of life, depression, functional disability, and leg pain status), implant procedure variables (the number and position of leads, paraesthesia coverage and amount of pain relief during the trial), and programming (number of programs, cathodes and anodes; pulse rate, pulse width, and percentage of device usage). **Conclusions**: While these analyses are exploratory and restricted to a limited sample size, they suggest variables that may play a role in predicting a therapeutic response. These results however are informative only and should be cautiously interpreted. Future research to validate the variables in a clinical study is needed.

Key words: Chronic back pain; Failed back surgery syndrome; Multivariate analysis; Consensus; Peripheral nerve field stimulation; Predictive factors

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Conclusions: While these analyses are exploratory and restricted to a limited sample size,

they suggest variables that may play a role in predicting a therapeutic response. These results however are informative only and should be cautiously interpreted. Future research to validate the variables in a clinical study is needed.

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INTRODUCTION

Chronic low back pain (CLBP), particularly in patients with failed back surgery syndrome (FBSS), negatively affects mental, emotional, physical and social aspects of life, resulting in a worse health-related quality of life (HRQoL) compared to other chronic painful conditions including complex regional pain syndrome, rheumatoid and osteoarthritis, and fibromyalgia.[1] Yet therapeutic options for the management of CLBP of FBSS are limited and often based on low quality evidence.[2] Since the 1970s, spinal cord stimulation (SCS) has been used in the treatment of chronic back and lower limb pain following lumbar spinal surgery and several studies have reported on its clinical effectiveness.[3-5] When using paresthesia based SCS, covering the area of pain with stimulation paresthesia is essential in order to be effective and for the low back area this has been proved not only difficult to accomplish but also to maintain.[6] Despite technical progress, axial low back pain in FBSS patients appeared to be less responsive to SCS compared to pain radiating into the lower extremities and therefore predominant low back pain exceeding leg pain was considered to negatively affect the long-term outcome of SCS.[7-9]

To overcome the difficulties in covering the low back area with stimulation paresthesia using SCS, an additional therapy was introduced in the early 2000s by means of peripheral nerve field stimulation (PNFS). PNFS involves subcutaneous placement of stimulator leads directly over the area of pain[10] and successful outcomes have been reported for a diversity of pain conditions, for instance pain in the chest wall, shoulder and pelvis.[11-13]

Good outcomes have been reported applying PNFS in the management of CLBP in patients with or without a medical history of lumbo-sacral spinal surgery and refractory to common therapies.[14-17] Recent evidence from randomized controlled trials (RCTs) indicates that the use of PNFS may significantly improve pain outcomes when used as a primary technique or as an add-on therapy to SCS.[18,19]

As the cornerstone of evidence-based medicine, RCTs provide information on the efficacy of the studied therapy. However, due to the restricted sample selection resulting from rigid inclusion criteria, they often fail to identify a responder profile. Recognition that multiple factors[20,21] may influence an individual's response to treatment has resulted in the acknowledgement that different clinical variables need to be taken into account, supporting the concept of personalized medicine whereby specific pain management is tailored to the specific needs and characteristics of the individual patient.[21] The question, therefore, should not be limited to how efficacious PNFS is in a clinical trial; it should also extend to what characterizes a patient who is likely to benefit from the therapy.

Characterization of optimal responders to a given therapy can be achieved by conducting subgroup analysis on large datasets aiming to identify variables that play a significant role in the effect of specific treatments namely prediction modelling.[22]

However, building prediction models has limitations depending on the number of potential predictors tested, the total number of observations (i.e., patients) and undetected bias resulting in poor generalizability of the outcomes.[23] To overcome the limitation of small sample sizes (N<100), which is commonly found in PNFS studies, univariate analysis in combination with the Random Forest (RF) method may be suitable for identifying a set of potential predictors. Indeed, it is well accepted that the RF technique enhances the interpretation of datasets containing a large number of variables and a small sample size.[24]

The objective of this study was to execute secondary data analyses to identify patient and procedural characteristics that are associated with best clinical outcomes to PNFS in treating CLBP in patients with or without FBSS.

METHODS

Study Overview

Separate analyses were performed on the datasets from three distinct clinical studies of PNFS for CLBP to identify variables that influence the response to PNFS therapy (analysis of predictors). An international panel of experienced clinicians then reviewed the variables identified during two face-to-face meetings to identify trends across the three PNFS-studies and to come to a consensus of the clinical relevance of each statistical identified variable.

Predictor Analysis

Datasets

Variables investigated in predictor analysis were sourced from three prospective studies including two randomized controlled trials (RCT) and a registry, referred to hereafter as SubQStim,[18] Dutch SubQ,[19] and the Austrian PNS Registry[25] respectively. Key study information is presented below, and full descriptions are provided elsewhere.[18,19,25]

In SubQStim, a prospective, multicentre, open-label, parallel-arm RCT (ClinicalTrials.gov Identifier NCT01711619), the effectiveness of PNFS (referred to as subcutaneous nerve stimulation (SQS)) plus optimized medical management (OMM) (SQS+OMM) was compared to OMM alone in subjects with CLBP due to FBSS.[18] The primary objective, demonstrating the proportion of subjects with ≥50% reduction in back pain intensity from baseline to the 9-month visit, was greater in the SQS+OMM group than in the OMM group. The SQS+OMM arm had a statistically significantly greater proportion of subjects with a ≥50 and ≥30% reduction in back pain intensity from baseline to the 6- and 9-month follow-up visits, respectively. The SQS+OMM arm showed a greater mean decrease in back pain intensity from baseline to the 6- and 9-month follow-up visits than the OMM arm.[18] The SQS+OMM arm also showed statistically greater improvements from baseline to 9-months in the following measures: the Oswestry Disability Index (ODI), European Quality of Life Five Dimensions (EQ-5D-5L), and the Mental Health Component Score of the Quality of Life

Short Form-36 questions (SF-36); however no statistical difference was found in SF-36 physical Component Score or leg pain intensity.

The Dutch SubQ trial is a prospective, multicentre RCT (Clinical Trials.gov Identifier: NCT01776749) designed to compare the effectiveness of PNFS (referred to as SubQ) in addition to SCS (SubQ ADD-ON) to SCS alone with the PNFS-leads turned off (SubQ-OFF (control)) in treating CLBP in subjects with back and leg pain due to FBSS, who were back pain non-responders to initial SCS-therapy that adequately reduced pain in the lower limbs.[19] A significantly higher percentage of subjects achieved at least a 50% reduction in back pain in the SubQ ADD-ON group (42.9%) compared to the control group (4.2%). At 3 months, the mean VAS score for back pain was significantly lower in the SubQ ADD-ON group compared to the control group.

The Austrian PNS Registry, a prospective, observational cohort study performed mainly in Austria (12 centres), with three centres in Switzerland and one in Ireland, was designed to evaluate the effectiveness of PNFS on CLBP, alone or in combination with SCS to treat a variety of CLBP conditions.[25] There were few restrictions regarding implant (leads, anchoring) and programming variables. A subcutaneous lead was percutaneously positioned directly into the area of maximum pain. If patients suffered from radiating pain due to a radiculopathy of the lower extremities, epidural leads were also implanted. All pain (mean pain VAS, ODI), psychological (Beck Depression Inventory (BDI)) and HRQoL (Short Form 12-item Health Survey (SF-12)) measures showed statistically significant improvement through 6 months, and opioid, nonsteroidal anti-inflammatory drugs, and anticonvulsants intake reduced significantly.

Statistical Analysis

The software package SAS (version 9.3, SAS Institute, Cary, NC, USA) was used to prepare the datasets, and analyses were performed using R software (version 3.3.3, Auckland, New Zealand). Each of the three studies was analysed individually. A limited number of 48 variables, with the potential to predict or impact therapy outcomes, was pre-selected from the three study's case report forms (CRF) for statistical analysis and grouped into 6 different categories including sociodemographic, medical history, pain aetiology, pain characteristics, implant and therapy information, and subject questionnaires (Table 1). While slightly

different variables were collected within each study, most overlapped across two or all three studies. Excluded variables were CRF elements deemed irrelevant to the analyses, such as date of patient consent signature, confirmation of study eligibility criteria, study visit dates, and patient-reported outcomes unrelated to pain scores or responder rates collected at follow-up visits (e.g., ODI, SF-36).

Each variable was assessed for a statistically significant difference between responder and non-responder groups at type I error of 10% through statistical tests (i.e., continuous variables were tested by T-test and Wilcoxon-Mann-Whitney test, categorical variables were tested by Fisher's exact test and Chi-squared test). Categorical variables were further tested against percent of pain reduction with T-test, Wilcoxon-Mann-Whitney test, ANOVA, or Kruskal-Wallis. A type I error of 10% was chosen as the analyses were not powered and false positives were deemed to be acceptable. Pearson correlation coefficient was computed between percent of pain reduction and each continuous variable. The variable was kept if the coefficient of correlation was higher than 0.2 or lower than -0.2.

All variables were also included in the multivariate analysis using the Random Forest (RF) method. RF analyses of variables with a sensitive amount of missing data were run separately. RF is a non-parametric regression and classification method, which combines results from an ensemble of individual decision trees. Each decision tree is unique as randomness is added through selection of observations used to build each tree and through selection of variables to be tested at each split of tree.[26,27] RF methodology provides an index of relative importance for variables in regard to classification or regression. RF classification on whether a subject was a responder to the therapy was performed using the R function Cforest with 1,000 trees. To check the robustness of the RF methodology, the analysis was run 10 times and the first 10 variables of each run were reviewed. The choice of considering only the first 10 variables of each analysis was based on the fact that variables coming after the 10^{th} one are less important. Model robustness was tested, by random defining whether a subject was a responder or not, using Bernoulli distribution (p=0.5); a balance was maintained between the two groups.

Subject Selection

The criteria for selecting subjects from the 3 different studies for the purpose of this particular study differ from those used in the original studies. An as-treated statistical approach was used as only implanted subjects with data available can inform predictive factors of the PNFS-therapy. Additionally, to optimize analysis efficiency, a balance is needed in the sample size between responder and non-responder groups. In each of the 3 clinical studies, conducted to assess statistical significance, the original definition of a responder was defined at ≥50% pain reduction from baseline. For these predictive responder-analyses, aimed to assess the clinical relevance of the outcomes of the clinical studies, a new definition of a responder was established for each of the studies to maintain an equal sample size between the responder and non-responder groups.[28]

For the SubQStim RCT, subjects were included in the analysis if they had a neurostimulator implanted and information on pain intensity at the 3-month visit was available. Responders were defined as subjects who achieved a reduction in VAS pain score of at least 70% at 3 months and non-responders were defined as subjects who achieved no more than a 50% reduction at 3 months.

For the Dutch SubQ RCT, subjects were included in the analysis if they had PNFS implanted with a programme set for back pain in addition to SCS therapy, and pain intensity data available at baseline and the 6-month follow-up. Responders were defined as subjects who achieved a reduction in VAS pain score of at least 58% at 6 months and non-responders were defined as subjects who achieved no more than 40% reduction in back pain.

For the Austrian PNS Registry, subjects were included in the analysis if they were implanted with a PNFS neurostimulator and had an indication of CLBP. Considering follow-up visits at 1-, 3-, 6-, and 12-months, a responder in the Austrian PNS Registry was defined as a patient with ≥50% reduction in back pain intensity for at least 75% of informed visits; whereas a non-responder was defined as a patient with no more than 25% of informed visits as a responder. To be considered in the analysis, patients should have completed at least three out of five follow-up visits.

Assessment of Clinical relevance

To investigate the clinical relevance of the variables, that were identified on account of statistical significance, in influencing a response to PNFS in routine clinical practice, clinical

experts (three neurosurgeons and six anesthesiology/pain medicine physicians) reviewed the results of the analyses.

These clinicians were asked to review the statistically identified variables by considering validity, correlation with other variables, relevance, and application in everyday practice, and to vote on whether or not each should be considered clinically relevant to include in a future therapy algorithm.

RESULTS

Predictive Modelling

Results of the statistical analyses performed for each of the three studies separately, are presented in Tables 2,3 and 4.

In the SubQStim study, of the 116 originally randomized subjects, 56 (48.3%) were assigned to the PNFS arms. Out of those 56 subjects, 40 (71.4%) were permanently implanted and had 3-month response data available. After applying the selection criteria described above, 32 subjects were included in the analysis (responders, n=16; non-responders, n=16). The analysis considered 115 variables from six categories: sociodemographic (n=2), pain aetiology (n=9), pain characteristics (n=40), including 31 pain areas), patient-reported scores (n=8), previous treatments (n=30) and PNFS treatment (n=26). Fifteen variables were removed due to not having variability in the dataset. One hundred variables were therefore tested in univariate analyses. Out of the 100 variables tested, 14 (14%) showed a p-value lower than 10% denoting a significant difference between responders and non-responders or/and a coefficient of correlation with percent reduction in pain intensity larger than absolute (0.2) (Table 2). Multivariate RF classification analyses were run 10 times on the 100 variables and resulted in identification of 14 variables likely to be sufficiently important to impact therapy response (Table 2). The mean misclassification rate for the RF model was 9.1% (Standard Deviation (SD), 0.98; median, 9.4%; n=10). Overall, 17 variables out of 100 were identified as potential predictors in univariate or/and RF analyses: sociodemographic (age), pain characteristics (number and location pain zones, time since one of back pain, DN4), patients reported baseline scores (ODI, EQ-5D self-care and SF-36 mental component), previous treatments (number of and time since last spinal surgery, and number of pain medications) and PNFS treatment (back pain score and relative reduction at trial,

position of leads, percent of device use, frequency, and number of anodes and cathodes) (Table 5).

Out of the 100 subjects enrolled in the Dutch SubQ RCT, 56 subjects with back or leg and back pain were implanted with a PNFS lead programmed for back pain and with pain intensity reported at baseline and six months. Applying the criteria described above resulted in 40 subjects included in the analysis (responders, n=20; non-responders, n=20).

One hundred and one variables organized in six categories were tested: sociodemographic (n=5), pain characteristics (n=54), including 45 pain areas), patient-reported scores (n=11), previous treatments (n=12), and PNFS treatment (n=19). Four variables were removed as having no variability in the dataset. Nine variables were identified through univariate analyses and 8 with RF (Table 3). The mean misclassification rate of the 10 runs was 15.25% (SD=0.79; median=15%; n=10).

Variables of interests (n=14) were linked with sociodemographic (age, working situation), pain characteristics (no loss of sensation, number of pain zones), patient-reported baseline scores (EQ-5D mobility, SF-36 physical component), previous treatments (number of pain medications) and PNFS treatment (number and position of PNFS leads, implantable nerve stimulator (INS) model, number of anodes and cathodes, and amplitude) (Table 5).

Of the original 157 patients in the Austrian PNS Registry, 106 (67.5%) were implanted with PNFS for chronic low back pain (i.e., non-back pain indications were excluded). Application of the responder/non-responder definitions resulted in the inclusion of 54 patients (responders, n=29 (54%); non-responders, n=25 (46%)). One hundred variables split into six categories were tested: sociodemographic (n=4), pain etiology (n=2), pain characteristics (n=29), including 25 pain areas), patient-reported scores (n=4), previous and current treatments (n=30), and PNFS treatment (n=31). Among the latter, six were excluded as having limited variability. Univariate analysis, comprising comparisons of responders/non-responders and correlation with reduction in pain, yielded 13 variables (Table 4). Results of the multivariate RF analysis showed that, out of 91 variables tested, 14 were associated with the responder variable (Table 4). The mean misclassification rate was 24.1% (SD=1.51; median=24.1%; n=10). The model was able to identify all responders (sensitivity: 100% (SD=0; median=100%; n=10)). The 14 potential predictors identified were linked to

sociodemographic (age), pain characteristics (back pain at baseline, having not stopped working due to pain, location pain zone), patient-reported baseline scores (Beck Depression Index (BDI), Oswestry Disability Index, SF-12 mental component), previous and current treatments (number of pain medications, medical history of specific pain medications, current pain treatments) and PNFS treatment (back pain score at trial and relative reduction at trial and implant, duration of trial, paraesthesia coverage at trial and implant, pulse width, and number of programs) (Table 5).

Across the three studies, a total of 29 variables were identified, in at least one of the studies, as being potentially predictive of a response to PNFS (Table 5).

The robustness of RF classifications was tested by randomly defining whether a subject was a responder or not. As a result, mean misclassification rates increased to around 50%, as expected (not shown). In addition, outputs included some variables identified above as potential predictors as well as others giving confidence to results obtained above (not shown). However, for all three datasets the ratio of identified variables to observations was still too large to build robust predictive models through standard multiple linear regression methods.

The variables identified by statistical analyses for each study were presented side-by-side to allow visual identification of trends and differences between the studies by clinical therapy experts. Majority clinician consensus opinion resulted in the selection of 17 of the 29 variables as feasible for application in everyday practice that should be considered clinically relevant to include in a future therapy algorithm (Table 5). These included patients presenting with CLBP of moderate to severe intensity, and a focal, defined area of back pain located below the rib cage and above the iliac crest. The area of worst pain should be no larger than about the size of 1-2 business cards to allow adequate paraesthesia coverage by the PNFS leads. Results across the studies suggest that patients presenting with overall better management of their health status (i.e., quality of life, functional disability, and depression scores) are more likely to be a responder, suggesting a patient profile of disability on ODI no worse than a category score of severe, no severe or untreated depression, and at least a moderate level of quality of life.

DISCUSSION

In this study, conducted to identify the optimal characteristics that may have a positive influence to PNFS in treating CLBP, executed by secondary data analyses of three major studies on the effects of PNFS on CLBP, we found variables with a potential to impact the outcome of PNFS in patients with CLBP mainly due to FBSS.

Common ground for PNFS and SCS in the management of chronic pain due to FBSS is the dearth of data describing patient-, implant- and technology-related factors that influence the success of therapy. A systematic literature review and multivariate meta-regression analysis of 74 studies in a total of 3,025 patients, conducted to investigate factors that predict pain relief in chronic back and leg pain following SCS, yielded none, even though SCS was effective in reducing pain.[29] In the univariate analysis, reported in the same manuscript, the only variable associated with SCS pain relief was mean duration of pain, showing that the less time since onset of pain, the more likely a patient will obtain pain relief. While this factor was not relevant in the Dutch SubQ RCT, it was in the univariate analysis of the SubQStim RCT, but showed the opposite in that the longer the mean time since onset of pain, the more likely a patient would be a responder.

For 12 variables investigated in these exploratory analyses the data were not considered strong enough or they did not have any practical application (e.g., working situation, longer duration of pain or since last surgery, greater number of prior back surgeries, pain less likely to be neuropathic). However, conflicting results were seen in some analyses. For example, a patient prescribed more pain medications was more likely to be a responder in the SubQStim and Dutch SubQ RCTs, but a patient prescribed fewer pain medications was more likely to be a responder in the Austrian PNS Registry. The type of pain medication prescribed was only relevant in one of the three datasets (Austrian PNS Registry). With conflicting results and a lack of confidence in application to everyday practice, these variables were discarded due to data limitations

In the case of age, all three studies suggested patients of older age were more likely to be a responder. However, this contradicts research by Verrills et al., 2009 who investigated the importance of age and gender (and the combined effect of age and gender) as outcome predictors based on the results of subgroup analysis. Only age influenced outcome in that younger patients reported greater pain reduction (<60 years) than older patients (>61 years).[30]

Beside patient-related characteristics we also found variables related to the implant procedure. Results show that a patient is more likely to be a responder with maximised paraesthesia coverage and lead placement along the cranial-caudal axis (vertical). An implanter may consider paraesthesia and pain coverage using 1-2 wide-spaced leads placed vertically in the centre of maximal pain. Lead placement should be avoided directly in areas of allodynia, by instead bracketing the area. A greater reduction in back pain during the screening trial was associated with longer-term pain relief. Results and experience suggest patients respond well to, or prefer, a lower frequency setting.[31] Therefore, beginning programming by assessing a single anode and cathode per lead in a wide array (e.g., using contact 0 and 3 on a quadripolar lead), with a frequency of 40 Hertz, pulse width of 210 μsec, and amplitude adjusted to comfort may be warranted. Programming should always be customized to ensure sufficient and comfortable paraesthesia coverage and pain relief. Allow a sufficient trial period duration to evaluate outcomes and encourage the patient to use stimulation as much as possible.

Within the Dutch SubQ RCT, conducted in 6 different centres, INS model type was identified as a potential variable, with patients implanted with a rechargeable more likely to respond than those with a non-rechargeable battery. All patients with a rechargeable INS were implanted in the same centre. However, study authors and the panel agreed this may be due to the more complex nature of the studied patients. The SubQ RCT included patients with both back and leg pain and consisted of a hybrid system combining the use of both SCS and PNFS. The hybrid system complicates programming and brings into question if parameters may have been set to optimize battery longevity, or at least balance battery life with pain relief.

The main limitation of the present statistical analysis is the small pool of patients considered, which casts doubt on the generalisability of the results. The limited number of observations impacts the power of univariate analysis: small differences might have not been identified as significant despite type-I error being increased to 10%.

Another limitation is the fact that the analysis was performed on heterogeneous populations regarding etiology of CLBP (CLBP of FBSS and CLBP without a history of spinal surgery), regarding treatment (PNFS alone or in combination with SCS) and criteria for success.

In addition, common predictive modelling methods as linear regression were not applicable due to the challenge of large numbers of variables for small numbers of observations (known

as “short and fat dataset problem”). For those types of data RF is considered as a suitable tool. Although this method allows to identify important variables it does not assess the expected level of pain reduction for each variable. To address the challenge of the limited available data and ensure the relevance of the results, it was important to perform the analysis on three independent studies and to have input from clinicians. Further analyses should be performed on larger datasets.

Finally, while a two-pronged approach (clinical experience and statistical analysis of three datasets) was adopted to identify key variables to apply to patient selection, implantation and programming in PNFS management, with limitations associated with each, the practical application of this approach remains hypothetical. Furthermore, because the predictive variables identified here may result in important decisions about patient care, it is imperative that they are validated in an independent study.

Conclusions

In this study, variables that may predict a successful outcome with PNFS for patients with CLBP, particularly due to FBSS, were identified by balancing the output of predictor analysis and clinical experience. Due to the small number of patients and heterogeneity of the study population, treatments and criteria for being a responder to PNFS, the results of this study should be interpreted very carefully and considered to be informative at least. Providing evidence of the validity of identified variables and confirming its clinical relevance in large independent datasets are essential next steps. Ultimately, until further analyses can be performed, clinician expertise remains the cornerstone for decisions relating to the application of PNFS. Our study lays the foundation for future research aimed at personalized medicine and improving patient outcomes.

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Table 1 Variables selected from the case report forms of the SubQStim and Dutch SubQ trials, and the Austrian PNS Registry with the potential to predict therapy outcomes

Categories	**Variables**
Sociodemographic	1. Age (years) 2. Gender (male, female) 3. Working status (stopped working due to pain; paid job, unemployed, disapproved/disability, partially disapproved/disability, retired) 4. Education level (middle/high school (VMBO, HAVO, MBO), university preparation/university (VWO/HBO)
Pain etiology	5. Indication and etiology (FBSS, herniated disk, injury, spondylolisthesis, osteoarthritis, spinal deformity, fracture, unknown, other)
Pain characteristics	6. Baseline back pain intensity (NPRS or VAS) 7. Baseline leg pain intensity (NPRS or VAS) 8. Size and location of back pain (cm^2, location and number of areas checked on pain maps) 9. Time since onset of back pain or diagnosis (years) 10. Pain type (neuropathic or nociceptive, DN4 mechanical/somatic, loss of sensation, loss of motor function, continuous or attack)
Patient reported questionnaires at baseline	11. ODI score 12. Health status (EQ-5D; domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression), utility score, health state VAS) 13. HRQoL (SF-12, SF-36 (Mental Component and Physical Component score)) 14. Anxiety and Depression (HADS, BDI)
Medical history	15. Time since last spinal surgery (years) 16. Number of previous surgeries 17. Type of previous spinal surgeries (decompression, disc replacement, discectomy, foraminotomy, fusion, laminectomy, laminotomy/fenestration, other, vertebroplasty) 18. Number of pain medications (total) 19. Pain medication type (Acetaminophen/paracetamol, NSAID, NSAID-cox-2 inhibitors, antidepressants (Tricyclics-Tetracyclics, SSRI, Other), anticonvulsants, benzodiazepines, cannabinoids, opioids (weak / strong) (oral / transdermal / intravenous), sedative hypnotics, steroids, topical transdermal anesthetics, other,, neuroleptics,) 20. Treatment history quantity and type: TENS, oral / transdermal opioids, NSAIDS, antidepressants, anticonvulsives, benzodiopines. 21. Current non-drug treatments (acupressure, acupuncture, massage/manipulation, osteopath, physical rehabilitation, psychological/behavioral rehabilitation, nerve block)
PNFS implant and therapy information	22. Result of trial/test stimulation (back pain intensity/relative percent pain reduction, 50% responder) for back 23. Result of trial/test stimulation (leg pain intensity/relative percent pain reduction, 50% responder) for leg 24. Type of trial (buried lead or temporary lead) 25. Duration of trial (days) 26. Paraesthesia coverage of painful area (percentage) 27. Lead type and model (Model: 4-contact or 8-contact) 28. Electrode spacing (compact, sub-compact, or wide spacing) 29. Number of leads (quantity 1-4) 30. Lead placement in relation to the painful area (within or center, bracket, adjacent or outside: medial or lateral) Lead placement – Direction (vertical, horizontal, diagonal) 31. Lead fixation (yes, no), type of fixation 32. Extension use and model 33. When to use hybrid SCS+PNFS (definition of population studied, back and leg pain scores) 34. INS type (primary cell or rechargeable, model)

	35. INS implant location (abdomen, left or right lower abdomen, buttock, left or right upper gluteal, flank, other) 36. Percent usage of device or continuous / on demand 37. Number of programs set 38-48Programming Rate [Hertz], Pulse Width [μs], Amplitude (volts), Number of cathodes, Number of anodes, 'crosstalk' programming between epidural and PNS leads, use of Soft Start/Stop, cycling, TargetStim™ and number of patient adjustments to settings

Table 2. Variables selected with each analysis in the SubQStim RCT

Variable category	Univariate analysis		Multivariate analysis
	Difference between responders and non-responders **OR on percentage change (p < 0.10)**	**Pearson's correlation coefficient** **(r higher/lower than 0.2/-0.2)**	**Random Forest** **(Importance of variable)**
Demographics		Age: r=0.28	Age
Pain	Time since onset back pain (Wilcoxon test, p=0.045) ODI score at baseline (T-test: p=0.097; Wilcoxon test: p=0.08) EQ-5D-5L (self-care) at base line (Fisher's exact test, p=0.074; Chi^2, p=0.076) Pain zones: 8,11,13,16, (p<0.1)	Time since onset back pain: r=0.23 EQ-5D-5L (self-care) score at baseline: r=-0.29	Number of pain zone selected Pain zone: 8,11,14,15 Time since onset back pain DN4 score at baseline ODI score at baseline EQ-5D (self-care) score at baseline SF36 - mental component score at baseline
Treatment	Time since last spinal surgery (T-test: p=0.036)	Time since last spinal surgery: r=0.33 Number of previous surgeries: r=0.24 Number of pain medications: r=0.39	Time since last spinal surgery Number of previous surgeries
Test stimulation	Relative reduction in back pain (T-test: p=0.087; Wilcoxon test, p=0.072) Back pain at test (T-test: p=0.092; Wilcoxon test: p=0.072)	Relative reduction in back pain: r=0.25 Back pain at test: r=-0.25	Relative reduction in back pain Back pain at test
Implant			Final lead position - vertical
Programming – last information	Use percent (T-test: p=0.037; Wilcoxon test, p=0.02) Number of cathodes (1) (Wilcoxon test, p=0.037) Number of cathodes (2) (T-test, p=0.089; Wilcoxon test, p=0.079) Number of anodes (1) (T-test, p=0.067; Wilcoxon test, p=0.038)	Use percent: r=0.41 Rate range: A1, r=-0.48; A2, r=-0.45; A3, r=-0.3 Number of cathodes: 1, r=-0.35; 2, r=-0.26 Number of anodes: 1, r=-0.34; 2, r=-0.24	

Table 3. Variables selected with each analysis in the Dutch SubQ RCT

Variable category	Univariate analysis		Multivariate analysis
	Difference between responders and non-responders **OR on percentage change (p < 0.10)**	**Pearson's correlation coefficient** **(r higher/lower than 0.2/-0.2)**	**Random Forest** **(Importance of variable)**
Demographics		Age: r= 0.2	Working situation
Pain	EQ-5D – mobility* (ANOVA: p=0.032; Kruskal-Wallis: p=0.075) Number pain zones selected (T-test: p=0.039; Wilcoxon test: p=0.065)	Number of pain zones selected (r=-0.31)	Loss of sensation Number of pain zones selected SF-36 - Physical component score
Treatment			Number of treatments
Test stimulation			
Implant	INS model (Fisher's exact test: p=0.022; Chi^2: p=0.02)	Number of SubQ leads: r=-0.22	INS model used Position of SubQ leads
Programming – **last information**		Number of cathodes / anodes: r=-0.26 Amplitude right: r=-0.3	
Month 6 visit	Paresthesia coverage (T-test: p=0.01; Wilcoxon test: p=0.0024)	Paresthesia coverage: r=0.43	Paresthesia coverage

Table 4. Variables selected with each analysis in the Austrian PNS registry

Variable category	Univariate analysis		Multivariate analysis
	Difference between responders and non-responders **OR on percentage change (p < 0.10)**	**Pearson's correlation coefficient** **(r higher/lower than 0.2/-0.2)**	**Random Forest** **(Importance of variable)**
Demographics			Age
Pain	Back pain score at baseline (Wilcoxon test, p=0.058) Stop working due to pain (ANOVA, p=0.067) BDI score at baseline (T-test, p=0.057; Wilcoxon test, p=0.035) ODI score at baseline (T-test, p=0.091)	Back pain at baseline [VAS]: r=0.21 BDI score at baseline: r=-0.34 ODI score at baseline: r=-0.3 SF-12 (mental component) score at baseline: r=0.26	Back pain at baseline Pain zone: 92 BDI score at baseline ODI score at baseline SF12 (mental component) score at baseline
Treatment	Medical history of not taking co-analgetica (Chi^2, p=0.072)	Number of pain medications: r=-0.24	Medical history – Success in oral opioids Current Pain treatment - Any non-drug treatment
Test stimulation	Reduction in back pain at test (T-test, p=0.12; Wilcoxon test, p=0.009) Back pain intensity at test (T-test, p=0.027; Wilcoxon test, p=0.02) Paresthesia coverage at test (T-test, p=0.022; Wilcoxon test, p=0.018)	Back pain at test: r= -0.48 Reduction in back pain a test: r=0.52 Paresthesia coverage: r=0.26	Reduction in back pain at test Paresthesia coverage at test
Implant	Reduction in back pain at implant (T-test, p<0.0001; Wilcoxon test, p<0.0001) Duration of trial screening (T-test, p=0.06; Wilcoxon test, p=0.06)	Reduction in back pain at implant: r=0.82	Duration of post-operative screening Paresthesia coverage at implant
Programming – last information	Pulse width programmed (T-test, p=0.046; Wilcoxon test, p=0.099)	Pulse width programmed: r=-0.37/-0.36	Pulse width programmed 1,2 Number of programs

Table 5. Variables associated with potentially predictive outcome of a positive response to PNFS selected by statistical analysis and clinician expertise by study

Variable Categories	SubQstim RCT n= 17	Dutch SubQ RCT n=14	Austrian PNS Registery n=14	Clinical Relevance
Sociodemographic				
Age	Higher	Higher	Higher	NO
Working status / Stopped working due to pain		Not occupationally disabled	Not stopped	NO
Pain characteristics at baseline				
Back pain (NPRS)			Higher	YES
Time since onset back pain	Longer			NO
DN4-score or Loss of sensation	Lower /less likely neuropathic	No loss of sensation		NO
Specific Pain zones	Specific zones identified			YES
Number of pain zones selected	Higher	Responders have fewer zones		YES
Patient reported questionnaires at baseline				
Oswestry Disability Index	Lower		Lower, less disability	YES
EQ-5D-5L (Self-care)	Lower	Less mobility		YES
SF-12/-36-mental + physical component	Higher mental component score	Higher physical component score	Higher mental component score	YES
Beck Depression Index Or HADS			Lower	YES
Medical history				
Time since last surgery	Longer			NO
Number of previous surgeries	Higher			NO
Number of pain medications	Higher	More medication, better response	Lower	NO
Class of pain medication			No history of co-analgetica, history of oral opioids success	NO
Prescribed drug / pain treatments			On any treatment	NO
PNFS Implant and therapy information				
(relative) back pain reduction after trial stim.	Higher		Higher	YES
Duration of trial screening			Shorter	YES
Paraesthesia coverage (%) of painful area		Higher (%) paresth. coverage	Higher	YES
Number of PNFS leads		Fewer leads		YES
Lead position: horizontal, vertical, diagonal	Vertical position	Vertical position		YES
INS model used		Yes		NO
Percent usage of device	Higher			YES
Number of programs			Higher	NO
Programming rate [Hertz]	Lower rate			YES
Programming Pulse width [μ s]			Lower	YES
Programming Amplitude [Volts]		Lower Amplitude		NO
Number of cathodes	Lower number	Lower number		YES
Number of anodes	Lower number	Lower number		YES