

Study Protocol

Efficacy of BurstDR Spinal Cord Stimulation versus Sham in Established Responders: A Randomized, Double-Blind, Two-Period Crossover Trial

Single-centre study conducted at Norrlands University Hospital, Umeå, Sweden

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Protocol Synopsis

Item	Description
Title	Efficacy of BurstDR Spinal Cord Stimulation versus Sham in Established Responders: A Randomized, Double-Blind, Two-Period Crossover Trial
Design	Single-centre, randomized, double-blind, two-period crossover study
Population	Adults with an implanted SCS system capable of BurstDR therapy who are established clinical responders on stable settings
Interventions	1 day baseline observation under finalized active settings, followed by 7 days active BurstDR stimulation and 7 days sham stimulation (therapy off) in randomized order
Washout	4 days after baseline and 4 days between treatment periods, therapy off
Randomization	1:1 allocation to active–sham or sham–active sequence
Primary Endpoint	Within-participant difference in period-level median NRS pain intensity derived from twice-daily diaries over each 7-day treatment period
Secondary Endpoints	Treatment satisfaction; daily PGIC domains for sleep, mood, daily activity, and social activity; pre-period and end-of-period blinding/perceptibility checks; safety
Sample Size	28 evaluable participants targeted; up to 35 recruited
Primary Analysis	Wilcoxon signed-rank test with Hodges–Lehmann median difference and 95% CI
Sensitivity Analyses	Median-based paired analyses using days 1–3 and days 3–5 only; exploratory mixed-effects model with treatment, period, and sequence as fixed effects and participant as random intercept

1. Background and Rationale

Chronic neuropathic pain and mixed chronic pain syndromes remain difficult to manage despite optimized pharmacological therapy, rehabilitation, and repeated procedural care. A substantial subgroup continues to experience disabling pain, impaired sleep, reduced function, and diminished quality of life. For such patients, spinal cord stimulation (SCS) has become an important treatment option, particularly when conservative treatment has failed.

BurstDR spinal cord stimulation is a paresthesia-free stimulation paradigm delivered through epidural leads over the dorsal columns. In contrast to conventional tonic SCS, BurstDR aims to provide analgesia without requiring concordant paresthesia and may influence both sensory-discriminative and affective-motivational dimensions of pain [1–7, 11]. Prior clinical studies, including the SUNBURST randomized crossover trial and the prospective TRIUMPH cohort, support the safety and clinical effectiveness of BurstDR in chronic trunk and/or limb pain, and mechanistic studies suggest distinct supraspinal effects relative to tonic stimulation [1–7]. Nevertheless, the specific contribution of ongoing BurstDR stimulation, as opposed to placebo-related effects, natural fluctuation, or regression to the mean, remains insufficiently defined.

This uncertainty is particularly important in chronic pain neuromodulation, where expectation effects, procedure-related contextual effects, and symptom variability can materially influence patient-reported

outcomes. Recent sham-controlled literature has intensified the need for more methodologically rigorous studies that isolate the effect of active stimulation under conditions of maintained blinding [8,9,12]. At the same time, de novo sham-controlled trials raise practical and ethical challenges because implantation itself may exert powerful contextual effects and because short trial stimulation and post-implant optimization can confound interpretation.

The present study addresses this evidence gap by using a randomized, double-blind, two-period crossover design in established BurstDR responders who already have a chronically implanted SCS system and stable therapeutic settings. This design isolates the effect of continuing active BurstDR therapy while avoiding implantation-related bias, minimizing between-subject variability, and reducing ethical concerns because each participant serves as his or her own control. The study will begin with 1 day of baseline data collection under the finalized active study settings, followed by a 4-day washout with therapy switched off, a first 7-day randomized treatment period, a second 4-day washout, and a final 7-day randomized treatment period. This sequence is designed to provide a rigorous estimate of whether ongoing BurstDR stimulation delivers clinically relevant benefit beyond sham.

2. Objectives and Hypotheses

Primary Objective

To determine whether ongoing BurstDR spinal cord stimulation reduces pain intensity compared with sham stimulation in adults with chronic pain who are established responders to BurstDR therapy.

Secondary Objectives

1. To compare patient satisfaction with therapy between active BurstDR stimulation and sham.
2. To compare patient global impression of change (PGIC) in sleep quality, mood, daily activity, and social activity between active and sham stimulation.
3. To assess the feasibility of maintaining blinding during paresthesia-free BurstDR programming.
4. To characterize safety and tolerability during active treatment, sham treatment, and washout.

Hypotheses

Primary hypothesis: In established BurstDR responders, active BurstDR stimulation will be associated with lower period-level pain intensity than sham stimulation.

Secondary hypotheses: Active BurstDR stimulation will be associated with higher treatment satisfaction and more favourable PGIC ratings for sleep, mood, daily activity, and social activity than sham stimulation.

3. Trial Design

This is a single-centre, randomized, double-blind, two-period crossover trial comparing active BurstDR spinal cord stimulation with sham stimulation (therapy off) in patients with chronic pain who are established responders to BurstDR therapy.

Each participant will first complete a 1-day baseline observation period under the finalized active BurstDR study settings. This will be followed by an initial 4-day washout period with stimulation switched off. Participants will then undergo two consecutive 7-day randomized treatment periods, one active and one sham, separated by a second 4-day washout period with stimulation switched off. The order of treatment conditions will be randomized 1:1 (active–sham or sham–active). Participants will therefore serve as their own controls.

The protocol is intentionally pragmatic with respect to the implanted hardware and underlying pain diagnosis, but explanatory with respect to treatment delivery, blinding, and endpoint derivation. No

implantation, lead revision, or hardware modification is performed as part of the trial. All study-specific procedures concern programming, blinding, diary capture, and follow-up.

4. Study Setting

The study will be conducted at the Neuromodulation Unit, Department of Neurosurgery, Norrlands University Hospital, Umeå, Sweden. Screening, consent, programming, follow-up, safety review, and database management will be coordinated at this centre using standard clinical infrastructure and the Patientkollen/Caremetrix electronic platform.

The centre is a tertiary neuromodulation referral unit with established workflows for device programming, longitudinal patient-reported outcome capture, and secure clinical data handling. This infrastructure is directly suited to a sham-controlled crossover neuromodulation study.

5. Eligibility Criteria

Inclusion Criteria

1. Age 18 years or older.
2. Implanted with an epidural spinal cord stimulation system capable of delivering BurstDR therapy.
3. Established responder to BurstDR therapy, defined as at least 50% reduction in pain intensity compared with the pre-implant or pre-Burst baseline, sustained for at least 3 months on stable BurstDR settings.
4. Stable analgesic regimen for at least 4 weeks prior to enrolment.
5. Ability to understand study information and provide written informed consent.
6. Willingness and ability to complete daily electronic diaries and comply with study procedures.

Key Exclusion Criteria

1. Active infection, wound complication, or other clinically relevant implant-site problem.
2. Suspected or confirmed hardware malfunction that could affect stimulation delivery or safety.
3. Major uncontrolled psychiatric illness, cognitive impairment, or other condition that could compromise consent, adherence, or data validity.
4. Planned surgery, stimulation reprogramming outside the study, or anticipated change in analgesic medication during the study period.
5. Pregnancy or breastfeeding.
6. Inability to use the electronic diary system without a feasible workaround.
7. Any other condition that, in the investigator's opinion, makes participation inadvisable or unsafe.

6. Recruitment, Consent, and Participant Flow

Potential participants will be identified from the Neuromodulation Unit's clinical follow-up population. Patients who appear eligible after chart review will be approached by the study team, receive written and oral study information, and be given adequate time to consider participation before written informed consent is obtained.

After consent, eligibility will be confirmed, baseline treatment settings documented, and the participant scheduled for randomization and study programming. A CONSORT-style flow diagram will be used in the final reporting to describe the number screened, eligible, consented, randomized, completing each treatment period, and included in each analysis population.

7. Interventions

Study Device and Programming Context:

All participants will already have an implanted spinal cord stimulation system that is used in routine care. The trial does not involve implantation, revision, or lead manipulation. Before randomization, the clinically established BurstDR program to be used during the active study period will be documented and locked for the duration of the study.

Active BurstDR Condition:

Active treatment consists of continuous BurstDR stimulation delivered for 7 consecutive days using the participant's established clinically effective settings. Electrode configuration, pulse pattern, pulse width, frequency structure, and amplitude will remain unchanged from the participant's therapeutic program unless a minor downward amplitude adjustment is required at the programming visit to preserve paresthesia-free blinding. Any such adjustment will be made before baseline data collection, confirmed during standardized perceptibility testing, and then kept fixed for all active exposure during the study.

Baseline Observation:

Before any randomized washout or treatment period, each participant will complete 1 day of baseline diary data collection under the finalized active study settings. Baseline-day pain and daily domain ratings will be summarized descriptively and will not contribute to the primary randomized treatment comparison.

Sham Condition:

During sham treatment the stimulator output will be switched off for 7 consecutive days. The handheld programmer will be locked, and visible device information that could reveal treatment allocation will be masked. Participants will otherwise receive the same study contacts, diary schedule, and follow-up procedures as during active treatment.

Washout Period:

Two 4-day washout periods with the stimulator switched off are planned: one after the 1-day baseline observation and before period 1, and one between periods 1 and 2. No primary or secondary efficacy endpoint analyses will include data from washout days. The purpose of the washout periods is to minimize residual treatment effects and strengthen the internal validity of the crossover comparison.

Concomitant Treatments:

Participants will be asked to keep all analgesic medications and non-pharmacological pain treatments stable throughout the study. Rescue medication may be used when clinically necessary, but all such use will be recorded prospectively and considered in interpretation of the data.

8. Randomisation and Blinding

Participants will be randomized 1:1 to one of two treatment sequences: active BurstDR followed by sham, or sham followed by active BurstDR. Randomization will be generated using a computer-based allocation schedule within the Patientkollen/Caremetrix platform or an equivalent secure study randomization system. Allocation concealment will be maintained until programming.

Participants, treating clinicians, investigators, outcome assessors, and data analysts will remain blinded to treatment allocation. Only the specifically designated programmer or study nurse performing the randomization-linked programming will have access to the allocation sequence, and that individual will have no role in outcome assessment or primary analysis.

Because BurstDR therapy is intended to be paresthesia-free, the study is particularly suitable for blinded comparison. Before the first randomized treatment arm begins, the active study program will be verified using a standardized perceptibility test with brief randomized ON/OFF intervals to confirm that the participant cannot reliably feel when stimulation is on. If treatment-specific sensation is perceived, the

amplitude may be reduced and retested until no consistent stimulation-related sensation remains. The participant-facing programmer will then be locked. After each 7-day treatment period, participants will be asked whether they felt stimulation or paresthesia at any point during that arm, in order to assess the integrity of blinding without asking them to guess treatment allocation. Emergency unblinding will be permitted only if essential for participant safety or urgent clinical management, and all such events will be documented.

9. Study Procedures and Assessments

The screening visit will confirm eligibility, obtain consent, and document diagnosis, device characteristics, medication stability, predefined pain areas, and established therapeutic BurstDR settings. At the programming/baseline visit, the active study settings will be finalized, a standardized perceptibility test will be performed to confirm imperceptibility, diary procedures will be reviewed, and 1 day of baseline diary data will be collected under the finalized active settings. Participants will then be randomized and enter the first 4-day washout with therapy off.

During each 7-day treatment period, pain diaries will be completed twice daily, once in the morning and once in the evening. Daily ratings for sleep, mood, daily activity, and social activity will also be collected. At the end of each treatment period, overall treatment satisfaction and a blinding/perceptibility assessment will be completed, including whether the participant felt stimulation at any point during that arm. A 4-day washout period with therapy off will occur both before period 1 and between the two randomized treatment periods; no primary endpoint data from washout days will be analysed.

At the end-of-study visit, adverse events, protocol deviations, diary completeness, and participant disposition will be reviewed. Participants will then be returned to their usual clinically indicated programming.

Study phase	Key procedures and assessments
Screening	Consent; eligibility; device and medication review; pain-area definition; diary training
Baseline day	Finalize active settings; standardized perceptibility test; 1 day of baseline diaries under active settings
Washout 1 (days 1–4)	Therapy off before period 1; no efficacy data; safety review as needed
Period 1 (days 5–11)	Randomized active BurstDR or sham; twice-daily NRS; daily sleep, mood, activity, and social ratings; end-of-period satisfaction and blinding question
Washout 2 (days 12–15)	Therapy off between periods; no efficacy data; safety review as needed
Period 2 / end-of-study (days 16–22)	Alternate treatment; same diary schedule; end-of-period satisfaction and blinding question; AE review; return to usual programming

10. Outcome Measures

Primary Outcome

Pain intensity during each 7-day randomized treatment period, measured twice daily (morning and evening) using an 11-point numeric rating scale (NRS; 0–10) for each predefined pain area. All NRS ratings within a participant and treatment period will be pooled, and the period-level median NRS will serve as the primary summary measure. Baseline-day NRS data will be summarized descriptively but will not be included in the primary endpoint.

Secondary Outcomes

1. Patient satisfaction with therapy after each treatment period, measured on a 0–10 scale.
2. PGIC ratings for sleep quality, mood, daily activity, and social activity recorded daily on a 5-point scale; for each domain and period, the period-level median will be analysed.
3. Blinding/perceptibility assessments comprising the standardized pre-period perceptibility check before period 1 and the end-of-period question after each arm on whether stimulation or paresthesia was felt during that arm.
4. Safety outcomes, including adverse events, serious adverse events, and stimulation-related complaints.

Exploratory Outcomes

1. Rescue medication use during each treatment period.
2. Within-period trajectory of pain ratings over time.
3. Descriptive comparison of treatment effects across prespecified pain areas where relevant.

11. Safety Monitoring and Stopping Rules

An independent Data Safety Monitoring Board (DSMB) or equivalent external safety oversight function will review accumulating safety information at prespecified intervals. All adverse events will be recorded from the baseline/programming visit through completion of the second randomized treatment period (Day 22 after baseline). Serious adverse events and device-related events of special interest will be reported according to applicable regulatory and institutional requirements.

If a participant experiences unacceptable pain worsening, requests discontinuation, or develops a safety concern that in the investigator's judgement warrants stopping the current treatment period, the period may be terminated early. As a practical threshold, an NRS score greater than 8 in the main pain area, persistent marked worsening relative to the participant's usual treated state, or other clinically relevant deterioration may trigger urgent review. Participants who stop early during period 1 may, after clinical reassessment and if they wish to continue, proceed to washout and crossover. Emergency unblinding may occur if necessary for safe management.

12. Sample Size and Power

The target sample size is 28 participants with evaluable data from both randomized treatment periods for the primary paired comparison. Up to 35 participants will be recruited to allow for approximately 20% attrition or nonevaluable treatment periods.

The sample size is based on a clinically relevant within-participant treatment difference of 2.0 NRS points between active BurstDR stimulation and sham, assuming a conservative standard deviation of 3.0 NRS points for the paired treatment differences and a two-sided alpha of 0.05. Under a normal model for the paired differences, Monte Carlo simulation of the planned two-sided Wilcoxon signed-rank test indicates

approximately 91% power with 28 evaluable participants. The crossover design improves efficiency by reducing between-participant variability.

13. Statistical Considerations

A detailed standalone Statistical Analysis Plan (SAP) accompanies this protocol. In brief, analyses will be conducted on blinded, coded data before treatment labels are revealed.

For the primary endpoint, the period-level pain score for each participant will be the median of all available NRS values recorded during each 7-day treatment period. The primary treatment effect will be the within-participant paired difference between active BurstDR and sham, analysed using the Wilcoxon signed-rank test. Hodges–Lehmann median difference and 95% confidence interval will be reported, together with the matched-pairs effect size $r = Z/\sqrt{n}$.

Secondary period-level outcomes will be analysed using the same paired, median-based approach. Baseline-day diary data and blinding/perceptibility variables will be summarized descriptively. Prespecified sensitivity analyses will assess robustness to within-period time effects by repeating the primary paired analysis using only days 1–3 and only days 3–5 of each treatment period. An exploratory linear mixed-effects model including fixed effects for treatment, period, and sequence, with participant as a random intercept, will also be fitted to the period-level median pain score.

No interim efficacy analysis is planned. All hypothesis tests will be two-sided with alpha 0.05. Secondary analyses will be interpreted as supportive or exploratory and will not be adjusted for multiplicity.

14. Data Management

All study data will be captured electronically in a secure clinical research environment. Daily pain ratings, PGIC ratings, satisfaction scores, adverse events, concomitant medication updates, and protocol deviations will be entered into Patientkollen/Caremetrix or an equivalent secure data platform with audit logging.

Participants will be identified in the study database by unique study IDs. Direct identifiers will be stored separately from analysis datasets. Access will be role-based and restricted to authorized study staff. Data quality procedures will include range checks, completeness review, source verification where appropriate, and blinded data review before database lock.

15. Monitoring and Quality Assurance

Study conduct will follow a risk-proportionate monitoring plan. Internal monitoring will verify informed consent, eligibility, randomization integrity, device programming documentation, endpoint completeness, and adverse event reporting. Deviations from protocol will be documented, reviewed, and classified.

Before unblinding, the database will undergo prespecified quality checks including review of missing values, consistency checks, sequence balance, and reconciliation of early treatment discontinuations. Any protocol amendments will be version-controlled and archived.

16. Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki, ISO 14155 principles for clinical investigation of medical devices, and applicable Swedish law and institutional requirements. The study has been approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten), Dnr 2026-03871-01. The study will be prospectively registered at ClinicalTrials.gov before enrolment of the first participant.

The ethical risk profile is acceptable because all participants are already implanted, have previously demonstrated clinical benefit from BurstDR therapy, and will participate only in short treatment and

sham periods with close monitoring and predefined stopping rules. The main foreseeable risk is transient pain worsening during sham or washout, which is mitigated by short exposure periods, rescue treatment, clinical access, and the possibility of stopping the study early if needed.

17. Dissemination

Results will be disseminated through peer-reviewed publication, conference presentation, and updates in the trial registry. Reporting will follow CONSORT guidance for crossover and sham-controlled clinical trials as applicable. Authorship will follow ICMJE criteria.

A de-identified analysis dataset and statistical code may be shared after publication subject to institutional governance, applicable law, and participant confidentiality protections.

18. Funding and Conflicts of Interest

Funding will be sought from competitive non-commercial and/or public research funding sources, including Swedish governmental or regional clinical research funding. The funder will have no role in data collection, data ownership, statistical analysis, interpretation, or publication decisions.

Any relevant financial, advisory, or educational relationships between investigators and device manufacturers will be declared in the ethics documentation, funding application, and final publication. Device support already in routine clinical use will be transparently disclosed.

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