Efficacy of Sub Threshold Dorsal Root Ganglion (DRG) Stimulation versus Sham in Established Responders: A Randomised, Double Blind, Two Period Crossover Trial

Single-centre study conducted at Umeå University Hospital, Sweden

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Innehållsförteckning

Purpose and Aims

DRG stimulation is today considered a standard therapy for several neuropathic pain conditions. Despite its widespread clinical use, a critical knowledge gap remains: the efficacy of DRG stimulation has never been validated against sham in a controlled trial. The only randomized controlled study conducted to date is an industry-sponsored comparison between DRG stimulation and spinal cord stimulation (SCS) (9), but no trial has directly tested DRG against placebo.

Umeå University Hospital is internationally recognized as a leading center for DRG stimulation. Patients from across Sweden are referred to our department, making our clinic the de facto national referral center for this therapy. In practice, DRG therapy is centralized to our unit. The resulting high patient volumes, together with our long-standing expertise and comprehensive quality database, provide unique opportunities to fill this knowledge gap—opportunities that no other center is currently positioned to offer.

The purpose of this study is therefore to rigorously evaluate whether ongoing sub-threshold DRG stimulation provides genuine analgesic benefit beyond contextual or placebo effects. Sub-threshold programming is already the accepted standard within DRG stimulation, but the specific contribution of this approach remains to be clarified in a placebo-controlled setting. Addressing this knowledge gap will provide robust scientific evidence to support or refute the physiological efficacy of sub-threshold DRG stimulation.

Our primary aim is to determine the impact of sub-threshold DRG stimulation on pain intensity in established responders, using a double-blind, crossover design. Secondary aims include assessing effects on sleep, mood, and activity, as well as evaluating the feasibility of maintaining blinding and capturing safety and tolerability data.

Significance

The efficacy of DRG stimulation has never been validated in a sham-controlled trial, leaving a critical knowledge gap that this study seeks to address. Without placebo-controlled evidence, the true physiological contribution of DRG stimulation remains uncertain and current clinical guidelines are built on a limited scientific foundation.

By conducting the first sham-controlled trial of DRG stimulation in this setting, we can generate definitive evidence on efficacy and safety, with findings likely to influence clinical practice and policy both nationally and internationally. The results will directly inform clinical guidelines, payer decisions, and programming strategies, and they will strengthen the scientific foundation of DRG stimulation as a safe, effective, and durable treatment for neuropathic pain.

Background & Rationale

Neuropathic pain affects roughly 6–10 % of the adult population and is notoriously refractory to pharmacotherapy, leaving many patients with disabling pain, sleep disturbance and mood disorders. Aberrant ectopic firing in the dorsal root ganglion (DRG)—where primary afferent somata reside—has been identified as a key generator and amplifier of neuropathic signalling (1–5). Therapeutically targeting the DRG is therefore conceptually attractive: modulating neuronal activity at this choke-point can quell both peripheral hyperexcitability and downstream central sensitisation.

Dorsal root ganglion stimulation (DRG-S) delivers biphasic electrical pulses via percutaneously placed leads anchored inside the intervertebral foramen. Unlike conventional spinal cord stimulation (SCS), in which lead migration and rostro-caudal current spread often blur coverage, each DRG occupies a stereotyped position and maps to a discrete dermatome. This anatomic precision translates into highly focal pain relief, fewer unwanted paraesthesias and reduced energy consumption (6,7). Over the past decade, DRGS has progressed from an experimental therapy to an established treatment for complex regional pain syndrome (CRPS), causalgia, postsurgical and post-traumatic pain, failed back surgery syndrome and chronic low-back pain (8–14). Contemporary consensus guidelines explicitly recommend sub-threshold programming as the default setting, citing improved patient comfort and comparable efficacy (6,7). Contemporary consensus recognises sub-threshold stimulation as an accepted and widely applied programming technique within DRG stimulation.

While early systems relied on supra-threshold amplitudes that elicited paresthesia, modern programmers default to sub-threshold output because patients find the absence of tingling more acceptable and battery longevity improves without an apparent loss of efficacy (9,12,19). Animal data suggest that tonic sub-threshold fields preferentially depress spontaneous DRG firing, inhibit dorsal horn wide-dynamic-range neurons and normalize thalamocortical connectivity—all without recruiting large-diameter Aβ fibers thought to mediate paresthesia (19). Yet the true clinical contribution of these physiological effects is unknown because, to date, no double-blind, sham-controlled randomized trial has directly compared DRG-S with placebo. Existing evidence consists mainly of open-label cohorts or active-control designs (e.g., DRG-S versus SCS), which cannot disentangle treatment benefit from expectation, interaction or regression to the mean. To our knowledge, no previous double-blind, randomized, and sham-controlled trial has specifically investigated DRG stimulation, highlighting the novelty of the present design.

The present study addresses this critical knowledge gap. By enrolling patients who have already demonstrated durable (> 3 months) and substantial (≥ 50 %) pain relief on DRG-S and randomizing them to short crossover periods of sub-threshold stimulation or sham, we can isolate the physiological effect of ongoing DRG-S while minimizing ethical concerns and placebo variability. A rigorous sham-controlled, crossover design will provide high internal validity and maximize power with a modest sample size. The resulting evidence will clarify whether sub-threshold DRG-S delivers genuine analgesia beyond contextual factors and will inform future guideline recommendations, payer decisions and programming algorithms. Testing in established responders is desirable to ensure safety, feasibility, and parameter optimization, and to confirm the capacity to maintain blinding. As a subsequent step following this trial, we plan to conduct a randomized, blinded study in de novo patients to validate efficacy in a primary implantation population.

Preliminary Results

Umeå University Hospital is internationally recognized as one of the leading centers in the world for DRG stimulation. Over the past decade, our department has established a comprehensive quality database with structured, prospective data collection, including patient-reported outcome measures (PROMs), patient-reported experience measures (PREMs), detailed device and implant information, and systematic adverse event reporting.

This database currently includes more than 100 patients with active DRG therapy, representing what is likely the largest clinical cohort worldwide. The longest follow-ups now exceed five years (Appendix 1: Data report from our quality database). Analyses of these data indicate that DRG stimulation is a safe and effective treatment for a broad spectrum of neuropathic pain conditions, with consistent and long-lasting analgesic effects. Our findings further suggest that treatment durability extends beyond pain reduction, positively influencing function, mood, and quality of life. Importantly, a comprehensive retrospective analysis of these data is being finalized and will be published during the second half of 2025, further underscoring the robustness and maturity of our clinical experience.

This extensive real-world experience and infrastructure provide a unique foundation for the proposed trial, ensuring feasibility, robust recruitment, and reliable follow-up. Moreover, our track record demonstrates both the scientific and clinical capability of our team to conduct a sham-controlled study of this scope with high internal validity.

Objectives & Hypotheses

- Primary Objective – To compare mean daily pain intensity during five days of sub-threshold DRG stimulation versus sham.
- Secondary Objectives – To compare sleep quality, mood, and daily activity between conditions; to assess safety and tolerability; to explore within-subject carry-over effects.
- Primary Hypothesis – Sub-threshold DRG stimulation will reduce mean Numeric Rating Scale (NRS, 0–10) pain scores compared with sham.

Study Design

- Randomized, double-blind, two-period crossover.
- Two treatment arms of 5 days each, separated by a 24 h wash-out.
- Order of conditions (Active → Sham or Sham → Active) allocated 1:1 using computer-generated random blocks.
- Participant, treating clinician, and outcome assessors blinded.

Participant Selection

Inclusion Criteria

1. Adults (≥ 18 y) with an implanted DRG stimulator for a chronic neuropathic pain condition (not necessarily focal).
2. ≥ 50 % pain reduction sustained for ≥ 3 months on standard (supra-threshold) therapy.
3. Stable analgesic regimen ≥ 4 weeks.
4. Ability to comply with diary completion and study visits.

Exclusion Criteria

1. Active infection or wound complication at implant site.
2. Significant psychiatric comorbidity (e.g. uncontrolled depression, psychosis).
3. Planned surgery, stimulation adjustments, or medication changes within 2 weeks prior to enrolment or at any time during the study period.
4. Pregnancy or breastfeeding.
5. Occurrence of any adverse event during the study that meets the predefined withdrawal criteria (see Safety Monitoring); such participants are withdrawn immediately and not re-randomized.

Interventions

- Active Sub-Threshold Stimulation – Device amplitude individually titrated to 80 % of perception threshold (no paresthesia felt), frequency and pulse-width unchanged from clinical settings.
- Sham – Stimulator switched off. Device interrogation logs masked from participants and outcome staff.

Randomisation & Blinding Procedures

Randomization is generated automatically within the Patientkollen® patient-management platform using concealed permuted blocks (1:1 allocation) and stored entirely inside the single-site environment at Umeå University Hospital; no files are exported outside the platform.

To maintain blinding: After each treatment period, participants will be asked whether they experienced any paresthesia during the preceding stimulation phase, in order to assess whether the study was genuinely blinded. We will not ask participants to identify whether they believe the period involved sham or active stimulation, as such judgements could be influenced by perceived analgesic benefit. Prior to study initiation, a pre-trial acute detection test will be performed in 10 participants: each will undergo 10 randomized one-minute sessions (stimulator ON at 80% perception threshold or OFF), and after each session indicate whether or not paresthesia was perceived. This will ensure the feasibility of maintaining blinding in the main trial. The programming nurse makes all parameter changes while the participant’s handheld programmer is hidden from view.

- After programming, the handheld unit is *locked* with a unique access code known only to the nurse and stored in the electronic Trial Master File (eTMF).
- In a documented emergency (e.g. device-related adverse event or intolerable pain), the code may be disclosed by an investigator uninvolved in outcome assessment. Disclosure automatically withdraws the participant from the study; the reason is logged in the eTMF.

Unblinding procedure: Once the final participant completes Day 10, Patientkollen runs automated integrity checks (range, consistency, missing-value rules) and locks the dataset. The platform then executes predefined statistical scripts comparing sequence labels A and B without human intervention. After the automated analysis is complete, the research team convenes, and the programming nurse activates the "reveal" function in Patientkollen to link each label to its actual treatment order. The validated dataset, analysis outputs, and audit trail then become accessible to the full study group.

Study Schedule & Assessments

Study Day	Activity
−7 to −1	Screening, informed consent, baseline questionnaires, recording perception threshold.
0	Randomization; begin first 24 h wash-out (device OFF).
1-5	Period 1 treatment (Active or Sham) + twice-daily electronic diary.
5	24 h wash-out (device OFF).
6-10	Period 2 treatment + diaries.
10	End-of-study visit, adverse event review, exit interview

Outcome Measures

Category	Measure	Time-Points
Primary	Average NRS pain (0–10) across 5 treatment days	Daily AM & PM
Secondary	Sleep quality (5-point PGIC)*	Daily AM
	Mood (5-point PGIC)*	Daily PM
	Daily activity (5-point PGIC)*	Daily PM
	Adverse events	Continuous
Exploratory	Device usage logs, rescue medication use	Daily

Data Collection & Management

All study data *remain entirely* inside Patientkollen®'s two mirrored on-premises physical servers located in secure Swedish data centres—no exports, downloads, or external copies are made during the trial. The analysis workspace is hosted *within* this mirrored infrastructure under read-only permissions.

- Randomization module – generates concealed allocation; visible only to the programming nurse.

- eConsent – digital Participant Information Sheet and Bank-ID e-signature; signed PDFs stored in-platform.
- eDiary – questionnaires (pain, sleep, mood, activity) are scheduled at 09:00 and 20:00 daily; SMS and e-mail prompts are sent, followed by an automated reminder after 1 h if still incomplete.
    - Missing > 2 consecutive diaries triggers an investigator alert.
- Real-time dashboards – colour-coded indicators flag missing entries and SAE alerts for investigators and the DSMB.
- Locked analysis workspace – pre-specified statistical scripts execute within Patientkollen on read-only copies of the dataset; a complete audit trail is archived.
- Comprehensive audit logging – every action by patients and study personnel (e.g., diary entry, parameter change, data review) is time-stamped and written to an immutable audit log within Patientkollen.

All data are encrypted at rest and in transit on the mirrored servers, which operate under ISO 27001-compliant security policies with role-based access control.

Statistical Analysis Plan

- Sample Size – Assuming within-subject SD = 1.5 NRS points, minimally important difference = 1 point, $\alpha = 0.05$, power = 0.90, two-sided paired test → 24 completers needed (calculated with G*Power). To accommodate 15 % attrition, target enrolment = 28.
- Primary Analysis – Paired t-test (or Wilcoxon signed-rank if non-normal) comparing mean NRS pain across days 3–5 between Active and Sham periods. If a period is aborted due to high pain, the last recorded score will be carried forward for the remaining days. Treatment order and carry-over tested via mixed-effects model with fixed effects for treatment, period, and sequence.
- Secondary Outcomes – Similar within-subject comparisons; Bonferroni correction applied.
- Missing Data – Multiple imputation if > 5 % diary fields missing.

Safety Monitoring

All adverse events (AEs) occurring between screening and study exit lead to the immediate withdrawal of the participant from the trial. If the AE is judged related to either the DRG stimulation or the sham condition, it is captured in the study database with these mandatory details: (i) AE type and MedDRA term, (ii) date/time of onset, (iii) action taken (e.g., device OFF, medical treatment), and (iv) final outcome/resolution.

The event report is recorded in Patientkollen within 24 h via the SAE portal and automatically forwarded to the Data Safety Monitoring Board (DSMB) for review at its next meeting.

Intraperiod stopping rule: If any diary entry records (i) an NRS pain score > 8 or (ii) an increase ≥ 4 points versus Baseline Day 0, the current treatment period is halted. The

participant immediately enters the 24 h wash-out and then crosses to the alternate arm. The episode is logged as an AE (device insufficient efficacy) and triggers a real-time alert to the DSMB.

Ethical Considerations

The study complies with the Declaration of Helsinki, ISO 14155 Good Clinical Practice, and Swedish regulations for medical-device research. Ethical approval has been obtained for this study from the Swedish Ethical Review Authority (Etikprövningsmyndigheten), DNR 2025-04065-01. It will be prospectively registered on the public registry ClinicalTrials.gov (identifier to be obtained) prior to enrolment of the first participant. All participants provide written informed e-consent via Patientkollen. Risks are minimal and relate mainly to temporary cessation of therapeutic stimulation.

Dissemination

Results will be submitted to peer-reviewed journals and presented at pain and neuromodulation conferences. De-identified data and statistical code will be made available via an open repository (OSF) within 12 months of publication.

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Appendix 1: Data report from our quality database for patients with DRG stimulation therapy