RegenMed

WHITE PAPER

CIRCLES FOR PERIPHERAL NERVE STIMULATION TREATMENT PROTOCOLS

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PNS FOUNDATIONAL SCIENCE

Peripheral Nerve Stimulation (PNS) represents a dynamic sector of clinical neuromodulation, offering increasingly sophisticated solutions for intractable pain. PNS efficacy hinges on complex biological interactions extending far beyond the initial, simplistic conceptual models. A detailed understanding of the mechanism of action (MOA) is crucial for guiding technological innovation and optimizing stimulation parameters.

Advanced Mechanisms of Action: Peripheral, Spinal, and Cortical Modulation

The theoretical foundation of PNS therapy traces back to the Gate Control Theory, proposed by Wall and Melzack in 1965. This classical model posits that electrical stimulation of large-diameter myelinated afferent fibers (Aβ) inhibits the transmission of pain signals carried by smaller C and Aδ fibers at the dorsal horn of the spinal cord, effectively "closing the gate" to nociceptive input.

However, clinical experience and advanced research indicate that the long-term analgesic effects of PNS are mediated by a much broader, multi-level neuromodulatory network.[1] Evidence confirms that PNS exerts effects both peripherally at the stimulation site and centrally within the spinal cord and brain.

Crucially, PNS demonstrates engagement with the Central Nervous System (CNS), fundamentally defining it as a central pain modulator, not merely a local interruptor. Neuromodulatory effects extend to higher brain centers, including the dorsal lateral prefrontal cortex (DLPFC), the somatosensory cortex, the anterior cingulate cortex (ACC), and parahippocampal areas.

The modulation of the ACC and DLPFC is particularly significant because these regions are primarily responsible for the affective, emotional, and cognitive processing of pain—the component that defines pain suffering and chronicity—rather than just the primary sensory input.

This central pathway engagement provides a robust explanation for the observed correlation between a patient's pre-treatment psychological status (e.g., depressive symptoms) and their long-term clinical response following PNS therapy. Optimizing stimulation settings must, therefore, evolve beyond simply maximizing paresthesia coverage (a sensory objective) to identifying parameters that effectively modulate these critical brain activity patterns linked to pain chronification and distress.

Furthermore, PNS modulates specific non-electrical physiological pathways:

Inflammatory Modulation: PNS influences local and systemic inflammatory processes.

Autonomic Nervous System (ANS): It affects the balance between sympathetic and parasympathetic function.

Endogenous Inhibition: PNS activates descending endogenous pain inhibition pathways.

Neurotransmitter Changes: The therapy is associated with changes in endogenous neurotransmitter levels and affects the plasticity of NMDA pathways, which are critical components in maintaining central pain sensitization.

Current and Emerging Indications for PNS Therapy

The clinical applicability of PNS has expanded rapidly, supported by growing evidence and formal coverage policies. Medicare Local Coverage Determinations (LCDs) provide a comprehensive view of established, commercially viable indications.

Therapeutic targets span multiple anatomical regions and include intractable neuropathic conditions:

Head and Face: PNS is indicated for the stimulation of occipital nerves to treat occipital neuralgia, treatment-resistant migraines, and cervicogenic headaches. Stimulation of the trigeminal nerves and their branches addresses post-traumatic and post-surgical neuropathic pain in the facial region.

Limbs and Trunk: PNS of nerves in the upper and lower extremities is used to manage Complex Regional Pain Syndromes (CRPS, both type 1 and 2), pain resulting from peripheral nerve injury, post-surgical scar formation, nerve entrapment, painful mononeuropathy, and painful amputation neuromas.

Specific neuropathic diagnoses supported by relevant ICD-10 codes for coverage include Trigeminal neuralgia (G50.0), Lumbosacral plexus disorders (G54.1), cervical root disorders (G54.2), postherpetic trigeminal neuralgia (B02.22), and diabetic mononeuropathy (E08.41, E09.41).

In addition to established indications, clinical evidence supports PNS in emerging niche areas, such as pain related to the Genitofemoral nerve. This neuropathy often arises secondary to surgical sequelae or trauma. Published evidence for Genitofemoral pain treated with PNS has demonstrated significant efficacy, reporting pain reduction in the range of 70–90%, alongside measurable improvements in functional ability and decreased reliance on opioid medication.

Critical Gaps in Efficacy Optimization

Despite strong clinical outcomes, the optimization of PNS therapy remains hindered by a substantial scientific deficit concerning the relationship between stimulation parameters and biological effect. A core gap in current practice is the lack of precision guidance for clinicians in selecting optimal stimulation frequency, pulse width, and amplitude to reliably achieve the most efficacious neuromodulation effect (whether peripheral sensory modulation or central neuroplasticity modulation).

Current clinical practice often relies on empirical adjustments based on patient feedback. To advance the field to a mature, predictable science, there is a recognized need to develop and validate accurate, computationally efficient methods for calculating the electric field (E-field) generated by the device and for predicting the peripheral nerve stimulation (PNS) thresholds within a patient's anatomy.

This scientific advancement is essential to transition PNS from an empirical practice to a predictive one. Rather than relying solely on patient subjective feedback during programming, a predictive model would allow clinicians to input patient anatomical data and target nerve location, leading to automated suggestions for optimized, hardware-limited stimulation settings. Furthermore, these predictive methods are critical for informing regulatory standards, ensuring patient safety (by managing unwanted nerve stimulation or motor capture), and setting appropriate hardware limits, particularly in complex safety environments such as Magnetic Resonance Imaging (MRI) compatibility.

Manufacturers that prioritize investment in advanced computational modeling, simulation, and E-field validation (such as finite element analysis) will establish a significant competitive advantage by offering devices capable of automated, personalized, and predictable therapy, directly addressing this critical scientific requirement.

MARKET OVERVIEW

The peripheral nerve stimulators market is experiencing robust expansion, driven by

favorable public health trends, demographic shifts, and significant technological improvements.

Comprehensive Market Sizing, Segmentation, and Growth Projections

The market for peripheral nerve stimulators is highly dynamic. The 2024 global market size was estimated at USD 273 million and is projected to reach USD 680 million by 2033. Market growth is fueled by four macro-factors:

Rising Chronic Pain Prevalence: The increasing incidence of neuropathic and chronic pain conditions worldwide provides a continually expanding patient pool.

Technological Advancement: Continuous innovation yields more efficient, user-friendly, and miniaturized devices.

Opioid Crisis Mitigation: The strategic shift toward non-pharmacological, minimally invasive pain management methods is driven by acute public health concerns regarding opioid abuse and addiction.

Aging Demographics: The global aging population is inherently more prone to chronic neurological and pain disorders, such as neuropathy, which drives sustained demand for these devices.

The Complex Regional Pain Syndrome (CRPS) segment is projected to be the fastest-growing area of the market through 2033. This rise is attributed to increased awareness of targeted treatment options for pain resulting from severe trauma, burn injuries, and surgical complications.

PNS as an Opioid-Sparing Adjunct Therapy

The role of PNS is strategically shifting from a treatment of last resort for established chronic pain to a proactive, non-pharmacologic intervention utilized in the acute and subacute settings to prevent pain chronification.

This paradigm shift is enabled by the development of temporary, percutaneous leads that can be implanted for up to 60 days. These temporary systems offer a low-risk profile, avoiding the infection risks associated with permanent implants in the immediate postoperative period. By providing a lower-cost, lower-commitment entry point, these systems are strategically crucial for broadening market access and accelerating adoption among providers reluctant to proceed directly to permanent implants.

Clinical evidence strongly supports this adjunct use in acute care:

Post-Amputation Pain (PAP): A pilot study demonstrated that PNS following lower extremity amputation significantly reduced average phantom limb pain and residual limb pain, coupled with a notable decrease in daily opioid consumption through the 3-month follow-up. The significant reduction in pain scores achieved during the 8-week treatment period often extended well beyond the removal of the device, suggesting a durable neuromodulatory effect.

Orthopedic Applications: PNS has been shown to reduce pain and subsequent opioid requirements after major orthopedic procedures, including total knee arthroplasty, and foot and shoulder surgeries. In chronic knee pain specifically, temporary percutaneous PNS targeting the genicular nerves yielded high clinical response rates, with 94% of patients achieving 50% pain relief.

The effectiveness of PNS applied immediately following trauma or surgery suggests that its ultimate strategic value lies in its prophylactic potential: interrupting the intense pain signals that drive central sensitization. By preventing this transition from acute to chronic neuropathic pain, PNS can target the root cause of conditions like CRPS, the market's fastest-growing segment. Consequently, future marketing and regulatory strategies are increasingly focused on securing clearance for "prevention of chronic pain" in high-risk surgical populations, rather than exclusively treating established chronic conditions.

REGULATORY COMPLIANCE AND REIMBURSEMENT

Market viability and growth in the United States are inextricably linked to navigating complex reimbursement policies, particularly concerning specific CPT codes and compliance with federal regulations.

Navigating FDA Pathways and Device Categorization

Most implantable PNS systems, such as the PNS System cleared by the FDA in 2017, utilize the 510(k) pathway, demonstrating substantial equivalence to existing devices. While FDA clearance addresses device safety and effectiveness, Medicare Local Coverage Determinations (LCDs) ultimately dictate the breadth of clinical coverage and market access.

CPT Coding, Payer Coverage Policies, and Financial Viability

Reimbursement relies on accurately classifying the procedure using Current Procedural Terminology (CPT) codes, which directly determine the financial value of the procedure.

The distinction between CPT codes for temporary versus permanent implants creates a significant financial disparity. Codes associated with the insertion of temporary leads, for example, provide a lower reimbursement rate, typically between $4,000 and $6,000. In contrast, CPT Code 64590 for the "Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling," yields a high reimbursement value, generally ranging between $16,000 and $18,000.

Medicare policies formally document coverage for PNS via LCDs, linking covered indications to specific anatomical targets and diagnosis codes.[4] For example, coverage exists for:

Trigeminal and Occipital neuralgia (G50.0).

Lumbosacral plexus disorders (G54.1).

Diabetic mononeuropathies (E08.41, E09.41).

Postherpetic polyneuropathy (B02.23).

Manufacturers must provide clinical evidence directly supporting these specific ICD codes to ensure broad market uptake and favorable payer reimbursement.

Legal Risk Assessment: Fraud, Compliance, and the False Claims Act

The high reimbursement value attached to CPT Code 64590 creates a substantial legal risk environment under the False Claims Act (FCA) in the United States. The FCA establishes liability for any party who knowingly presents, or causes to be presented, a false or fraudulent claim for payment to the government. The statutory definition of "knowingly" is broad, encompassing actual knowledge, reckless disregard, and deliberate indifference.

The critical importance of compliance was tragically demonstrated by the Stimwave case (2018–2020), where executives and the company knowingly caused medical providers to submit false claims using CPT Code 64590 for the implantation of a "receiver" when they were, in fact, implanting an inert dummy component that possessed no receiver functionality. This fraudulent scheme resulted in improper reimbursements by the

government.

This highly publicized case underscores the acute necessity for robust corporate compliance and stringent manufacturing quality controls. Any company operating in this space must ensure that components billed under the high-value CPT 64590 designation are fully functional as described in their FDA clearance and billing documentation.

This regulatory burden significantly increases the operational costs and legal exposure for all PNS market participants. The consequence of compliance failure under the FCA can lead to massive statutory penalties, effectively acting as a substantial non-price barrier to entry for smaller or less capitalized competitors. Therefore, financial due diligence in the PNS sector must place equal weight on clinical efficacy and the integrity of operational controls regarding CPT code assignment.

REAL-WORLD EVIDENCE (RWE) OBSERVATIONAL PROTOCOLS

To generate the necessary evidence for expanded coverage and optimized patient selection, this paper proposes three structured Real-World Evidence (RWE) Observational Protocols (OPs). (Final protocols are to be designed by appropriate clinical/scientific experts.)

These draft OPs leverage temporary and permanent PNS systems to address key clinical needs identified in the market analysis. Standardized outcomes assessment requires the validated Patient-Reported Outcome Measures (PROMs) that capture pain, function, and psychosocial factors.

Circles OP 1: Post-Amputation Pain (RWE)

This draft protocol focuses on validating PNS as an adjunct, prophylactic intervention immediately following major amputation surgery, targeting both opioid reduction and the prevention of chronic phantom limb pain.

Anatomical Area	Pathology/Diagnosis (ICD-10)	Treatment Protocol (General Setting)	Standardized Outcomes Assessment (PROMs)
Major Peripheral Nerves of Residual	Post-Amputation Pain (Phantom Limb and	60-day temporary percutaneous	Pain Intensity (NRS/VAS,

Limb (e.g., Sciatic, Tibial, Peroneal nerves proximal to amputation site)	Residual Limb Pain). *ICD-10:* G57.7 (Causalgia of amputated limb)	PNS system. Low-frequency (50-100 Hz), low-amplitude (sub-motor threshold) continuous output, or burst pattern. Stimulation initiated within 7 days post-amputation.	residual and phantom limb pain separately). Opioid Consumption (Morphine Milligram Equivalents - MME). Patient Global Impression of Change (PGIC). PROMIS Depression T-score (Baseline and 3 Months).

The critical timing of this protocol—initiating PNS immediately post-amputation—is designed to leverage the anti-chronification potential of the therapy. By quantifying both pain reduction and the mandatory reduction in MME, the protocol directly generates data points that address both clinical efficacy and the broader public health need for opioid sparing.

Inclusion of the PROMIS Depression score is necessary for refining patient selection criteria, as pre-treatment psychological status is a known predictor of long-term therapeutic success.

Circles OP 2: Genicular Nerve Stimulation for Chronic Knee Pain

This draft protocol targets a high-volume orthopedic market segment, focusing on validating the efficacy and durability of temporary PNS systems for localized chronic joint pain, often refractory to conservative management.

Anatomical Area	Pathology/Diagnosis (ICD-10)	Treatment Protocol (General Setting)	Standardized Outcomes Assessment (PROMs)
Genicular Nerves (Superior Medial, Superior Lateral, Inferior Medial branches)	Chronic Post-Surgical Knee Pain (e.g., following Total Knee Arthroplasty) or Chronic Osteoarthritis Knee Pain. *ICD-10:* M25.56 (Pain in knee)	60-day temporary percutaneous PNS system. Dual-electrode configuration optimized for nerve field coverage. High-frequency stimulation mode (e.g., 10kHz, if available) or high-density programming, adjusted for maximal paresthesia coverage/relief.	Percentage Pain Relief (using 50% threshold for responder classification). Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Score (function/stiffness). Knee Outcome Survey Activities of Daily Living (KOS-ADL) Scale.

Building upon retrospective data that suggests high responder rates (e.g., 94.4% achieving 50% relief), this draft OP aims to confirm these outcomes in a standardized RWE setting.

The inclusion of functional PROMs like the WOMAC and KOS-ADL is crucial, as payers increasingly demand evidence linking pain relief to demonstrable functional improvement, ensuring that the therapy provides durable patient value. Successful RWE here would substantially accelerate adoption within the orthopedic pain management community.

Circles OP 3: Targeted Stimulation for Refractory Postherpetic Neuralgia

This draft protocol targets a severe, intractable neuropathic pain syndrome—Postherpetic Neuralgia (PHN)—that is explicitly codified for Medicare coverage. It is designed to validate the long-term effectiveness of permanent PNS systems in high-burden chronic

conditions.

Anatomical Area	**Pathology/Diagnosis (ICD-10)**	**Treatment Protocol (General Setting)**	**Standardized Outcomes Assessment (PROMs)**
Specific Peripheral Nerves (e.g., Intercostal, Trigeminal, or Occipital nerves depending on site of PHN).	Refractory Postherpetic Neuralgia (PHN). *ICD-10:* B02.22 (Postherpetic trigeminal neuralgia), B02.23 (Postherpetic polyneuropathy).	Permanent implantable system. Cycling or intermittent stimulation (e.g., 8-12 hours per day). Paresthesia-based settings optimized for 100% coverage of the affected dermatome, followed by potential transition to sub-perception settings (e.g., high frequency) based on patient response.	Average Daily Pain Score (NRS). Numeric Rating Scale (NRS) for worst breakthrough pain. Pain Catastrophizing Scale (PCS). Sleep Interference Score. Zoster-Specific Quality of Life Index (ZQLI)

Due to the high regulatory alignment (specific ICD codes covered by Medicare), robust RWE from this protocol will solidify justification for the substantial reimbursement required for permanent implants.

PHN often results in severe quality of life deficits beyond pain, necessitating the inclusion of comprehensive measures such as the Zoster-Specific Quality of Life Index (ZQLI) and Sleep Interference scores to demonstrate holistic clinical benefit. Observing efficacy in this condition, which involves severe central sensitization, will also provide valuable data to correlate specific stimulation settings with presumed underlying biological mechanisms (e.g., inflammatory or neuroplastic modulation).

CONCLUSIONS

The peripheral nerve stimulation market is positioned for exceptional growth, driven by the urgent clinical requirement for non-opioid pain solutions and the expanding clinical scope

of PNS beyond end-stage chronic pain.

The central finding of this analysis is the dual nature of PNS's mechanism of action: it not only acts locally via the gate control theory but also functions as a powerful central neuromodulator, affecting areas of the brain responsible for the affective and cognitive processing of pain (DLPFC, ACC). This central modulation implies that for optimal long-term success, future treatment protocols must systematically integrate psychological screening, as pre-treatment mental health status is predictive of long-term response.

For sustained market maturation, the field must overcome a critical scientific hurdle: transitioning from empirical parameter selection to a predictive model. Investment in computational E-field modeling is necessary to optimize stimulation settings precisely, ensuring reproducible efficacy and informing regulatory safety standards.

Strategically, the adoption of temporary, 60-day PNS systems represents a vital shift toward prophylactic therapy. Their demonstrated effectiveness in acute/subacute settings (e.g., post-amputation) transforms PNS into a potential intervention for preventing pain chronification, creating a high-volume adjacent market segment in surgical and trauma care.

Finally, market profitability, particularly in the US, is heavily dependent on high-value reimbursement codes (CPT 64590). The severe legal consequences demonstrated by historical fraud cases emphasize that rigorous corporate compliance and the absolute integrity of device functionality are paramount, representing a non-price barrier to entry that new participants must fully address to mitigate exposure under the False Claims Act.

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