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Transcranial Vibration, Magnetic, and Peripheral Stimulation (TVMPS) in Subacute Stroke: Feasibility and Concept Viability Study

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Transcranial Vibration, Magnetic, and Peripheral Stimulation (TVMPS) in Subacute Stroke: Feasibility and Concept Viability Study

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Abstract

Background

Permanent gait impairment affects up to 80% of stroke survivors and remains a major cause of long-term disability. Multi-modal non-invasive brain stimulation (NIBS) frameworks offer a potential avenue to engage compromised sensorimotor networks by combining central and peripheral inputs. This study evaluated the feasibility and preliminary concept viability of a novel Transcranial Vibration, Magnetic, and Peripheral Stimulation (TVMPS) protocol in subacute stroke to determine whether a sufficient rationale exists to proceed to a randomized controlled trial.

Methods

To evaluate protocol execution and compare movement changes following TVMPS versus sham treatment, fifteen subacute stroke participants completed a 5-day protocol comprising three intervention sessions (Days 1, 2, and 4) and five daily instrumented gait assessments. Participants were allocated to real multi-modal stimulation ($n = X$) or an expectancy-modulated sham control ($n = Y$). Skull treatment sites were localized using functional manual muscle testing (fMMT) paired with focal vibration. The real protocol combined static transcranial magnetic stimulation (sTMS), somatotopic map activation, and paired associative stimulation (PAS).

Results

All fifteen participants completed the 5-day protocol with 100% adherence. Outcome trends revealed distinct performance divergences between groups: while both cohorts demonstrated cumulative functional gains through Day 4 (real TVMPS: +18.9% vs. sham: +8.2%), structured expectancy removal on Day 4 caused sham group gains to regress to +5.9% at Day 5, whereas the real TVMPS group continued to improve, reaching a +32.1% overall functional gain at final outcome.

Conclusion

This study evaluated the feasibility and concept viability of TVMPS in subacute stroke. Given the small cohort and brief intervention window, gait kinematics and movement parameters, interpreted alongside the observed expectancy removal effect, were selected as indicators of response. At final, the magnitude of change observed in the TVMPS group supports considering a fully powered randomized controlled trial.

Trial Registration

ISRCTN, ISRCTN16123403. Registered 14 April 2021 [Retrospectively registered]

Keywords

Stroke rehabilitation, non-invasive neuromodulation, transcranial static magnet stimulation, paired associative stimulation, functional manual muscle testing, gait kinematics, feasibility study.

Key Messages Regarding Feasibility

1. **What uncertainties existed regarding the feasibility?**

   The TVMPS protocol employs a multi-modal neuromodulation methodology that includes transcranial magnetic stimulation, paired associative stimulation, and somatotopic map activation. Because this multifaceted intervention integrates distinct diagnostic and therapeutic steps, uncertainties remained regarding whether we could sufficiently isolate operational variables and manage patient tenure constraints without compromising methodological integrity. The small cohort and short duration of the trial added to the doubt that the study could demonstrate sufficient plausibility to support a future, fully randomized, double-blind trial.

2. **What are the key feasibility findings?**

   The methodology demonstrated operational viability across recruitment, randomization, and blinding procedures. Though small and of short duration, outcomes were indicative of greater functional improvements in the real treatment group as compared to the sham. The extra effect, as a result of expectancy removal, noted a further decline in sham final outcomes as compared to the real treatment group.

3. **What are the implications of the feasibility findings for the design of the main study?**

   The conclusions gleaned from the feasibility study showed that TVMPS may have a positive effect on post-stroke rehabilitation, though improvements to the feasibility methodology are needed. The main study design should be updated with a much larger cohort and a long-term post-treatment evaluation. The randomization process should be changed from equal to stratified, or minimization so that characteristic

imbalances are reduced between treatment groups. Finally, the feasibility study has indicated that expectancy removal be retained.

Background

Gait restoration is a primary objective in subacute stroke rehabilitation, given that residual locomotion deficits impact roughly 80% of survivors[1, 2]. Achieving meaningful functional recovery continues to present major therapeutic challenges, often leaving conventional therapies struggling to significantly improve gait quality[3]. To address these persistent limitations in post-stroke rehabilitation, non-invasive brain stimulation techniques have emerged as promising adjuncts to target lower extremity motor function, balance, and gait performance[4]. Driving lasting neuroplastic gains in gait recovery relies on engaging targeted Hebbian mechanisms to reorganize compromised sensorimotor networks[5].

While single- or dual-channel non-invasive brain stimulation approaches show potential, conventional brain stimulation often relies on standard anatomical landmarks and unimodal interventions frequently yield modest or highly variable clinical outcomes[6]. Furthermore, one important critique is that the brain is often treated as a black box, ignoring internal state dynamics at the time of stimulation, contributing to higher outcome variability[7]. To improve stroke recovery, transcranial stimulation has recently been applied while patients perform voluntary movements as state-dependent coupling is thought to induce more specific neural plasticity during rehabilitative motor training[8]. Building upon these principles, the novel Transcranial Vibration, Magnetic, and Peripheral Stimulation (TVMPS) protocol was designed to integrate precise target identification in the lesioned hemisphere combined with multi-modal neuroplastic stimulation. TVMPS delivers an individualized, network-level approach to neural rehabilitation by directly coupling central neuromodulation with real-time peripheral somatosensory feedback. What distinguishes the TVMPS framework from conventional single-modality protocols is its integrated, two-stage operational workflow:

- **Diagnostic Targeting:** Unlike conventional methods, TVMPS targeting avoids structural anatomical landmarks. Instead, the diagnostic phase uses Transcranial Vibration Stimulation (TVS) as a central sensory challenge. Although TVS as applied here is a novel approach not yet established in the literature, it shares a methodological bridge with the well-documented Skull Vibration-Induced Nystagmus Test (SVINT)[9, 10]. While SVINT drives central vestibular pathways to produce a vestibulo-ocular output, TVS is paired here with functional manual muscle testing (fMMT)[11, 12]. This pairing uncovers real cortical motor deficits, enabling precise, site-specific localization over the lesioned hemisphere. [Figure 1]
- **Therapeutic Delivery:** Treatment uses a synchronized multi-modal stimulation triad.

Transcranial static magnetic stimulation (sTMS)[13, 14], is applied to the identified skull site alongside paired associative stimulation (PAS) on the targeted distal limb.[15–17]. Furthermore, the placement of the patient's hand on or near the magnet over the cranial site activates the primary somatosensory cortex, thereby facilitating a more focused stimulation input[18, 19]. [Figure 2]

This investigator-initiated study evaluated the operational feasibility and preliminary concept viability of the TVMPS protocol in a subacute stroke cohort by tracking functional gait kinematics. This multi-modal strategy provides a new clinical workflow for assessing whether to launch a large-scale clinical trial. Because of the small sample size, formal inferential p-value testing was omitted to prevent Type II statistical errors[20, 21]. Instead, the study focuses on functional movement and gait kinematic trends to determine if a fully powered randomized controlled trial is warranted.

Methods

Study Design and Setting

This investigator-initiated study evaluated the feasibility and preliminary concept viability of the TVMPS protocol in a subacute stroke cohort over a 5-day trial period. Interventions were administered on Days 1, 2, and 4. Day 3 served as an assessment-only rest day to evaluate short-term retention, while Day 5 was dedicated exclusively to final functional assessments. Gait kinematic and functional mobility trajectory outcomes were used to quantify change.

To evaluate protocol stability and control for placebo effects, a structured unblinding procedure (expectancy removal) was executed after the third intervention session on Day 4. Participants were informed that all treatments had concluded and that Day 5 would consist solely of functional assessment.

The trial was conducted over a 7-month period, from December 2020 through July 2021, at the Evexia Rehabilitation Centre in Halkidiki, Greece. The assessment schedule and timeline unblinding procedure are illustrated in Table 1.

Assessment Schedule

Day	Instrumented Gait Assessment	Intervention Administered	Expectancy Status
Day 1	Baseline and post-intervention	TVMPS or sham	Active expectancy
Day 2	Baseline and post-intervention	TVMPS or sham	Active expectancy
Day 3	Assessment only (rest day)	None	Active expectancy
Day 4	Baseline and post-intervention	Final TVMPS or sham	Expectancy removal
Day 5	Final functional assessment	None	Expectancy removed

Table 1: Experimental Timeline and Intervention Schedule

Participant Selection and Allocation

The study population comprised patients in the subacute phase of ischemic post-stroke recovery (defined as a rapid-onset event of vascular origin with focal cerebral disturbance persisting longer than 24 hours).

Inclusion Criteria:

- **Age:** 18 to 87 years.
- **Clinical Presentation:** Referral for rehabilitation of right- or left-sided hemiparesis secondary to a unilateral cerebral hemispheric stroke.
- **Functional Deficit:** Manifested gait disorder
- **Functional Baseline:** Ability to ambulate independently without a mobility aid for a minimum of 20 meters.

Exclusion Criteria:

- **Medical Contraindications:** Presence of a pacemaker, defibrillator, or intracerebral clip.
- **Cognitive Capacity:** Cognitive deficits precluding comprehension or compliance with testing protocols.
- **Surgical History:** Lower limb surgery within the preceding 6 months.
- **Comorbidities:** Concomitant, progressive, or systemic diseases limiting standard rehabilitation.

Fifteen eligible participants were allocated to either real TVMPS ($n = 9$) or a sham control ($n = 6$). Both groups received three real or sham treatments and daily functional outcome measurements over a five-day period. On the fourth day, both cohorts underwent expectancy modulation by being informed that treatments had concluded. All participants remained concurrently enrolled in standardized, state-funded institutional rehabilitation programs at the facility, which stayed uniform and uninterrupted throughout the 5-day study period.

Randomization and Blinding

Participant Randomization and Allocation Concealment

Participants were randomized according to their arrival date at the center. Given the inconsistent arrival intervals, frequently spanning days or weeks between presentations, sequence generation was conducted using a simple coin toss with a 1:1 allocation ratio. To ensure strict allocation concealment, an independent researcher not involved in recruitment or outcome assessment performed the coin toss. The resulting assignment was communicated directly and exclusively to the unblinded interventionist. The double-blind (participant- and evaluator-blinded), sham-controlled design was maintained throughout. Clinical roles were strictly segregated:

- **The Interventionist:** A single unblinded examiner performed target localization and administered all real or sham interventions. The interventionist was completely excluded from outcome assessments, data collection, and statistical analysis.
- **The Evaluators:** Dedicated clinical assessors, completely segregated from treatment allocation and scheduling, conducted all instrumented gait analyses while remaining strictly blinded to group assignments.

Inter-patient communication within the clinical facility was restricted, and all participants remained naïve to the mechanical distinctions between real and sham apparatuses. Real and sham sessions were identical in duration, environmental setting, and physical execution.

Diagnostic Workflows and Target Localization

Functional cortical target coordinates on the lesioned hemisphere were mapped prior to intervention using transcranial vibration stimulus TVS combined with a fMMT protocol.

- **Transcranial Vibrational Challenge:** Transcranial mechanical vibration was delivered as a standardized sensory challenge by systematically positioning a

handheld device (FLEXXSONIC™, Flexxsonic Ltd., UK) over different areas of the skull on the lesioned hemisphere.

- **Neuromotor Assessment:** Concurrently with vibration placement, fMMT was performed on the non-paretic extremity ipsilateral to the stroke lesion. [Figure 3]
- **Target Identification:** A skull coordinate was operationally identified as a positive target site when focal cranial vibration induced a transient, localized alteration in fMMT resistance (joint-fixation failure).

Instrumented Gait Analysis and Spatiotemporal Metrics

Evaluation Schedule

A total of seven standardized evaluations were conducted for each participant across the 5-day trial period, comprising 2 functional movement assessments and 5 kinematic gait evaluations. On treatment days (Days 1, 2, and 4), quantitative assessments were performed prior to the administration of either real TVMPS or sham protocols to establish unconfounded daily baseline measurements.

Quantitative Data Acquisition

Functional Mobility Assessment

Functional mobility, lower extremity strength, and fall risk were quantified using the Timed Up and Go (TUG) test and the 5-Times Sit-to-Stand Test (5XSST). For both assessments, participants utilized a standard armchair (seat height: ~45 cm) and wore their habitual footwear.

TUG: Administered twice, comprising an initial untimed practice trial followed by a timed test. Participants began seated with back support. Upon the verbal "go" command, they stood, walked along a marked 3-meter linear path, turned 180 degrees, and returned to sit in the chair[22, 23].

5XSST: Administered twice, beginning with an untimed practice trial. Participants sat with their arms crossed over their chest and completed five consecutive repetitions of standing upright and sitting down as quickly and safely as possible[24].

Kinesis Gait Evaluation

Objective, real-time spatiotemporal gait metrics were captured using a validated inertial sensor system (Kinesis Gait™ v1.4.1; Kinesis Health Technologies Ltd., Dublin, Ireland[25,

26]. At the start of each testing session, synchronized wireless inertial measurement units (IMUs) were securely attached to the mid-calf (shank) region of both lower extremities via adjustable straps [Figure 4].

Participants were instructed to navigate a straight, unimpeded 20-meter indoor walkway at their maximum safe velocity ("walk as fast as possible without compromising safety"). To ensure participant safety and prevent falls, a blinded clinical assistant walked alongside each participant without providing physical contact or manual assistance unless necessary to prevent an imminent fall.

Raw tri-axial accelerometer and gyroscope data were automatically processed by the integrated Kinesis software to quantify spatiotemporal variables across five core categories:

- **Spatial Parameters:** Gait velocity (m/s) and linear stride length (cm).
- **Temporal Parameters:** Stride time (s; heel-strike to successive ipsilateral heel-strike), step time, swing time, and double-support duration.
- **Cadence:** Total steps per minute (steps/min).
- **Symmetry and Ambulatory Competence:** Gait asymmetry profiles and composite Ambulation Index scores computed via quantitative comparison of bilateral limb parameters.

Real Intervention Protocol (TVMPS)

Once the cortical target coordinate was established, the real therapeutic triad was delivered:

- **sTMS:** The north pole of a composite ring magnet assembly (A1 Magnetics Ltd., UK; outer field strength up to 3,500 Gauss) was held in place over the identified cranial coordinate.
- **Somatotopic Mapping:** To reinforce localized afferent input through somatosensory map activation, the participant was asked to maintain direct tactile contact with the magnetic assembly using one hand. In cases where the paretic limb was involved, a member of the research staff assisted.
- **PAS:** One of ten pre-established PAS areas was identified through superficial skin stimulation (stroking). Manual manipulation of the area was then applied until localized tissue tension and pressure sensitivity resolved, typically within 1 to 2 minutes. Target resolution was confirmed by repeating the fMMT and TVS tests for joint fixation normalization.

Sham Intervention Protocol

For the sham control cohort, a mock diagnostic sequence was implemented to ensure participant blinding. The procedure mimicked the physical setup, sensory feedback, and clinician interaction of the real group using simulated manual muscle testing paired with brief, non-targeted vibration (1 to 2 minutes). Crucially, no functional target pairing was established, and no sTMS or PAS interventions were applied.

Feasibility and Outcomes

The study evaluated motor performance changes and the operational feasibility of TVMPS in participants with subacute stroke.

Feasibility

Feasibility metrics were based on patient compliance and the clinical practicality of delivering the diagnostic and therapeutic protocols across the 5-day assessment schedule.

Functional Movement and Gait Outcomes

Longitudinal changes were tracked across six specific parameters grouped into three clinical categories:

1. **Functional Movement Performance**
    - *Functional Mobility:* Timed Up and Go (TUG) completion time (s).
    - *Transitional Power:* Five Times Sit-to-Stand (5XSST) completion time (s).
2. **Gait Speed & Tempo**
    - *Gait Speed:* Average walking velocity (m/s).
    - *Gait Cadence:* Step rate (steps/min).
3. **Gait Kinematics & Timing**
    - *Spatial Kinematics:* Stride length (m).
    - *Temporal Phase Durations:* Step and stride times (s).

Sample Size Rationale and Statistical Analysis

As this study evaluated concept viability rather than definitive clinical efficacy, formal sample size calculations were omitted. The estimated sample size of 17 randomized

participants was determined by patient referral rates and the operational capacity of the rehabilitation center during the 7-month study window.

Feasibility outcomes are analyzed using descriptive statistics. Recruitment and retention proportions are reported as absolute numbers and percentages. Completion rates and missing data are tracked as counts and percentages. Longitudinal clinical evaluations focus on descriptive trajectory mapping and relative change estimation rather than formal inferential hypothesis testing, avoiding misleading statistical inferences from an exploratory cohort[20, 27].

The primary aim of this exploratory phase was to evaluate functional movement and gait outcome parameters, alongside retention and adherence rates, to determine whether a full trial is deemed a possibility. Because the cohort size aligned well with standard feasibility study guidelines, it provided sufficient operational data to identify workflow bottlenecks and uncover relevant logistical challenges. Furthermore, while unpowered for definitive clinical efficacy, this sample size provides sufficient information to observe preliminary outcome trajectories. Because operational metrics only require a general estimate to confirm viability rather than precise population parameters, this predictable margin of error is entirely appropriate for evaluating whether to advance to a larger trial[28].

To better evaluate the TVMPS potential in this feasibility phase, pre-determined progression benchmarks were used to track safety and compliance, including a study retention rate of 80% or higher, protocol adherence of 90% or greater, and zero protocol-related serious adverse events. Combined with observed outcome trajectories, these metrics help establish an operational basis of adequate strength leading to an informed decision of whether to proceed to a definitive trial.

Results

Participant Flow and Recruitment

From December 2019 to July 2020, 17 subacute stroke survivors were randomized at the Evexia Rehabilitation Centre. Two participants allocated to the sham control arm withdrew prior to trial completion due to acute, unrelated medical conditions. Fifteen participants completed the full 5-day trial protocol and were included in the final analysis (Real TVMPS group, $n = 9$; Sham control group, $n = 6$).

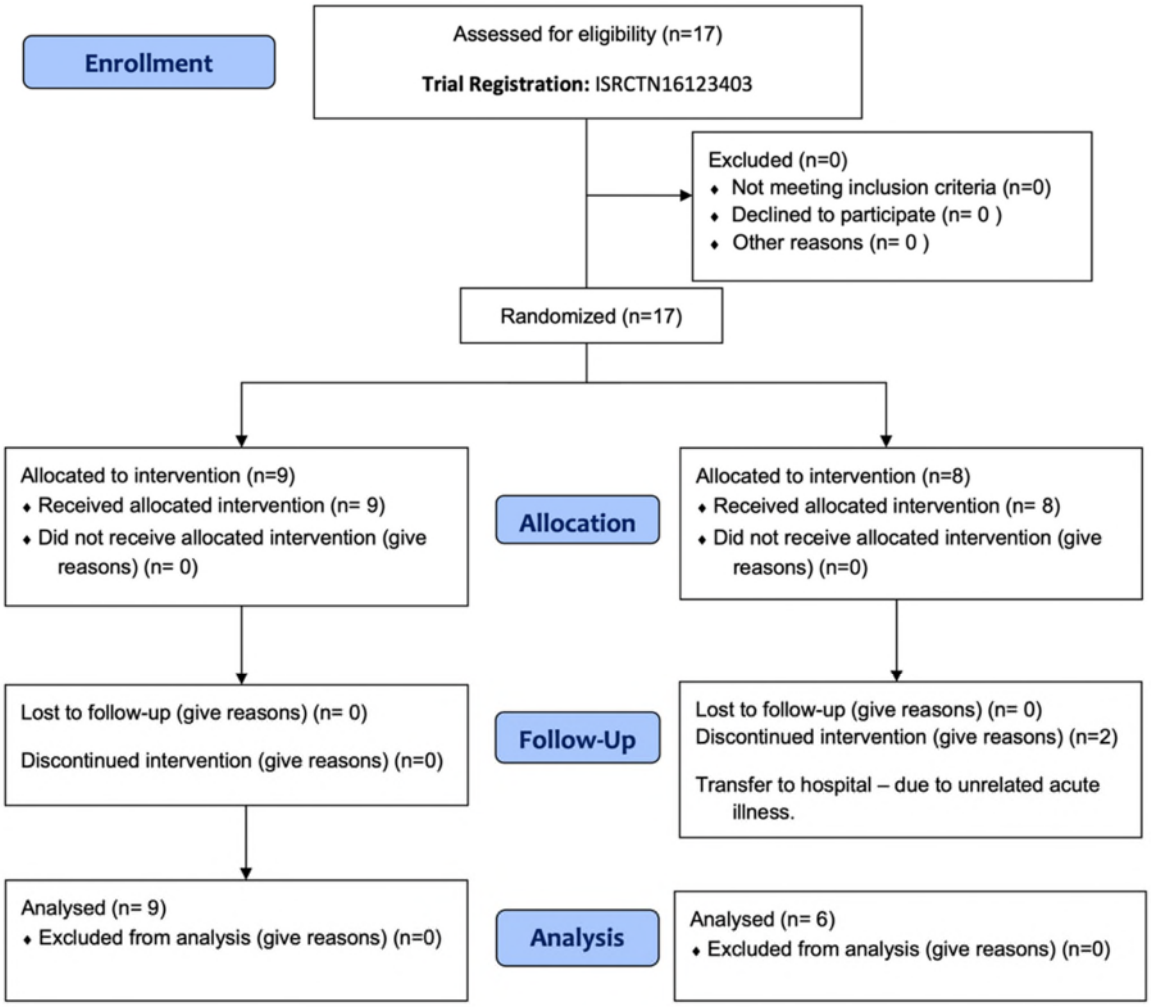


Table 2: CONSORT Participant Flow Diagram. Screening, randomization, allocation, and final analysis tracking for the real TVMPS and sham control cohorts.

Baseline Demographics and Clinical Characteristics

Participant age, time post-stroke, stroke etiology (unilateral ischemic cerebral hemispheric stroke), and functional mobility status were recorded at enrollment. All participants received identical state-funded physical rehabilitation programs for the duration of the trial.

Baseline demographics

Qualitative variables are expressed as frequencies and percentages (%) and quantitative

variables are expressed as mean values ± standard deviation (SD).

	Sham-treatment (n=6)	Real-treatment (n=9)
Gender	4M/2F	7M/2F
Age (years)	66.5±11.6	70.6±11.7
Body Mass Index (BMI)	25.4±1.2	24.4±1.2
Time from stroke onset (days)	94.0±38.2	84.6±35.4
Affected hemisphere		
Left	3 (50.0)	4 (44.4)
Right	3 (50.0)	5 (55.6)

Table 3: Baseline demographics

Protocol Feasibility, Adherence and Tolerance

- **Tolerability:** No adverse events or procedure-related complications were reported during any real or sham intervention sessions.
- **Procedural Feasibility:** The fMMT diagnostic workflow was completed for all real intervention sessions. The unblinded clinician localized an operational cranial treatment coordinate for every participant in the real group without inducing localized muscle fatigue or testing failure.
- **Adherence and Retention:** Adherence was 100%, with all 15 participants attending every scheduled session and completing all five daily assessments.

Functional Mobility and Kinematic Outcomes

Group outcomes were evaluated by blinded examiners, tracking daily changes and longitudinal trends over the 5-day trial period across seven parameters: (1) TUG and 5XSST for functional movement assessment, and (2) five gait kinematic parameters comprising average stride time, step time, stride length, stride velocity, and cadence [Additional File 1].

Expectancy Removal (Day 4 vs Day 5)

Following the execution of the structured expectancy removal protocol after the final treatment on Day 4, subsequent performance changes through Day 5 were evaluated to isolate

residual treatment effects from participant expectation against baseline values (Day 1) [Figure 5].

Real TVMPS Cohort

The real intervention group demonstrated progressive, multi-parameter performance gains, achieving a net mean functional improvement of 18.9% on Day 4 and advancing to 32.1% on Day 5 relative to baseline. By Day 5, following the execution of the expectancy removal protocol, mean stride velocity increased by 55.0% and mean stride length expanded by 22.4% above baseline values. Additionally, average step and stride time symmetry improved by 21.6%, accompanied by a 28.5% increase in cadence.

Sham Cohort

On Day 4, the sham group exhibited transient gains in four of the five measured parameters. However, these gains were offset by a 4.1% decline in mean stride length, yielding a net mean change of +8.2% relative to baseline. Following expectancy removal, net mean performance scores on Day 5 declined to +5.9% above baseline. Notably, mean stride velocity returned completely to baseline levels (0.0%), and mean stride length remained suppressed at -3.4% below baseline. In contrast, cadence retained a 15.7% increase, while step/stride time improvements diminished to 3.0%.

Real vs Sham Comparison

Following expectancy removal on Day 4, the sham cohort experienced an average performance decline of 2.3% from Day 4 to Day 5. Conversely, the real TVMPS cohort maintained an upward trajectory, demonstrating an additional 13.2% increase in average performance at the final Day 5 assessment.

Discussion

The primary objective of this study was to evaluate the feasibility and concept viability of the multi-modal TVMPS protocol, establishing whether sufficient rationale exists to support a future, fully powered randomized trial. All participants successfully completed the protocol without adverse events, undue procedure-related discomfort, or testing-induced fatigue. Initial findings indicate that the two-stage clinical workflow, combining diagnostic target localization with multi-modal neuromodulation, shows feasibility and is well tolerated in a clinical setting. While this feasibility study was not powered to establish definitive clinical efficacy, the divergent performance trajectories observed between the real intervention and

sham cohorts, particularly following structured expectancy removal on Day 4, suggest a viable mechanistic rationale for controlled investigation in the future.

Mechanistic Divergence and the Impact of Expectancy Removal

When compared to the real cohort, performance trajectory shifts within the sham group point toward an anticipatory, behavior-driven mechanism rather than true neuromotor adaptation. During the real anticipation phase (Days 1-4), sham participants demonstrated transient gains, including a 9.2% increase in mean stride velocity. However, following structured notification of therapy completion on Day 4, these initial gains rapidly collapsed by Day 5. Most notably, mean stride velocity descended back to baseline levels (0.0%), while mean stride length remained below baseline (−3.4%).

Functional mobility scores in the sham group plateaued following expectancy removal, shifting marginally from 14.9% at Day 4 to 14.2% at Day 5. Interestingly, the sham group maintained a 15.7% increase in cadence on Day 5 despite the loss of spatial stride length. This divergence illustrates how spatial and temporal gait parameters can decouple under psychological or cognitive influence[29, 30]. In this context, sustained stepping frequency likely reflects habitual effort or rapid, compensatory stepping with the non-paretic extremity rather than true functional recovery[31, 32]. Thus, elevated cadence in isolation does not signal genuine neural restoration; rather, meaningful neuroplastic reorganization is characterized by concurrent enhancements across cadence, step-length extension, and forward propulsion.

In contrast, the real cohort proved resilient to expectancy removal, continuing to demonstrate progressive functional and kinematic gains through Day 5. Between Days 4 and 5, mean stride velocity in the real group advanced from a 34.0% increase to a 55.0% increase relative to baseline. While a velocity change of this magnitude within an exploratory cohort warrants cautious interpretation, several physiological factors suggest this finding represents genuine neuromotor adaptation rather than a statistical artifact or placebo response.

Crucially, random variance or compensatory strategies typically manifest as asymmetrical spikes in isolated metrics—such as elevated cadence paired with abbreviated stride length. Conversely, velocity progression in the real cohort was driven by balanced, simultaneous expansion across independent biomechanical domains: increased cadence (28.5%), expanded stride length (22.4%), and improved step-time symmetry (21.6%). The internal consistency and spatial-temporal harmony across these distinct kinematic variables provide preliminary

evidence that real TVMPS drives a coherent, systemic enhancement in gait dynamics[33, 34].

This physiological divergence is further reflected in overall functional mobility. While scores stalled in the sham cohort, the real group achieved an additional 13 percentage point gain between Days 4 and 5, progressing from 19.9% to 33.1% above baseline. Taken together, these data suggest that the multi-modal TVMPS protocol induces systemic improvements in multi-joint walking coordination that persist independently of psychological anticipation.

Velocity and Stride Length: Central Integration Indicators

In post-stroke rehabilitation literature, gait velocity and stride length are widely recognized as primary indicators of functional neuromotor recovery[35, 36]. Unlike isolated changes in cadence, concurrent increases in velocity and stride length require real paretic propulsion, adequate ankle push-off, and hip flexion pull-off[37]. This multi-joint coordination relies heavily on single-limb stance stability and precise forward movement control of the paretic limb[38]. Consequently, the coupling of stride velocity with spatial stride length serves as a sensitive indicator of the central integrative state[39, 40]. Accelerated walking speeds coupled with increased stride length impose stricter temporal constraints on sensorimotor coordination, thereby reducing the available window for predictive error correction and dynamic postural recovery[41–43].

The 55.0% stride velocity improvement observed in the real cohort points toward a consolidation of motor output across the treatment period. Rather than isolated mechanical adjustments, the concurrent gains in multi-joint coordination and dynamic gait control following the TVMPS protocol support the premise that central processing and sensorimotor network integration were enhanced.

Literature Alignment

These exploratory observations align with established literature on multi-modal non-invasive neuromodulation[44]. Interventions that combine central stimulation with concurrent peripheral somatotopic map activation are thought to enhance network-level sensorimotor integration[45]. While single-modality non-invasive stimulation often yields variable outcomes in stroke cohorts[46], emerging evidence suggests that multi-channel stimulation frameworks promote greater network stabilization and neuroplastic engagement[47, 48]. Through the concurrent pairing of sTMS, PAS, and targeted somatotopic map activation, the TVMPS protocol embodies this multi-modal strategy. Although evaluated over a brief

five-day intervention window, the kinematic and functional mobility gains point toward facilitated central sensorimotor processing, providing a strong rationale to evaluate the TVMPS protocol in a fully powered randomized trial.

Limitations

- **Sample Size and Duration:** The small sample size (N = 15) and short 5-day trial period evaluate immediate feasibility but preclude broad generalizations, subgroup analyses, or definitive conclusions regarding long-term therapeutic efficacy and functional carryover.
- **Examiner-Dependence:** The TVMPS, fMMT workflow is an operator-dependent clinical skill rather than an automated, objective neurophysiological marker. It serves as a pragmatic targeting tool rather than an independent verification of cortical changes.
- **Concomitant therapies:** To maintain ethical standards, participants continued uniform, pre-existing stroke rehabilitation programs. The observed gains therefore represent the additive therapeutic effect of the sham vs real treatment methodology layered over standard care, rather than a completely isolated monotherapy.
- **Absence of Post-Trial Follow-Up:** The evaluation concluded immediately on Day 5 following the expectancy removal protocol, leaving the medium- to long-term persistence of the observed functional and kinematic gains unquantified.

Implications for a Randomized Trial

Accepting the fact that these results are preliminary, the trends observed in functional mobility and gait parameters offer initial support for exploring this protocol in a larger randomized trial.

- **Protocol Feasibility:** Complete protocol execution without adverse events or dropouts demonstrates that this intervention schedule represents a safe, practical framework within real stroke rehabilitation workflows.
- **Blinding Integrity:** Methodological segregation of participant cohorts and isolation of treating clinicians from outcome assessors prevented bias and cross-contamination, establishing a reproducible structural blinding model for future trials.
- **Targeted Outcomes:** The real cohort demonstrated consistent improvements across functional mobility measures (TUG and 5XSST) and gait kinematic parameters, maintaining a positive trajectory even following structured expectancy removal.

The most prominent trend observed at the final assessment was a marked increase in mean stride length and stride velocity over baseline within the real cohort. When examining the gait-specific profile independently from the transitional mobility captured by the TUG and 5XSST, expansions in these spatial parameters typically depend on enhanced cortical integration rather than isolated changes in temporal or rhythmic stepping rates alone.

Together, these initial observations across both steady-state gait and transitional mobility support the core aims of feasibility and concept viability in this preliminary investigation. While definitive conclusions regarding therapeutic efficacy cannot be drawn from an exploratory sample, these initial trends suggest that the multi-modal TVMPS protocol is structurally viable, safe, and merits further systematic evaluation in a larger, fully powered randomized controlled trial.

Conclusions

Conducted within a 5-day assessment schedule, this early-stage concept viability and feasibility study supports the operational practicality and clinical feasibility of the multi-modal TVMPS protocol in subacute stroke. Concept viability is supported by positive, measurable kinematic shifts in the real TVMPS group, particularly in gait velocity and stride length.

Post-treatment retention and expansion of physical gains in the TVMPS cohort, especially noted following structured expectancy removal, support the plausibility of enhanced central sensorimotor integration. While the brief intervention window and restricted cohort size preclude definitive claims of long-term therapeutic efficacy, these observations do tend to highlight the structural viability of the protocol, suggesting an empririal rationale for a fully powered randomized controlled trial.

Declarations

Ethics approval and consent to participate

All procedures performed in this study involving human participants were in strict accordance with the ethical standards of the institutional and national research committees, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was formally reviewed and approved by the Evexia Rehabilitation Centre Institutional Ethics Committee prior to trial initiation (Approval No.

01.12.2019-001). The full trial protocol is available from the corresponding author, Emmanouil Kandylakis, upon reasonable request.

Consent for publication

Written informed consent for the publication of accompanying clinical images was obtained from the specific participant featured in this study. For all other participants, no identifiable individual data or images are presented, and consent for publication is not applicable. Copies of the signed consent forms are retained by the institution and are available for review by the Editor-in-Chief upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JS:Methodology, Original draft preparation, Reviewing and Editing. EK: Investigation, Methodology, Project Administration, Reviewing and Editing. AY: Resources, Project Administration, Supervision. EB: Reviewing and Editing. GT: Data curation, Formal analysis. All authors read and approved the final manuscript.

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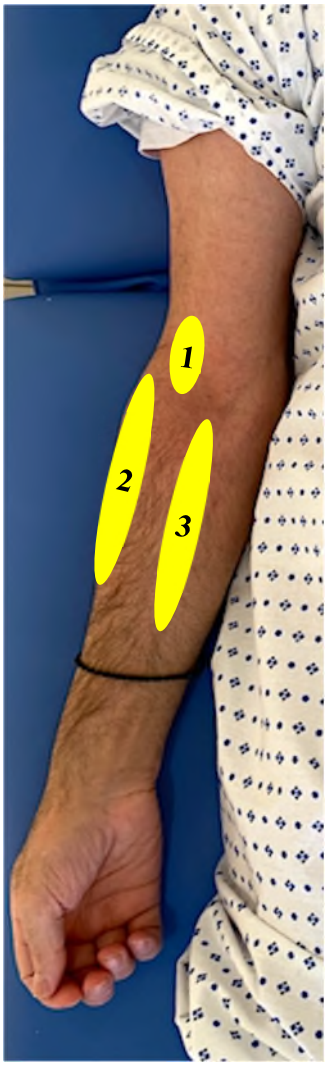
Figure 1: Transcranial Vibration Stimulus (TVS) with Functional Manual Muscle Testing (fMMT).
Vibrational stimulus applied to the skull along with a neuromotor coordination assessment.

Note: Written informed consent for open-access publication of these photographs was obtained from the subject prior to study inclusion.

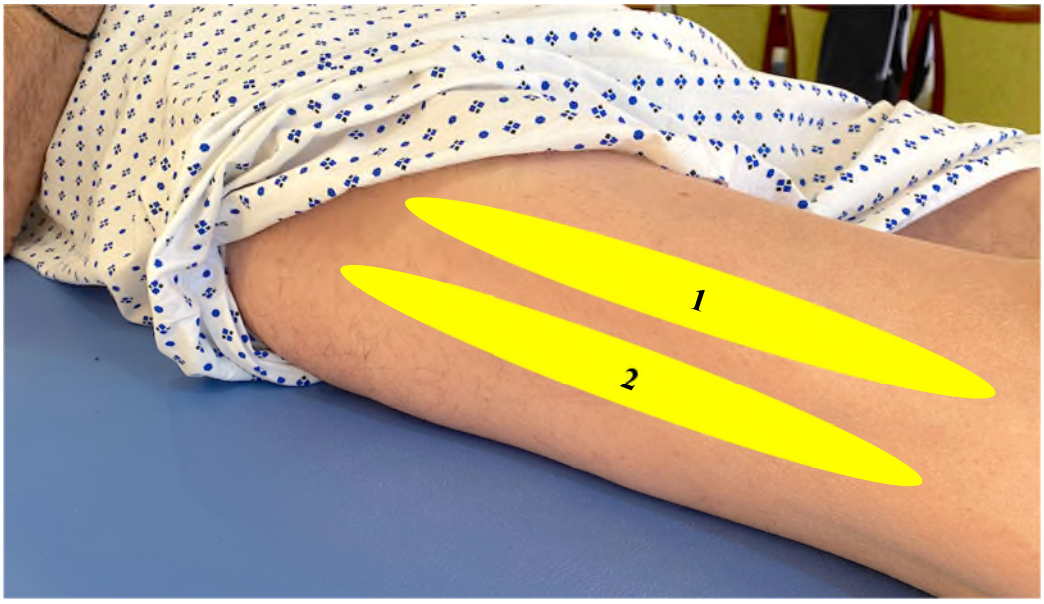


Figure 2: Intervention Triad. *Conceptual schematic of the multi-modal TVMPS intervention triad, demonstrating the concurrent integration of static transcranial magnetic stimulation (tSMS), somatosensory localization, and manual paired associative stimulation (PAS).*

Note: Written informed consent for open-access publication of these photographs was obtained from the subject prior to study inclusion.



Panel A



Panel B

Figure 3 (Panels A and B): Paired Associative Stimulus (PAS) Areas. *Clinical surface reference photography utilized for localized peripheral mechanosensory input, highlighting PAS target areas.* ***Panel A*** *– (supinated upper limb areas: 1, 2 and 3)* ***Panel B*** *– (anterolateral lower limb areas: 1 & 2)*

Note: Written informed consent for open-access publication of these photographs was obtained from the subject prior to study inclusion.



Figure 4: Experimental setup for quantitative gait analysis and neuromotor evaluation during the active trial phase. *Clinical trial execution displaying the bilateral Shimmer Kinesis GAIT™ wireless inertial sensor placement relative to the tibial tubercle and the proximal aspect of the tibialis anterior muscle.*
Note: Written informed consent for open-access publication of this photograph was obtained from the subject prior to study inclusion.

Figures 5a to 5e

Performance scores for sham ($n = 6$) and real TVMPS ($n = 9$) cohorts.
Assessments: Day 4 expectancy maintained and Day 5 expectancy removed.

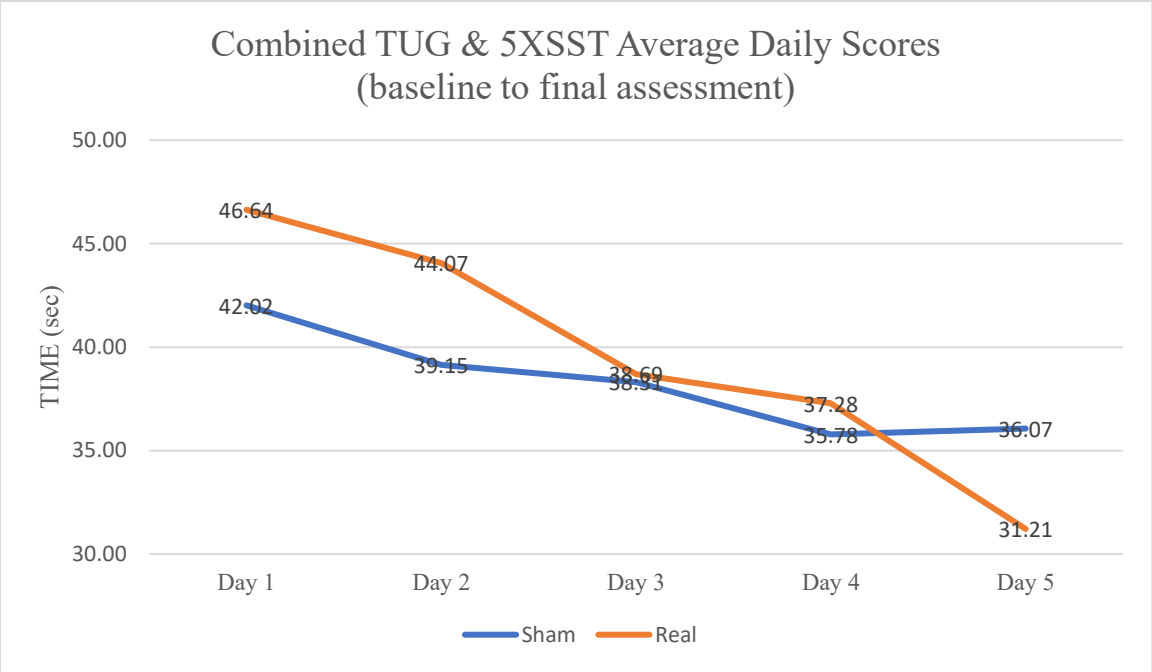


Figure 5a: Percentage change from baseline in combined Timed Up and Go (TUG) and 5-Times Sit-to-Stand Test (5XSST) performance scores on Day 4 (Sham: +14.9%, Real: 19.9%) and Day 5 (Sham final assessment: +14.2%, Real TVMPS final assessment: +33.1%).

Figures 5a to 5e

Performance scores for sham ($n = 6$) and real TVMPS ($n = 9$) cohorts.
Assessments: Day 4 expectancy maintained and Day 5 expectancy removed.

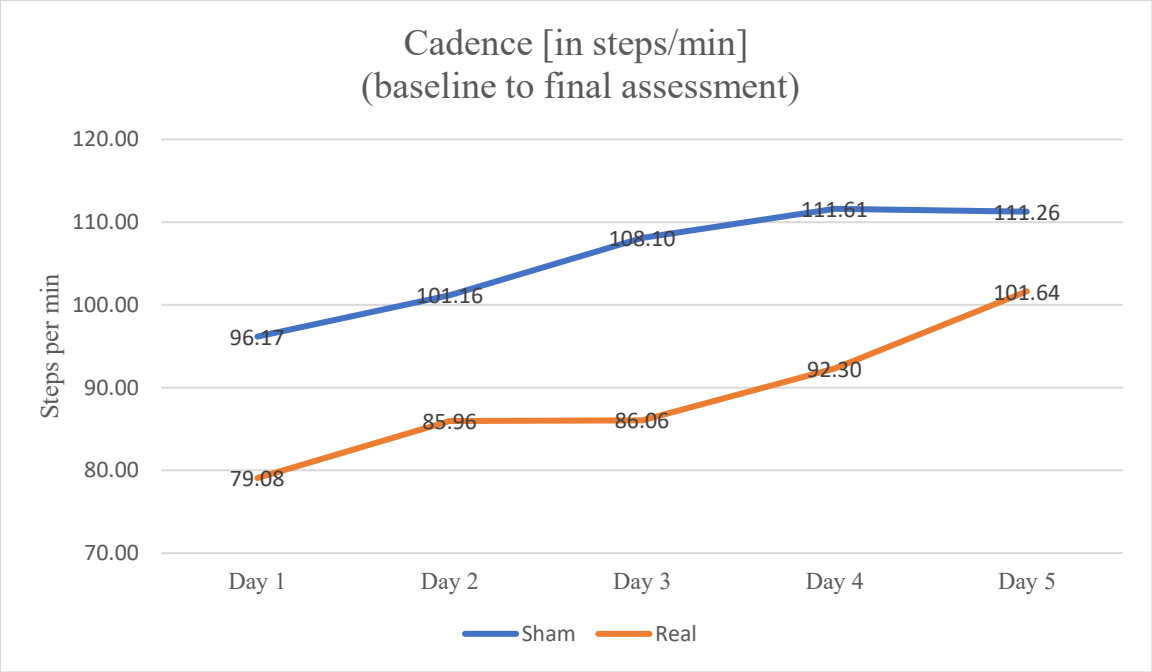


Figure 5b: Percentage change from baseline in Cadence on Day 4 (Sham: +16.1%, Real TVMPS: +16.7%) and Day 5 (Sham – final assessment: +15.7%, Real TVMPS – final assessment: +28.5%).

Figures 5a to 5e

Performance scores for sham ($n = 6$) and real TVMPS ($n = 9$) cohorts.
Assessments: Day 4 expectancy maintained and Day 5 expectancy removed.

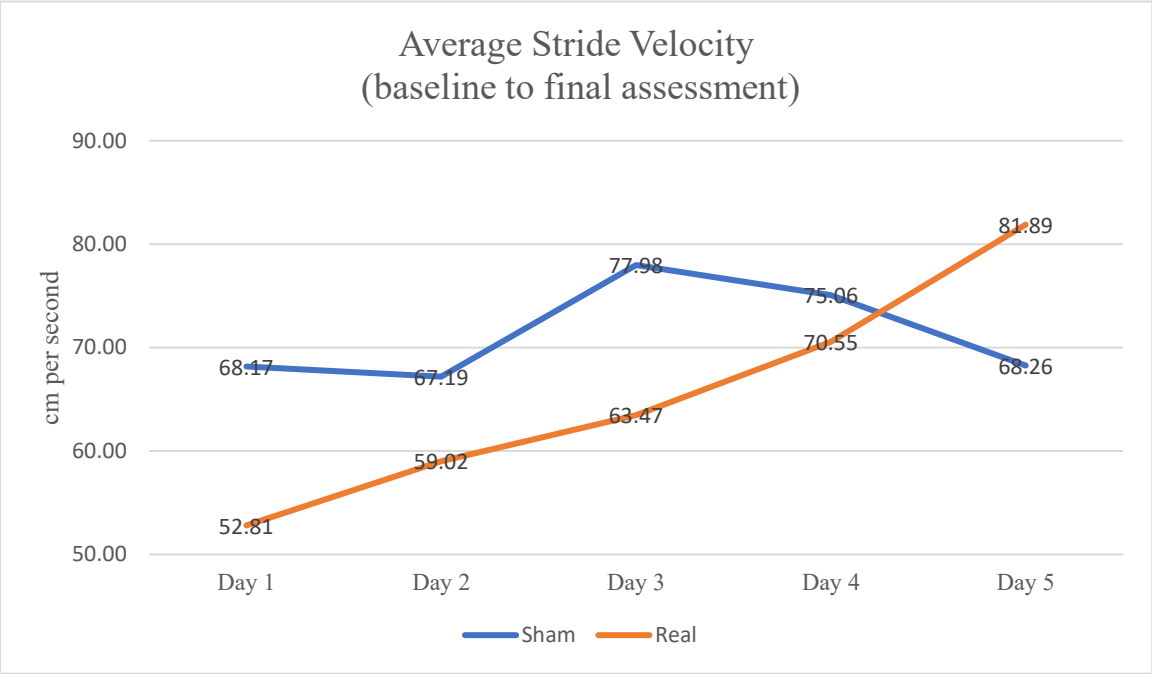


Figure 5c: Percentage change from baseline in Average Stride Velocity on Day 4 (Sham: +9.2%, Real TVMPS: +34.0%) and Day 5 (Sham – final assessment: +0.0%, Real TVMPS – final assessment: +55.0%).

Figures 5a to 5e

Performance scores for sham ($n = 6$) and real TVMPS ($n = 9$) cohorts.
Assessments: Day 4 expectancy maintained and Day 5 expectancy removed.

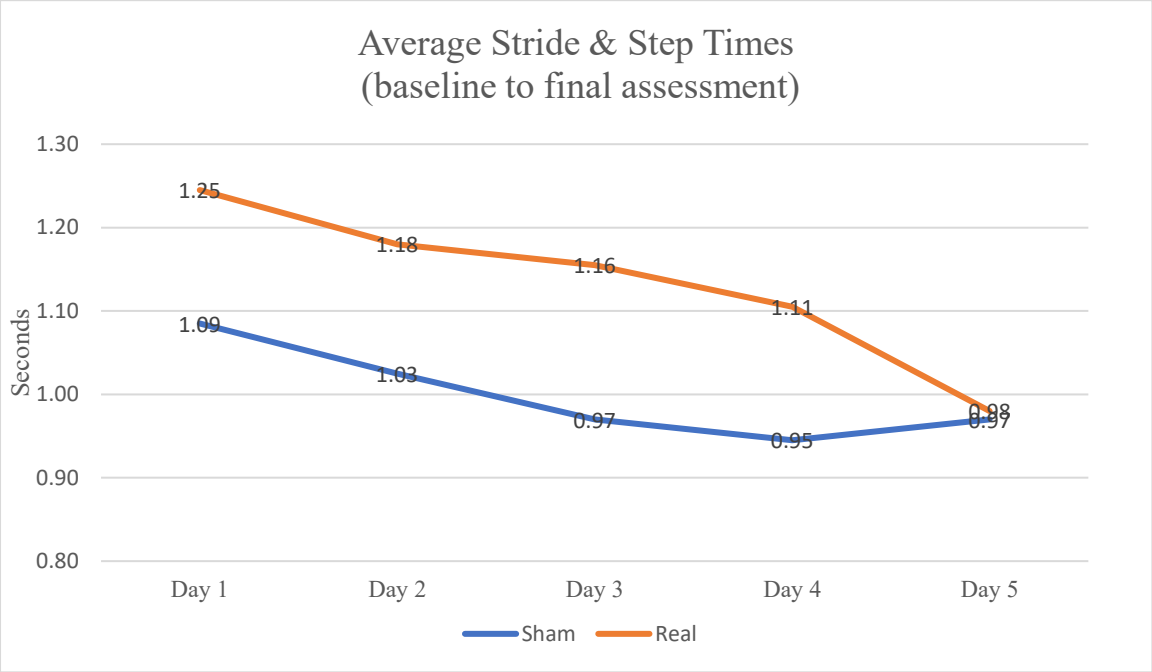


Figure 5d: Percentage change from baseline in Average Stride and Step Times on Day 4 (Sham: +5.0%, Real TVMPS: 11.2%) and Day 5 (Sham – final assessment: +3.0%, Real TVMPS – final assessment: +21.6%).

Figures 5a to 5e

Performance scores for sham ($n = 6$) and real TVMPS ($n = 9$) cohorts.
Assessments: Day 4 expectancy maintained and Day 5 expectancy removed.

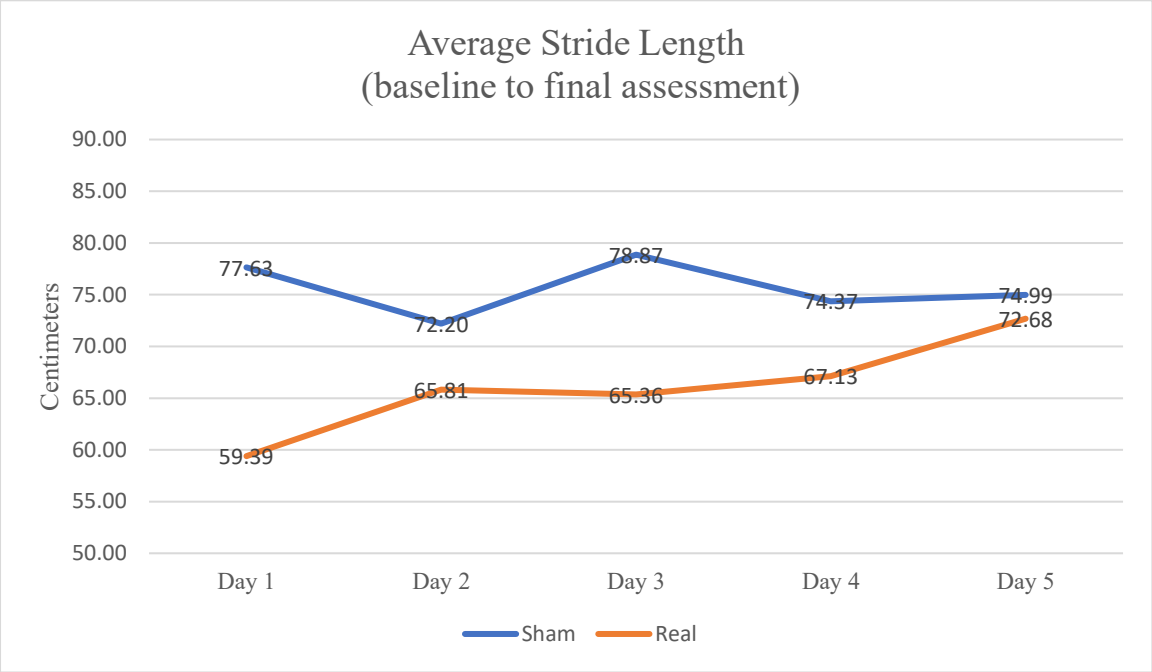


Figure5e: Percentage change from baseline in Average Stride Length on Day 4 (Sham: -4.1%, Real TVMPS: 13.0%) and Day 5 (Sham – final assessment: -3.4%, Real TVMPS – final assessment: +22.4%).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTextensionPilotandFeasibilityTrialsChecklist.doc