Study Protocol Document

Title: Targeted Ankle Proprioceptive Training to Improve Balance, Gait, and Functional Mobility in Chronic Stroke Survivors: A Multicenter Randomized Controlled Trial with Longitudinal Follow-Up

Protocol Version: 1.0 (Pre-trial, submitted for ethics approval) **Date:** December 2022 **Principal Investigator:** Muslim Khan, Associate Professor, Faculty of Rehabilitation Sciences, IQRA National University, Swat, Pakistan **Email:** drmuslim17@gmail.com / dr.muslim@inuswat.edu.pk **ORCID:** 0000-0002-9916-9337

Collaborating Centers:

- Psychiatric Care & Rehabilitation Center (SPCRC), Swat, Pakistan
- Al-Makki Rehabilitation Center, Swat, Pakistan
- Hashoo Foundation Rehabilitation Center & Model Addiction Treatment & Rehabilitation Centre (MATRC), Swat, Pakistan
- Saidu Group of Teaching Hospital & IQRA National University, Swat, Pakistan
- Additional sites: Taibah University, Prince Sattam bin Abdulaziz University, Armed Forces Hospital Southern Region, Medina Health Cluster, Albaha University, Cairo University, King Salman Hospital (Riyadh)

Trial Registration: OSF [https://osf.io/ps26x/overview]

Study Design: Multicenter, parallel-group, randomized controlled trial (RCT) with 1:1 allocation, assessor-blinded, intention-to-treat analysis. Includes a longitudinal observational subsample for acute-to-chronic proprioceptive changes.

Background and Rationale: Stroke is a leading cause of long-term disability, with balance and gait deficits affecting >80% of survivors and increasing fall risk. Emerging evidence links ankle proprioceptive impairment—particularly inversion/eversion acuity—to these deficits, often bilateral and central in origin. Cross-sectional studies show strong associations, but causality, temporal progression, and intervention efficacy (especially in severe/non-ambulatory cases) remain unproven. This trial tests a targeted proprioceptive protocol against standard care.

Objectives: Primary: To evaluate the causal effect of 12-week targeted ankle proprioceptive training on weight-bearing ankle proprioception (AMEDA) in chronic stroke survivors. **Secondary:** To assess effects on balance (Berg Balance Scale), gait speed (10m walk test), mobility (Timed Up and Go, Functional Ambulation Category), lower extremity motor function (Fugl-Meyer), and sustainability at 6-month follow-up. To describe longitudinal proprioceptive changes in a subsample from acute to chronic stages. **Hypothesis:** Intervention group will show

significantly greater improvements in proprioception and functional outcomes, mediated by inversion proprioception gains.

Participants: Inclusion Criteria:

- Adults ≥18 years
- Chronic ischemic/hemorrhagic stroke (≥12 months post-stroke)
- Moderate-to-severe lower extremity impairment (Fugl-Meyer LE ≤28 or NIHSS motor leg ≥2)
- Documented ankle proprioceptive deficit (AMEDA AUC <0.7)
- Ability to follow instructions and provide informed consent

Exclusion Criteria:

- Acute medical issues (e.g., uncontrolled hypertension)
- Other neurological disorders
- Severe cognitive impairment (MMSE <24)
- Exercise contraindications
- Concurrent conflicting trials

Sample Size: 140 participants (70 per group), calculated using G*Power for detecting a 5-point difference on Berg Balance Scale (SD=8, power=80%, α=0.05, two-tailed), accounting for 20% attrition. Oversized by ~40% for subgroup analyses (severity, ambulatory status). Longitudinal subsample: n=42 (convenience from acute data availability).

Randomization and Blinding:

- Computer-generated block randomization (blocks 4–6), stratified by severity and ambulatory status.
- Allocation concealment: Sequentially numbered opaque sealed envelopes.
- Blinding: Outcome assessors and data analysts blinded; participants partially (sham elements in control); treating therapists not blinded.

Interventions: Both groups: 12 weeks, 3 sessions/week × 60 min, supervised. **Intervention Group (n=70):** Progressive targeted ankle proprioceptive training:

- Phase 1 (Weeks 1–4): Robotic-assisted sensory discrimination (inversion/eversion, plantar/dorsiflexion; reduce angles, remove visual feedback).
- Phase 2 (Weeks 5–8): Functional weight-bearing challenges (e.g., balance boards, textured surfaces, dynamic tasks).
- Phase 3 (Weeks 9–12): Advanced integration (e.g., gait with proprioceptive cues, dual-task). **Control Group (n=70):** Standard rehabilitation (lower-limb strengthening,

- stretching, over-ground gait training per guidelines; no specialized proprioceptive/robotic components). Fidelity: Therapist training, session logs, random audits.

Outcome Measures: Primary: Active Movement Extent Discrimination Apparatus (AMEDA) – weight-bearing ankle proprioception (focus on inversion). **Secondary:** Berg Balance Scale, Timed Up and Go, 10-meter walk test (speed), Fugl-Meyer Lower Extremity, Functional Ambulation Category. Assessments: Baseline, post-12 weeks, 6-month follow-up. Longitudinal subsample assessed from acute (<1 month) to chronic.

Statistical Analysis Plan:

- Intention-to-treat with last-observation-carried-forward for missing data.
- Primary: Mixed-model ANOVA for group × time effects.
- Secondary: Effect sizes (Cohen's d), mediation analysis (inversion proprioception as mediator of functional gains).
- Subgroup analyses: Severity levels.
- Significance: $p<0.05$, two-tailed.

Data Management and Monitoring:

- Secure electronic database, double-entry verification.
- No formal DSMB (low-risk intervention); adverse events monitored and reported to IRBs.
- Confidentiality per Helsinki Declaration.

Ethical Considerations:

- Informed written consent from participants (or representatives).
- Right to withdraw at any time.
- Risks: Minimal (standard rehabilitation exercises; monitored for fatigue/pain).
- Benefits: Potential functional improvement.
- Approved by institutional review boards at all centers: Ref#: SGTH/RR-22-234 & Ref#: INU/REHAB/XC94 .
- Conducted per Declaration of Helsinki and ICMJE recommendations.

Timeline:

- Recruitment: January 2023 – June 2024 (planned; actual extended to December 2024 per manuscript note).
- Intervention/Follow-up: Up to 6 months post-enrollment.
- Analysis: 2025.

Funding: No external funding. **Conflicts of Interest:** None declared. **Protocol Amendments:** Any changes will be documented and reported to ethics committees.