STUDY PROTOCOL

Official Title: Intervention Effectiveness Towards Improving Physical and Mental Health for Post-stroke Patients.

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Background and Rationale

Stroke is a leading cause of long-term disability and the second leading cause of death worldwide [1]. Many stroke survivors suffer from post-stroke depression (PSD), fatigue, cognitive impairments, and reduced functional abilities, which significantly hinder rehabilitation outcomes and quality of life [2-5]. Early detection and intervention for these physical and mental health issues are crucial for optimal recovery. However, most studies to date have addressed either physical rehabilitation or psychological therapy alone, rather than an integrated approach targeting both aspects [6, 7]. In Vietnam, there has been a lack of comprehensive intervention studies for post-stroke patients, and access to specialized inpatient rehabilitation is limited. This gap has led to increased demand for home-based rehabilitation and innovative strategies to support stroke survivors' mental health in the community.

Motivational Interviewing (MI) is a client-centered counseling technique effective in enhancing motivation and treating depression and fatigue in various conditions [8, 9]. Home-based rehabilitation programs, especially with family involvement and guided exercises, have been shown to improve functional independence and accelerate recovery in stroke patients [10]. We hypothesize that combining MI therapy with a structured home-based exercise program (a multifaceted intervention) will yield synergistic benefits, improving both mental health (e.g., reducing depression and fatigue) and physical function beyond what standard care achieves.

In addition, traditional neuroimaging methods to monitor mental health recovery (e.g. fMRI, PET, EEG) are often impractical in routine care due to cost and limited portability [11-13]. Functional Near-Infrared Spectroscopy (fNIRS) offers a noninvasive, portable, and low-cost brain monitoring tool that can track changes in cerebral blood oxygenation with high temporal resolution [14]. fNIRS has been used successfully to evaluate depression and other mental health conditions by detecting hemodynamic changes in the prefrontal cortex [15, 16]. Applying fNIRS in post-stroke patients could provide an objective biomarker of improvement in depression and cognitive function in response to our intervention [15]. This study is pioneering in Vietnam as it combines physical rehabilitation, MI, and fNIRS-based monitoring to address post-stroke health comprehensively. The knowledge gained may guide future stroke care programs and health policy in resource-limited settings.

Trial Objectives and Hypotheses

Primary Objective: To evaluate the effectiveness of a 6-month multifaceted intervention (Motivational Interviewing plus a home-based rehabilitation program) in improving the mental health (reducing depressive symptoms, fatigue, and cognitive impairment) and physical

functional status of post-stroke patients, compared to standard care alone. The primary endpoints include changes in depression severity, fatigue level, cognitive function, and activities of daily living from baseline to 6 months.

Secondary Objectives: (1) To assess the impact of the intervention on post-stroke quality of life. (2) To explore neurobiological changes associated with depression improvement by measuring prefrontal cortex oxyhemoglobin concentration changes using fNIRS, and determine whether fNIRS biomarkers can serve as predictors of depression status in stroke survivors.

Hypotheses: We hypothesize that stroke survivors receiving the combined MI and home-based rehabilitation intervention will show significantly greater improvements in mental health outcomes (lower Patient Health Questionnaire-9 depression scores and Fatigue Severity Scale scores, improved Mini-Mental State Examination scores) and physical function (higher Barthel Index scores) over 6 months, compared to those receiving standard care. We also hypothesize that the intervention group will exhibit measurable increases in prefrontal cortical activation (oxyhemoglobin levels) on fNIRS correlating with reduction in depressive symptoms, and that specific fNIRS-derived metrics will predict depression remission status with reasonable accuracy.

Study Design

This study is a single-center, parallel-group randomized controlled trial with a 1:1 allocation ratio to intervention versus control. The trial was conducted at the Vietnam National Geriatric Hospital from 2021 to 2022. A total of 92 stroke survivor participants were enrolled and randomly assigned to either the Intervention group, which received a multi-component program (Motivational Interviewing plus a home-based rehabilitation regimen), or the Control group, which received standard care and general health advice. The study duration for each participant is approximately 6 months, with assessments at baseline and follow-up at 1, 3, and 6 months post-enrollment. Figure 1 presents the planned participant flow per CONSORT guidelines (see Schedule of Events below for timeline of activities). The trial is open-label: due to the nature of the interventions, neither participants nor intervention providers were blinded to group assignment. To reduce potential bias, outcome assessments were standardized, and the data analyst/statistician remained blinded to group labels during analysis.

Eligibility Criteria

Inclusion Criteria: Adults aged ≥45 years who have a confirmed clinical diagnosis of stroke (ischemic or hemorrhagic) according to WHO criteria [17]. Eligible patients must be 1 to 12 months post-stroke (stroke onset between 1 month and 1 year before enrollment), and be medically stable enough to participate in outpatient rehabilitation activities. Participants should have sufficient cognitive capacity and communication ability to engage in interviews and therapy sessions, and be willing to provide informed consent. They must be capable of taking part in the intervention protocols, including attending counseling sessions and performing exercises (with assistance from caregivers if needed).

Exclusion Criteria: Patients with a history of serious mental illness prior to stroke (e.g. major depressive disorder, anxiety disorder, schizophrenia, or other psychiatric illnesses diagnosed before the stroke) are excluded to avoid confounding pre-existing conditions. We also exclude those with other significant neurological disorders unrelated to stroke (e.g. Parkinson's disease, dementia) or those who experienced only transient ischemic attacks. Patients with unstable medical conditions that would interfere with participation (such as severe consciousness

disorders, uncontrolled comorbid illness, or inability to communicate) are excluded. Finally, patients who are unable to provide informed consent (for example, due to severe cognitive impairment with no available legally acceptable representative) are not enrolled.

Description of Interventions

Intervention Group: Motivational Interviewing + Home-Based Rehabilitation

Participants randomized to the intervention group receive **Motivational Interviewing (MI) therapy** in conjunction with a structured **home-based rehabilitation exercise program**, in addition to standard post-stroke care.

- ***Motivational Interviewing (MI):*** MI is delivered through one-on-one counseling sessions aimed at enhancing the patient's motivation and psychological adjustment post-stroke. The sessions are facilitated by trained nurses and social workers who completed a formal MI training program (including an MI in Healthcare course and practice sessions supervised by certified MI trainers). Ongoing supervision and fidelity checks were in place: sessions were audio-recorded (with consent) and reviewed by MI experts to ensure adherence to MI principles, such as expressing empathy, supporting patient autonomy, and eliciting "change talk". Facilitators failing to meet competence standards received additional training. Each participant in the intervention arm receives a total of **eight MI sessions** over three months. Sessions are front-loaded weekly in the first month (approximately 4 sessions in Month 1), then held biweekly during Months 2 and 3. Each session lasts ~1 hour and is conducted face-to-face in a private room at the hospital to maintain confidentiality and focus. The MI intervention content is tailored to post-stroke adjustment, covering: (1) building rapport and discussing the challenges of life after stroke; (2) helping the patient identify personal recovery goals and barriers; and (3) resolving ambivalence and reinforcing optimism and self-efficacy for achieving those goals. Participants are encouraged to summarize their goals and commitments, especially by the end of the early sessions, to reinforce their motivation moving forwar. MI facilitators do not overlap with outcome assessors and are not involved in patient recruitment, to minimize bias.

- ***Home-Based Rehabilitation Program:*** In addition to MI, intervention group patients engage in a personalized home exercise program guided by rehabilitation therapists. A physical therapist provides an initial assessment of each patient's functional abilities and limitations (covering mobility, basic activities of daily living, etc.) and, together with a multidisciplinary team (including occupational and speech therapists as needed), develops an individualized exercise plan. Therapy guidance is delivered through scheduled home visits and coaching sessions over the 6-month intervention period. Specifically, a therapist conducts home visits once a week during months 1–2, every 2 weeks during months 3–4, and once every 4 weeks during months 5–6. This tapering schedule provides more intensive support early on and encourages growing independence later. In total, participants receive approximately 12 home visit sessions (weekly for 8 weeks, biweekly for 8 weeks, monthly for 8 weeks). During each visit (~1 hour), the therapist trains the patient (and caregiver) in exercises and activities aimed at improving strength, balance, mobility, and self-care skills. Standard rehabilitation techniques are employed (passive/active range-of-motion exercises, strength training, task-oriented practice for daily activities, etc.), often using an audiovisual instructional DVD to standardize exercise routines. Example activities include gait training with a cane or wheelchair, practicing transfers and stair climbing, and fine motor tasks like using a key or preparing a drink. Caregivers are instructed on

how to assist and encourage the patient's independent function as much as possible. Patients keep a daily exercise log or diary to record their at-home practice outside of the supervised visits. The therapist's contact information is provided so patients/caregivers can consult with questions between visits. Any issues encountered at home are addressed through counseling or adaptation of the exercises (including additional education for caregivers on managing common problems). This home-based rehabilitation component is designed to complement the MI sessions by improving physical capabilities and thereby enabling patients to pursue the goals they set during MI.

- ***Periodic Health Checks:*** Throughout the study, intervention group participants also receive routine medical monitoring and standard stroke care. Doctors at the hospital's outpatient clinic see the patients at baseline, 1, 3, and 6 months for general health evaluations, management of comorbid conditions (e.g. hypertension, diabetes), and reinforcement of healthy behaviors. This ensures any new medical issues are addressed promptly and that participants receive equivalent medical attention as the control group.

Control Group: Standard Care

Participants in the control arm receive standard post-stroke care and follow-up as per usual practice, without the specialized MI or home-visit exercise program. All control group patients undergo the same schedule of periodic health check-ups at baseline, 1, 3, and 6 months with their physicians at the National Geriatric Hospital. During these visits, any medical or rehabilitation needs are managed according to routine care protocols. If a control patient is identified (during assessments or clinic visits) to have significant depression or other mental health issues, they are referred for appropriate evaluation or treatment by a psychiatrist as needed. Control participants and their families are provided with general written educational materials on post-stroke care and rehabilitation (e.g. standard pamphlets from the Ministry of Health). They are encouraged to continue any home exercises advised during their hospital discharge, but no structured, therapist-guided home exercise sessions or motivational counseling sessions are provided to the control group during the study period. Any additional treatments or services the control participants receive outside the study (e.g. if they seek physiotherapy on their own) are documented in case report forms for transparency. By comparing this group to the intervention group, we can isolate the effect of the motivational interviewing and guided home rehab program over and above usual care.

Outcome Measures

All participants are assessed at four time points: baseline (pre-intervention), 1 month, 3 months, and 6 months post-enrollment. Evaluations are conducted by a trained research nurse or clinician (who was not involved in delivering the intervention) using standardized instruments. The primary outcomes are divided into mental health outcomes and physical health outcomes, reflecting the dual focus of the intervention:

- ***Depressive Symptoms:*** Measured by the **Patient Health Questionnaire-9 (PHQ-9)**, a validated 9-item self-report scale for screening and severity of depression [18]. Each PHQ-9 item is scored from 0 ("not at all") to 3 ("nearly every day"), yielding a total score from 0 to 27, with higher scores indicating more severe depression. The PHQ-9 has been validated in Vietnamese stroke populations for detecting PSD [19]. A decrease in PHQ-9 score over time signifies improvement in depressive symptoms.

- ***Fatigue:*** Measured by the **Fatigue Severity Scale (FSS)**, a questionnaire assessing the impact of fatigue on daily functioning [20]. Participants rate 9 statements about fatigue (e.g. impact on physical functioning, motivation) on a 7-point scale (1 = strongly disagree to 7 = strongly agree). The scores are summed to give a total from 9 to 63 (occasionally a 10th item is included, in which case the range is 10–70). Higher FSS scores mean greater fatigue severity. In this study, FSS is treated as a continuous outcome; a reduction in score indicates fatigue improvement. Notably, the FSS demonstrated excellent internal consistency in our sample (Cronbach's α ~0.97–0.99 across time points) [20].

- ***Cognitive Function:*** Assessed by the **Mini-Mental State Examination (MMSE)**, an 11-item test of global cognitive status [21]. The MMSE evaluates domains such as orientation, immediate and short-term memory, attention/calculation, language, and visuoconstructional skills. Scores range from 0 to 30, with scores ≤24 commonly indicating cognitive impairment in stroke survivors [21]. The MMSE has been validated for use in Vietnam [22]. An increase in MMSE score from baseline indicates cognitive improvement.

- ***Physical Function (Activities of Daily Living):*** Measured by the **Barthel Index (BI)** for activities of daily living. The BI rates a person's independence in 10 daily tasks (feeding, bathing, grooming, dressing, bowel/bladder control, toilet use, chair transfer, ambulation, and stair climbing). Total scores range from 0 (completely dependent) to 100 (fully independent). The Barthel Index is well-established and has been culturally adapted in Vietnam [23]. Improvement in BI score reflects gains in the ability to perform daily activities without assistance.

These four measures (PHQ-9, FSS, MMSE, and Barthel Index) are considered the primary outcomes, representing mental and physical health domains targeted by the intervention. In addition, we track a secondary outcome of overall post-stroke recovery:

- ***Quality of Life:*** Evaluated using the **Stroke Impact Scale 3.0 (SIS-16)**, a stroke-specific quality-of-life questionnaire [24]. The SIS assesses 8 domains including strength, hand function, mobility, ADL/IADL, memory, communication, emotion, and social participation. Domain scores and an overall composite can be calculated on a 0–100 scale, with higher scores indicating better functioning and quality of life [24]. We will primarily use the total SIS score as an outcome of global recovery. (This measure is secondary/exploratory; not all participants may complete the full SIS due to time constraints.)

- ***Neuroimaging Biomarkers (Exploratory):*** Changes in cerebral oxyhemoglobin concentration in the prefrontal cortex, as measured by fNIRS, serve as an exploratory biomarker of depression and cognitive improvement. A portable 48-channel fNIRS device (NIRSIT, OBELAB, South Korea) is used to record cortical hemodynamic responses while participants perform a brief cognitive task (e.g. verbal fluency task) at baseline, 3 months, and 6 months (fNIRS is not administered at the 1-month visit). The fNIRS optode array is positioned over the forehead (frontopolar and lateral prefrontal regions) to capture activity in brain areas implicated in mood regulation (such as the orbitofrontal cortex). Oxyhemoglobin (HbO_2) and deoxyhemoglobin signals are calculated using the modified Beer–Lambert law and are sampled at high temporal resolution during the cognitive challenge [25]. For analysis, we will examine the mean change in HbO_2 from baseline during task performance for specific regions of interest

(e.g. left orbitofrontal cortex, ventrolateral PFC) and how these values change from pre- to post-intervention. Prior studies suggest that greater increases in prefrontal HbO_2 activation correspond to better emotional and cognitive outcomes [26]. We will explore whether our intervention group shows increased HbO_2 responses over time relative to controls, and whether certain threshold values of HbO_2 change can distinguish participants with resolved depression from those with persistent depression by 6 months. These **fNIRS measurements** are considered an exploratory outcome and will not be used as primary endpoints, but rather to supplement and biologically contextualize the clinical findings.

All outcome instruments (questionnaires and cognitive tests) are administered in the Vietnamese language by research staff. Standardized, validated Vietnamese versions are used for all scales (e.g. the PHQ-9 and MMSE have validated translations). For quality control, the same instruments are used at each follow-up, and staff members were trained to maintain consistency in administration.

Schedule of Events (Study Timeline)

The schedule of enrollment, interventions, and assessments is based on SPIRIT guidelines and is summarized below:

- ***Screening & Baseline (Month 0):*** Potential participants are screened against inclusion/exclusion criteria and provide written informed consent. At enrollment (pre-intervention baseline), we collect demographic information and stroke history (including stroke type, time since onset, lesion location, disability status by Modified Rankin Scale, etc.). Baseline assessments include the PHQ-9, FSS, MMSE, Barthel Index, and SIS administered via interview, as well as the first fNIRS measurement during a cognitive task. After baseline assessments, participants are randomized to either the intervention or control group. For those in the intervention arm, the first MI session typically occurs immediately or within a week after randomization, and the home-based rehab program is initiated with a visit scheduling within the first week.

- ***Intervention Period (Month 0 to Month 6):*** The intervention group undergoes the structured program as described: MI sessions weekly in Month 1 and biweekly in Months 2–3 (8 sessions total), and physical therapist home visits weekly in Months 1–2, biweekly in Months 3–4, and monthly in Months 5–6. All intervention activities are logged. The control group receives no intervention during this period beyond usual care, though both groups continue to attend routine medical appointments as scheduled.

- ***1-Month Follow-up (Month 1):*** Both groups return for a follow-up visit at ~1 month post-baseline. Outcome assessments at this visit include PHQ-9, FSS, MMSE, Barthel Index, and SIS. These are administered by the study assessor to track early changes. (No fNIRS measurement is performed at 1 month in this study design.) The intervention group will have completed roughly four MI sessions by this point (if on schedule) and continues with weekly rehab visits through Month 2. The control group's visit consists of their routine check-up and outcome questionnaires.

- ***3-Month Follow-up (Month 3):*** A mid-point evaluation is conducted at 3 months for all participants. Outcome measures (PHQ-9, FSS, MMSE, Barthel, SIS) are administered again, and the **second fNIRS** assessment is performed for both groups under the same protocol as baseline. By Month 3, participants in the intervention arm will have completed the course of eight MI sessions (the final MI sessions occur around

week 10–12). They will also have had biweekly rehab visits through Month 3. The 3-month follow-up allows assessment of mid-intervention improvements and provides data for any necessary intervention adjustments. Control group participants continue to receive standard care and are assessed in parallel.

- ***6-Month Follow-up (Month 6, end of study):*** At the end of the 6-month study period, all participants undergo the final evaluation. The same battery of outcome measures (PHQ-9, FSS, MMSE, Barthel Index, SIS) is administered, and the **final fNIRS** measurement is conducted. The 6-month outcomes represent the primary endpoint for evaluating intervention effectiveness. By this time, the intervention group has concluded all activities (the last home visit by the physical therapist typically occurs around month 5 or 6 with the monthly schedule). We document any post-study referrals or ongoing care plans for both groups. After completing the 6-month assessment, participants are thanked and exit the study. Those in the control group are offered an opportunity to receive the intervention program after study completion, if appropriate, as an ethical consideration.

Sample Size and Justification

The sample size was determined based on detecting a clinically meaningful difference in depression outcomes between the two groups at 6 months. Using a two-sample comparison of mean change in PHQ-9 scores (intervention vs control), we assumed a difference in mean PHQ-9 reduction of approximately 3.43 points with a standard deviation of about 5.5, based on prior research on post-stroke depression interventions [27]. With a two-sided α=0.05 and power (1–β) of 0.80, the estimated minimum sample required was 43 patients per group (calculated via the formula for comparing two means). We planned to enroll 46 patients in each group (total N=92) to account for potential drop-outs and ensure adequate power. This sample size also offers >80% power to detect medium-to-large effects on secondary continuous outcomes like FSS and Barthel Index, given similar variance assumptions. The actual achieved sample size was 92, which meets these targets. No interim analyses for efficacy were planned (due to the relatively short intervention duration and moderate sample size), so the full sample contributes to the final analysis.

Randomization, Allocation Concealment, and Blinding

Participants who met inclusion criteria and provided consent were randomized into one of the two study arms in a 1:1 ratio. Randomization was performed using a computer-generated random sequence of group codes (A = Intervention, B = Control). To ensure allocation concealment, the group assignments were placed in sequentially numbered, opaque, sealed envelopes prepared by an independent researcher not involved in participant recruitment. After a participant completed all baseline assessments, the research coordinator opened the next envelope to reveal the group assignment and then informed the intervention team accordingly.

Due to the nature of the behavioral interventions, blinding of participants and intervention providers was not feasible. Participants were informed that different rehabilitation strategies were being compared but were not explicitly told which arm was considered the experimental intervention, to minimize expectation bias. The therapists (counselors and physiotherapists) obviously knew whom they were treating, and the control group received no therapist contact, so blinding at the provider level did not apply. The primary outcome assessor (the nurse conducting follow-up surveys) was not blinded to group by necessity, since participants might mention aspects of their care; however, this assessor followed a standardized script and objective questionnaires to reduce bias. Importantly, the data analyst/statistician remained

blinded to group labels during the analysis phase – the groups were coded as non-identifiable labels (e.g., “Group X” vs “Group Y”) for statistical analysis, and the key was only revealed after primary analyses were completed. This single-blind data analysis helped prevent bias in interpretation of results. No formal blinding of outcome adjudication was required since outcomes were based on quantitative scales and not subjective clinical adjudication. We acknowledge that the open-label design could introduce performance or response bias, but our use of objective measures and blinding of the statistician aimed to mitigate these concerns.

Data Collection, Management, and Quality Control

All study data were collected in case report forms (CRFs) by the research staff at each visit. Baseline CRFs captured demographics and clinical history, while follow-up CRFs captured outcome assessments and any adverse events or additional treatments. Each participant was assigned a unique study ID; all data and samples (if any) were labeled with this ID to maintain confidentiality. The completed CRFs were double-checked by the study coordinator for completeness and accuracy after each visit. Data from CRFs were entered into a secure electronic database (password-protected) by two independent data entry personnel, with a third person performing comparisons to resolve any discrepancies (double data entry verification). The electronic dataset did not contain personal identifiers; a master link file connecting IDs to patient names was kept separately by the PI in a locked file.

Participants’ intervention adherence was monitored through session attendance logs, therapist records, and patient diaries (for home exercises). MI session attendance and quality were further monitored via the audio-recordings and supervision described earlier. Physical therapy home visit reports were reviewed weekly by the principal investigator to ensure the rehabilitation content was delivered as per protocol and to note any significant issues or deviations. Any protocol deviations or unexpected events were documented and discussed in weekly research team meetings.

Data quality control included range checks for data values (e.g., valid score ranges for questionnaires), and periodic audits of the consent forms and source data against the database entries. All original consent forms and paper records are stored in a locked cabinet in the Institute for Preventive Medicine and Public Health at Hanoi Medical University. Only the PI and authorized study team members have access to the keys and database password. We ensured compliance with Good Clinical Practice (GCP) guidelines in handling the data.

After study completion, the database will be locked and exported for analysis. The final de-identified dataset will be archived at Hanoi Medical University for a minimum of 5 years. Any blood samples or imaging data (if applicable, e.g. raw fNIRS recordings) will be stored without identifiers and used only for the purposes outlined in the study (with any future use requiring new ethical approval).

Ethics and Dissemination

This study protocol was reviewed and approved by the Institutional Review Board for Ethics in Biomedical Research at Hanoi Medical University (IRB approval number: 494/GCN-HDDDNCYHN-DHYHN, dated 05/12/2021). All participants (or their legal guardians for those with impaired capacity) provided written informed consent prior to enrollment, consistent with the principles of the Declaration of Helsinki. The consent process was conducted in Vietnamese, using an IRB-approved information sheet and consent form that explained the study aims, procedures, risks, and benefits in lay language. Participants were assured that they could withdraw from the study at any time without any effect on their ongoing medical care.

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