Research Protocol with Statistical Analysis Plan

Title: Effects of Using Advanced NEUROreabilitation TECHnologies in Upper Limb Motor Function and Capacity Recovery in People with Stroke: a pilot single-cohort study

Acronym: NEURO-TECH

Background

Stroke is the second leading cause of death and the third leading cause of disability worldwide (1). The prevalence of Upper Limb (UL) motor impairments ranges approximately between 40-50% in the chronic phase, six months after the event (2). The most common UL impairments after stroke include paresis, altered muscle tone, reduced somatosensation, and loss of coordination (3). These deficits compromise the ability to perform activities of daily living, such as opening a door, grasping a key, or using a computer. Consequently, UL motor function and capacity recovery represents one of the primary goals of neurorehabilitation.

The literature further highlights that treatment intensity, defined as a high number of repetition, and task-oriented approaches are among the main determinants of rehabilitation effectiveness after stroke (4). In this context, rehabilitation technologies allow clinicians to automate and intensify treatment paradigms, enhance access to therapy, and provide innovative tools for physiotherapists (5). These technologies can be classified into three main categories according to their specific purpose: Virtual Reality (VR), Robot-Assisted Therapy (RAT), and Telerehabilitation (TR) (5,6). VR is a computer-based technology that enables users to interact with a simulated multisensory environment, with the aim of enhancing rehabilitation impact and providing performance-related feedback (7). VR can be defined as:

- **non-immersive**, when the user interacts with a digital environment through a screen (7);
- **semi-immersive**, when the environment consists of stereoscopic projections on curved or convex surfaces (8);
- **immersive**, when the user is fully surrounded by an artificial environment (9,10).

RAT is an umbrella term encompassing different types of devices with specific technical characteristics, including exoskeletons and end-effector systems (11). Exoskeletons are external structural devices with axes aligned to human anatomical joints, capable of directly controlling individual articulations; end-effector systems, instead, apply mechanical forces to the distal segment of the limb through a single point of contact (5,6). TR consists of delivering rehabilitation services through information and communication technologies, using devices such as smartphones, tablets, and video cameras (12).

The application of these technologies in neurorehabilitation, particularly for upper limb motor recovery in adults with stroke, has led to numerous clinical studies investigating their effectiveness. Robot-assisted rehabilitation has been shown to improve upper limb motor function; specifically, Kwakkel et al. (13) and Verbeek et al. (3) reported favorable results for RAT, with a more pronounced

advantage for end-effector systems compared to exoskeletons. Everard et al. (7), in a network meta-analysis, compared the effects of VR, RAT, and TR on upper limb motor recovery, showing that in subacute patients all three categories of devices, when used in addition to Conventional Treatment (CT), are more effective than CT alone. RAT appears to be particularly effective in individuals with moderate to severe deficits, whereas in the chronic phase both VR and RAT seem beneficial for motor recovery (7). More recently, Don Yoo et al. (14), in a systematic review with meta-analysis, confirmed the superiority of RAT over CT in improving upper limb motor function.

Despite the growing body of evidence, several challenges remain, including population heterogeneity, variability in device characteristics, non-standardized treatment dosage, and the lack of specific intervention parameters. These elements complicate comparisons across studies and limit the ability to define optimal evidence-based protocols.

Contextually, in the Italian rehabilitation landscape, technologies have been included in the Essential Levels of Care (LEA) of the National Health Service (SSN) since 2018 (8), promoting their adoption in clinical practice across accredited healthcare facilities. In this context, the Azienda Unitaria Sanitaria Locale (AUSL) of Piacenza–Fiorenzuola d'Arda Hospital represents a consolidated example of integration of technologies within rehabilitation pathways for patients with neurological conditions (e.g., stroke, spinal cord injury, traumatic brain injury). Technology-based treatments are delivered as adjunctive interventions to conventional therapies, such as physiotherapy, hydrotherapy, occupational therapy, speech therapy, and neuropsychology, with the aim of enhancing rehabilitation effectiveness and addressing patients' functional needs.

For upper limb rehabilitation, four devices with complementary purposes are currently available:

- **Intensive Visual Stimulation – IVS3** (Dessintey, France), a system for mirror therapy and motor imagery, targeting motor planning and movement control;
- **Gloreha Professional 2 + Active Package** (BTL Robotics, Italy), a soft robotic glove for hand rehabilitation;
- **PABLO®** (Tyromotion, Austria), a multifunctional rehabilitation device based on sensors and interactive interfaces;
- **DIEGO®** (Tyromotion, Austria), an end-effector device designed for assistive and interactive therapies.

The selection of the device(s), dosage, intensity, and type of exercises is determined by the physiotherapist, who tailors the intervention according to the patient's clinical characteristics and functional deficits.

In light of current evidence and the rehabilitation context of Fiorenzuola Hospital, the aim of this preliminary study is to evaluate the effect of a personalized technology-based treatment approach on upper limb motor function and capacity in individuals with stroke.

Primary and Secondary Objectives

The primary objective of the study is to evaluate the effect of a personalized technology-based rehabilitative intervention on UL motor function and capacity recovery in adult PwS. A secondary objective is to quantify the changes induced using these technologies through instrumental assessments and to correlate them with clinical outcomes.

The primary endpoint of the study is the improvement in upper limb motor function and capacity, measured using the **Fugl-Meyer Assessment for Upper Extremity** (FMA-UE) and the **Action Research Arm Test** (ARAT). Clinically meaningful improvement, defined as the **Minimal Clinically Important Difference (MCID)**, corresponds to **≥ 10 points** on the FMA-UE (15) and **≥ 12 points** on the ARAT (16).

The secondary endpoint is the improvement in active **Range of Motion** and muscle strength, measured using the **PABLO®** device (Tyromotion, Austria).

Study Design

This single-cohort study will be conducted at the Intensive Rehabilitation Medicine Unit of Fiorenzuola d'Arda Hospital (Piacenza) – AUSL Piacenza. The planned duration of the study is 18 months, from April 2026 to August 2027.

Study Population

The study population consists of adult patients with stroke sequelae admitted to the Intensive Rehabilitation Medicine Unit (code 56) for intensive inpatient rehabilitation. Adult PwS admitted to the Intensive Rehabilitation Unit at Fiorenzuola d'Arda hospital. Sampling will be consecutive and carried out on the basis of feasibility and the flow of admissions to the Clinical Unit, amounting to approximately 3-5 individuals per month. The study will include PwS who meet eligibility criteria at the time of recruitment and who are able to understand and provide informed consent to participate.

Inclusion Criteria:

- Age ≥ 18 years;
- First-ever unilateral ischemic or hemorrhagic stroke;
- Presence of upper limb motor impairment;
- Modified Ashworth Scale (MAS) < 3;
- Montreal Cognitive Assessment (MoCA) > 24 (17);
- Medically stable and able to participate in an intensive rehabilitation programme;
- Ability to understand and follow study procedures;
- Written informed consent.

Exclusion Criteria:

- Diagnosis of severe aphasia, based on medical records, preventing participation;
- Bilateral hemisphere lesions;
- Severe and unstable medical conditions (e.g. untreated seizure, heart failure) that preclude participation in rehabilitation;
- Other neurological and/or psychiatric diseases;
- Recent and unstabilized upper limb fracture.

Sampling Strategy

Sampling will be consecutive and based on feasibility and the admission flow to the Unit, estimated at approximately 3–5 patients per month. Participants who meet the eligibility criteria at the time of assessment and are able to understand and provide informed consent will be included.

Given these constraints, it is not feasible to achieve a sample size sufficient to reliably estimate a moderate treatment effect. A potential enrollment of approximately 20–30 participants is expected. This sample size is intended to generate preliminary data to inform the planning of future studies.

For reporting, the study will adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement (19).

Intervention

Participants will undergo clinical and instrumental assessments at two timepoints: at baseline (T0), coinciding with enrollment, and at follow-up (T1), at the end of the 4-5 weeks of observation. During this period, participants will receive conventional treatments, including neuromotor, occupational therapy, speech therapy and/or neuropsychology treatments, as clinically indicated. In addition, they will undergo a personalized and specific UL technology-based rehabilitation programme, delivered 3 times per week, for a total of 12 – 15 sessions. Each session will last 1 hour and will be conducted in a 1:1 format (physiotherapist : participant). Data on rehabilitation dosage will be collected, including the total number of hours of rehabilitation received. Physiotherapists who will have in charge participant, will compiled a treatment diary for each technology session in which they will record: number of session, total hour of technology-based treatments, type of device used and any adverse events.

Participants may be exposed to the following technology-based upper limb rehabilitation devices:

- Intensive Visual Stimulation -IVS3(Dessintey, France): a camera-based system that generates visual illusions for the patient, recreating the motor image of upper limb. The system replaces the visual representation of the affected upper limb with the movement performed by the less-affected limb.

- Gloreha Professional 2 + Active Package (BTL Robotics, Italy): a soft-robotic glove that assists movements of the arm, wrist and fingers, providing an interactive experience that enriches the real world with computer-generated perceptual information through exergames.
- PABLO (Tyromotion, Austria): a multifunctional, sensor-based rehabilitation designed for interactive therapy of entire UL. It enables task-oriented exercises with real-time feedback
- DIEGO (Tyromotion, Austria): a robotic sensor-based UL rehabilitation system that provides assisted and interactive therapy

Outcome Measures

Primary Outcomes

- **Fugl-Meyer Assessment for Upper Extremity (FMA-UE)**
- **Action Research Arm Test (ARAT)**

Secondary Outcomes

- Instrumental Active Range of Motion (AROM);
- Grasping and pinches strenght

Clinical assessments will include validated scales defined according to the International Classification of Functioning, Disability and Health (ICF) (20,21):

- **National Institutes of Health Stroke Scale – Italian version (NIHSS-IT)**, to determine stroke severity. NIHSS-IT is a standardized ordinal scale determining stroke severity. The scale includes the following domains: level of consciousness, eye movements, integrity of visual fields, facial movements, arm and leg muscle strength, sensation, coordination, language, speech and neglect. Each impairment item is scored ranging from 0 to 2, or 0 to 3 or 0 to 4, depending on the specific domain assessed. The total score results from the sum of all item scores and range from 0 to 42, where 0 indicates the absence of impairments, whereas 42 reflects the most severity stroke. (22)
- **Oxford Community Stroke Project (OCSP)** classification, used to predict the lesion site involved in the stroke event is a clinical classification used to predict the lesion site after stroke. The scale identifies 4 subgroups of cerebral infarction: 1. Total Anterior Cerebral Infarction (TACI): cortical and subcortical involvement; 2. Partial Anterior Cerebral Infarction (PACI): predominantly cortical involvement; 3. Posterior Circulation Infarcts (POCI): vertebrobasilar territory involvement; 4. Lacunar Infarcts (LACI): deep perforating arteries territory involvement. (23)

"Body Structures and Functions"(24,25)

- **Fugl-Meyer Assessment for Upper Extremity (FMA-UE) – primary outcome -** is an ordinal scale used to assess sensorimotor function following stroke. The upper extremity motor function section includes four subscales assessing synergistic and non-synergistic movements of shoulder, elbow, wrist and hand, as well as coordination/speed. The maximum score is 66 points, indicating normal upper limb motor function. In addition to motor function,

the FMA-UE assesses Non-motor domains (i.e., sensation, passive joint movement and pain), with a maximum total score of 60 points (26).

- **Modified Ashworth Scale (MAS):** It is a clinical scale to assess muscle tone during passive mobilization. The score ranges from 0 (no muscle tone increase) to 4 (spasticity). In this study it will be evaluated only for biceps brachii and flexor carpi (27).
- **Motricity Index (MI):** This outcome measure identifies and quantifies the strength of three UL movements: pinch grasp, elbow flexion and shoulder abduction. Each item is classified similarly to the Medical Research Council (MRC). The total scores range from 0 (no movement) to 100 (normal strenght) (28).

"Activities"

- **Action Research Arm Test (ARAT):** It consists of 19 items grouped in subtests (i.e., grasp, grip, pinch, and gross arm movement) and performance of each item rated on a 4 points scale (from 0 - no movement possible, to 3 - movement performed normally (29).
- **Box and Block Test (BBT):** It is a clinical test that measures gross manual dexterity. The patient is asked to move in 60 seconds the highest possible number of wooden blocks from one side of a box to the other, over a central partition (30);
- **Barthel Index (BI):** It is a 10-item ordinal scale used to measure person's ability to complete Activity of Daily Living (ADL). The score varies from 0 (totally dependent) to 100 (completely independent). Items assess ability inferring, transfers (moving from wheelchair to bed and return), personal toilet, getting on and of toilet, bathing self, walking, ascend and descend stirs, dressing, controlling bowels and controlling bladder (31).

"Participation"

- **EuroQuol-5D (EQ-5D):** It is a subjective questionnaire used to assess the patient's perception of their quality of life in relation to their health status

The instrumental assessment will be executed using PABLO (Tyromotion, AU) device:

- The instrumental assessment of the Active Range of Motion (AROM) of the upper limb includes shoulder flexion-extension/abduction and adduction, elbow flexion-extension, wrist flexion-extension/ulnar-radial deviation, and forearm pronation-supination.
- The instrumental assessment of the Gross and fine motor grip strength of hand affected includes grasping and releasing, pincer grip, three-finger grip, lateral grip and interdigital grip. This will be performed using Handesensor within the PABLO device (Tyromotion, AU)

Statistical Analysis Plan

The distributions of the variables will be tested using the Shapiro-Wilk test. Depending on the distributional properties, the data will be summarised and described using the mean and standard deviation or the median and interquartile range.

To assess the comparison between measurements taken before and after the intervention, either the Student's t-test for paired samples (normal distribution) or the Wilcoxon signed-rank test (non-

normal distribution) will be used. The effect size will be calculated for the FMA-UE and ARAT scales using Cohen's d.

In order to explore the relationships between rehabilitation dosage and motor recovery of the upper limb, correlation tests will be carried out. In particular, the Pearson correlation coefficient (or Spearman's in the case of non-normal distributions) will be calculated between the quantitative measures of rehabilitation dose (e.g. number of sessions, total hours of treatment) and functional improvement, measured by the change in scores: (ΔFMA-UE) and (ΔARAT).

The analyses will be conducted using STATA software, with a significance level set at $p<0.05$. Any missing data for the observed variables may be handled using multiple imputation.

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