INTERVENTIONAL STUDY PROTOCOL

Study Title:
Auto-calibrating System for Upper Limb Disability Assessment, Neurological and Occupational Rehabilitation (AS-ULDAR)

Acronym: AS-ULDAR

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BACKGROUND AND RATIONALE

Activities of Daily Living (ADLs) are closely associated with upper-limb function. As functional impairment progressively worsens, patient autonomy in performing ADLs is increasingly compromised, as observed in neuromuscular diseases, neurodegenerative disorders, and post-stroke conditions. Activities such as writing, using cutlery, drinking, grasping objects, using a computer, or operating a mobile phone become increasingly difficult, significantly affecting the quality of life of both patients and caregivers. Consequently, the assessment of upper-limb functional deficits and their impact on ADLs represents a major focus in both clinical practice and research[1].

Technological assistive devices, including biorobotic systems, constitute an important component of the technological solutions available for individuals affected by disabling conditions. These technologies should be integrated into a multidisciplinary management approach for patients with acquired neurological disorders (e.g., stroke sequelae) or chronic neurological diseases such as Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and Mild Cognitive Impairment (MCI)[2].

Parkinson's disease (PD) is a chronic neurodegenerative movement disorder characterized by progressive impairment of motor initiation. In particular, reaching and grasping movements as well as fine manual skills of the upper limb become slow and difficult to perform. Upper-limb motor impairment in PD results from both plastic rigidity, which affects agonist and antagonist muscles equally and reduces the range of motion (ROM) at the shoulder, elbow, and wrist, and deficits in the ability to initiate simple and complex voluntary movements or rapidly execute coordinated multi-joint motor sequences.

Amyotrophic Lateral Sclerosis (ALS) is a fatal syndrome characterized by degeneration of upper and lower motor neurons, leading to progressive weakness involving bulbar, limb, thoracic, and abdominal musculature. Upper-limb onset is the most common presentation, accounting for approximately 30–40% of cases. Rehabilitation in ALS aims to identify residual functional capabilities throughout disease progression and to maximize patient independence, functional performance, and management of disease-related symptoms[3].

Stroke is the leading cause of acquired disability among adults in developed countries. Recovery outcomes are highly heterogeneous due to both lesion characteristics and

rehabilitation interventions. Depending on the study population, between 25% and 74% of stroke survivors experience chronic deficits requiring assistance in ADLs. Recovery of upper-limb function is generally more complex and prolonged than recovery of lower-limb function, where ambulation may be regained through more elementary motor patterns[4].

Patients with Mild Cognitive Impairment (MCI), classified in the DSM-5 as having mild neurocognitive disorder, may present with vascular, medical, or neurodegenerative etiologies, including prodromal Alzheimer's disease. These individuals often experience early limitations in ADLs associated with deficits in upper-limb function. However, the relationship between cognitive impairment and motor disability remains only partially understood[5].

Technological solutions applied to motor and cognitive rehabilitation offer significant opportunities for restoring or maintaining patient autonomy, independence, and social participation. Nevertheless, successful rehabilitation requires personalized identification of technological interventions based on the patient's interests, residual abilities, and appropriate clinical support[6].

Individuals with upper-limb disabilities frequently experience difficulties with hand use, motor coordination, object manipulation, and essential daily activities such as dressing, eating, and writing. Furthermore, upper limbs contribute significantly to mobility and balance-related independence.

Evidence suggests that rehabilitation plays a crucial role in preserving and improving long-term functional abilities. Automated systems, including robotic devices, are increasingly important for both disability assessment and personalized rehabilitation planning. In addition to their rehabilitative role, robotic systems equipped with sensors can collect precise quantitative data regarding patient status and performance, thereby supporting clinicians during assessment procedures and reducing subjectivity[7].

Within the context of self-directed practice, exergames—video games combining physical exercise with interactive gameplay—have emerged as valuable tools for motor rehabilitation in patients with disabilities. These systems enable intensive and repetitive practice, engage both upper limbs, and provide immediate feedback. Previous studies have demonstrated beneficial effects of exergames on upper-limb recovery, balance, and functional independence[8-11].

Two principal categories of robotic systems are currently used in upper-limb rehabilitation:

1. **Exoskeletons**, which follow the biomechanical structure of body segments and guide joint-specific movements.

2. **End-effector-based systems**, which can be used with either upper limb and are suitable for both rehabilitation and assistive applications, including autonomous and home-based rehabilitation settings.

The physiotherapist's role is to evaluate the patient's condition and prescribe exercises tailored to individual physical and neurological needs. Therefore, the first function of any personalized rehabilitation system should be the objective assessment of patient disability.

One of the most commonly employed exercises in robotic rehabilitation and assessment is the **Center-Out Point-to-Point (CO-PTP) task**. During this exercise, the patient moves the robot end-effector on a planar surface from a central position toward eight targets arranged on a circumference and subsequently returns to the center after each outward movement[12].

Kinematic and dynamic indices derived from the CO-PTP task have been shown to correlate with clinical scales routinely used to quantify motor disability, including the Medical Research Council Muscle Power Scale, the Fugl-Meyer Assessment Scale, and the Modified Ashworth Scale. Furthermore, the CO-PTP task can identify movement directions associated with greater difficulty and effort for individual patients.

STUDY OBJECTIVES

The primary objective of this study is to evaluate the **usability** of a prototype bio-cooperative robotic system designed to deliver robot-mediated occupational therapy interventions for individuals affected by neurological disorders, including ALS, stroke, Parkinson's disease, and Mild Cognitive Impairment, who present with partial or complete upper-limb motor impairment or motor deficits secondary to cognitive dysfunction.

The study will also assess the **feasibility** of implementing a treatment protocol based on the device within the target population.

Primary Objectives

- Evaluation of device usability.
- Evaluation of device feasibility.

Secondary Objectives

- Assessment of patient and operator safety during device use.
- Evaluation of the impact on upper-limb motor performance.
- Evaluation of cognitive outcomes.
- Evaluation of quality-of-life outcomes.
- Comparison of conventional rehabilitation versus conventional rehabilitation combined with device-assisted therapy.
- Comparison between movement measurements obtained through the robotic system and those obtained using standard clinical assessment methods.

DESCRIPTION OF THE TECHNOLOGY

The AS-ULDAR robotic system has been designed for the rehabilitation of upper-limb function in individuals affected by neuromotor disorders.

The system consists of the following components:

- An anthropomorphic collaborative robotic manipulator equipped with a customized end-effector;
- A set of wearable inertial sensors for patient motion capture;
- A personal computer (PC) equipped with Gigabit Ethernet connectivity and Ubuntu 22.04 operating system;
- An anti-spasticity assistive glove designed to facilitate grasping of the robotic manipulator in subjects presenting with severe spasticity.

No previous technical knowledge is required for system use, as all instructions and training will be provided by the study personnel.

Franka Emika Panda Robotic Arm

The Franka Emika Panda robotic arm is a collaborative anthropomorphic robot manufactured and marketed by Franka Robotics (Germany).

The robot is characterized by seven motorized joints, providing seven degrees of freedom and high end-effector positioning repeatability (±0.01 mm).

Joint control is performed through modulation of electrical signals by a dedicated control unit, which receives higher-level commands such as position, velocity, and torque references from a connected PC through the User Datagram Protocol (UDP). Communication between the PC and the robot controller is implemented through the Franka Control Interface (FCI) software library provided by the manufacturer.

Due to its relatively low weight (approximately 18 kg), the robot can be easily transported and mounted on a laboratory table equipped with counterbalancing systems and height-adjustment mechanisms. This configuration allows use by patients seated on standard chairs, chairs with armrests, or wheelchairs.

When patients are unable to actively grasp the robot end-effector, the wrist can be connected to the customized handle using an adjustable anti-spasticity assistive glove described below.

Figure 1: Franka Emika Panda Robot

Anti-Spasticity Assistive Glove

Depending on the severity of the neurological condition, some patients may be unable to grasp and manipulate the robot end-effector within three-dimensional space.

To address this limitation, a custom-made end-effector produced through three-dimensional (3D) printing technology has been developed. The patient's hand can be secured to the customized handle through the use of an adjustable anti-spasticity assistive glove.

This solution allows patients with severe motor impairment, including those with marked spasticity, to safely interact with the robotic platform and participate in both assessment and rehabilitation procedures.

Figure 2: Anti-spasticity Assistive Glove

MTw Xsens Magneto-Inertial System

The MTw Xsens system is a CE-marked motion capture solution composed of 18 wearable wireless inertial measurement units (IMUs) and one wireless receiving station. Each sensor incorporates a three-dimensional accelerometer, a gyroscope, a magnetometer, a barometer. The sensors communicate wirelessly with the receiving station through a proprietary protocol. The receiving station is connected to the PC via USB interface. Each sensor provides real-time measurements at a sampling frequency of 60 Hz. By combining sensor measurements with a Kalman filter specifically developed by Xsens and the biomechanical model integrated within the MVN software platform, it is possible to generate a virtual representation of the patient and extract detailed kinematic information regarding movement execution.

SOFTWARE

The software platform supports two operational modes: Assessment Mode and Rehabilitation Mode

During the assessment phase, the patient performs the **Center-Out Point-to-Point (CO-PTP)** task. The exercise requires the patient to move the robot end-effector on a planar surface from a central position toward eight targets arranged around a circumference and subsequently return to the center after reaching each target. For patients unable to grasp the handle independently, the adjustable anti-spasticity glove is used to secure the hand to the robot end-effector. During task execution, the system continuously records: End-effector position, End-effector velocity, Forces exerted by the patient on the robot;, Additional kinematic and dynamic variables. These measurements are used to compute quantitative performance indicators capable of characterizing movement quality, including accuracy, smoothness, motor control efficiency.

All exercises are performed while the patient is seated on a standard chair (with or without armrests) or in a wheelchair.

Rehabilitation Mode

Two categories of rehabilitation exercises are available. The difficulty level of each exercise is determined according to the results obtained during the assessment phase and the patient's performance during previous rehabilitation sessions.

1. CO-PTP Task Combined with Cognitive Training

In this exercise, the patient performs the CO-PTP movements according to a sequence that changes dynamically rather than following a fixed order. Before execution, a sequence of targets is displayed on the screen. After presentation of the sequence, the patient must reproduce the target order from memory. Initially, only one target is presented. If the patient correctly remembers and reaches the target, the subsequent sequence is increased by one additional element. Target directions are not selected randomly. Instead, they are

determined according to the patient's motor performance observed during the assessment phase, thereby providing individualized cognitive-motor training.

This exercise simultaneously stimulates motor planning, working memory, executive functioning and upper-limb motor control.

2. Trajectory Tracking Exercise

In the trajectory tracking task, patients are required to perform more complex movements. Trajectories may be designed and recorded by the therapist or physician and subsequently reproduced by the robotic system which is supposed to guide the hand of the patient.

VISUAL FEEDBACK DISPLAY

During both assessment procedures and rehabilitation exercises involving planar trajectories, patients receive real-time visual feedback through a display interface. The display allows patients to compare the desired trajectory and the actual trajectory performed. The target to be reached is highlighted on the screen, facilitating motor learning through visual guidance.

SOFTWARE–HARDWARE INTEGRATION

Communication among sensors, robotic hardware, and software modules is implemented through the **Robot Operating System 2 (ROS2)** framework.

ROS2 enables the development and integration of complex robotic systems through independent software nodes written in multiple programming languages, including C++ and Python. Data exchange between nodes is performed through UDP or TCP communication protocols according to the required balance between transmission speed and reliability.

ROS2 serves as the central middleware coordinating Robot control, Sensor acquisition, Data processing, Rehabilitation exercises, User feedback interfaces.

STUDY DESIGN

This study is a multicenter, non-profit, low-intervention interventional clinical study. The planned duration is 6 months, while the expected Start Date is June 2026. Thirty patients will be enrolled and randomized through a simple randomization procedure into two treatment arms.

Group A – Conventional Rehabilitation + AS-ULDAR

- 10 patients with upper-limb motor impairment (QuickDASH score 20–90) due to Parkinson’s disease, ALS, or stroke;
- 5 patients with Mild Cognitive Impairment (MCI), with or without upper-limb motor impairment.

Participants in Group A will receive robotic treatment sessions using the AS-ULDAR system in addition to conventional rehabilitation therapy.

Group B – Conventional Rehabilitation Only

- 10 patients with upper-limb motor impairment (QuickDASH score 20–90) due to Parkinson's disease, ALS, or stroke;
- 5 patients with Mild Cognitive Impairment (MCI), with or without upper-limb motor impairment.

Participants in Group B will receive standard rehabilitation therapy alone. The two groups will subsequently be compared in order to evaluate safety, feasibility, effects on upper-limb motor function, fatigue, and cognitive performance.

Both groups will undergo 12 sessions of 60 minutes each, three times per week, of conventional therapy according to clinical practice; patients in Group A will additionally receive device-use sessions lasting a maximum of 30 minutes with the rehabilitation staff involved in the study. The session includes a set of exercises identified on the basis of the patient's abilities.

The sessions are structured as follows:

- Session 1: Group A and B: collection of demographic data (date of birth, sex, weight, height) and medical data (past medical history, concomitant diseases, medications, date of disease onset, specific data regarding the specific pathology: type and site of stroke, ALS phenotype, PD phenotype); assessment of motor and cognitive abilities and performance in ADLs using the assessment scales included in the protocol; assessment of the patient's upper limb motor abilities.
- Session 2: Group A: the study therapist and physician instruct the patient regarding use of the device. Devices useful for monitoring vital parameters will be worn (Heart Rate (HR) and Oxygen Saturation measured through pulse oximeters commonly used in clinical practice), while Blood Pressure (BP) will be measured at the beginning and end of the session. The patient is required to perform the CO-PTP exercise and, during this performance, data are collected and metrics are calculated to quantify the quality of the movements performed. Group B: no activities planned.
- Sessions 3–11: Group A and B: the patient carries out regular conventional rehabilitation sessions with the referring therapist. Group A: after an adequate rest period following the conventional session, the patient carries out device-use sessions together with the study therapist while wearing devices useful for monitoring vital parameters (HR, Oxygen Saturation), whereas BP will be measured at the beginning and end of the session. During each session, the patient will be assisted by the therapist in wearing the Xsens sensors and, where necessary, in

connecting to the robot through the assistive glove. For each session, the activities performed will be recorded in terms of duration in minutes and type of activity. During each rehabilitation session, the parameters regulating exercise difficulty will be selected on the basis of the patient's performance during the previous session.

- Session 12: during the final session, the following final evaluations will be carried out:

  - Administration of system usability scales. (Group A)

  - Assessment of changes in motor and cognitive abilities and in the performance of ADLs using the assessment scales included in the protocol (Group A and B) and the movement measurements recorded by the system during the sessions (Group A).

  - Psychosocial impact of the system. (Group A)

  - Level of satisfaction with the assistive device. (Group A)

  - Incidence of adverse events. (Group A)

  - System error history. (Group A)

Any protocol deviations (number of missed sessions, non-compliance with session frequency) will be recorded by the investigators. Patients who do not complete at least 80% of the planned rehabilitation sessions or who attend sessions with a frequency of < 2/week will be withdrawn from the study.

SETTINGS

Three Maugeri Scientific Clinical Institutes (IRCCS Milano Camaldoli, IRCCS Pavia, and IRCCS Montescano) and the Department of Industrial and Information Engineering (DIII) of the University of Pavia will participate in the study.

The Department of Industrial and Information Engineering (DIII) aims to promote scientific and socioeconomic progress, with a strong commitment to education, innovation, and technology transfer. Specialized in mechanical, electronic, computer, and automation engineering, the Department excels in applying its multidisciplinary expertise across a wide range of sectors. Among its areas of interest, automation and robotics stand out for their innovative impact. The DIII approach is characterized by the cross-disciplinary integration of technology, which is applied in various contexts ranging from manufacturing industries to energy sustainability. This versatility reflects the Department's objective of actively contributing to technological advancement through cutting-edge research.

The ICS Maugeri Rehabilitation Institutes involved in the project are all accredited for Code 56 rehabilitation services (which include the neurological conditions of interest for this study), are located in the Lombardy region, and belong to the same healthcare organization, ICS Maugeri.

Patients admitted to Code 56 beds belong to MDC 1 and present neurological disorders. They are referred either from acute-care wards following events such as stroke, neurosurgical procedures, or Guillain–Barré syndrome, or by their specialist physician (within the community setting or from the acute-care ward in the case of hospitalization) following significant functional deterioration associated with chronic diseases, such as Parkinson's disease, Amyotrophic Lateral Sclerosis, or cognitive impairment. In the inpatient setting, multidisciplinary rehabilitation services are provided at a high level of intensity, with the need for continuous medical and nursing care throughout the day.

The Institutes also provide outpatient rehabilitation services for patients affected by the same conditions but presenting different levels of severity and requiring multidisciplinary rehabilitation interventions that can be delivered in an outpatient setting.

ICS Maugeri represents a national center of excellence in neurological rehabilitation. It has been operating throughout Italy for more than 50 years through a network of Scientific Institutes and Rehabilitation Units integrated into the healthcare services available to citizens and the community. Its headquarters are located in Pavia.

Rehabilitation treatment across the various care settings is guided by up-to-date scientific evidence and is based on the definition of functional goals that are meaningful to the patient, as outlined in the Individual Rehabilitation Program (IRP), whose implementation relies on coordinated multidisciplinary interventions. Functional goals in the various treatment areas are established by the multidisciplinary team on the first day of admission and are periodically reassessed. ICS Maugeri has developed a database that enables integrated interaction among healthcare professionals for the identification of patients' functional limitations and the functional goals to be achieved during hospitalization. The various rehabilitation activities are recorded for each patient in a dedicated database in terms of duration, type of activity, and procedures performed. Personal care and nursing assistance are provided by healthcare professionals and rehabilitation nurses working within the Institutes and are part of routine clinical practice.

Two cohorts of patients diagnosed with stroke, Parkinson's disease, Amyotrophic Lateral Sclerosis, and Mild Cognitive Impairment will be enrolled in the study and randomly assigned to two treatment arms.

Group B: conventional treatment; Group A: use of the device in addition to conventional treatment.

Patients eligible for enrollment will be identified by specialist physicians or by the referring occupational therapist/physiotherapist from the inpatient wards and outpatient/MAC services operating within the participating facilities.

The activities will be carried out in the rehabilitation gyms of the three Institutes where the devices will be installed in agreement with the Institute Management and in compliance with all applicable legal requirements. A single system will be used and transported among the three facilities.

STUDY POPULATION

Inclusion Criteria

- Adult patients aged between 18 and 80 years.
- Confirmed diagnosis of one of the following chronic neurological conditions: stroke, Parkinson's disease, amyotrophic lateral sclerosis (ALS), or mild cognitive impairment (MCI).
- Presence of upper-limb motor impairment defined by QuickDASH scores ranging from 20 to 90.
- Ability to understand and follow the study protocol instructions.

Exclusion Criteria

- Patients with severe psychiatric disorders or cognitive disorders that compromise their ability to complete cognitive tests and self-assessment scales.
- Subjects unable to provide informed consent.
- Subjects with moderate to severe cognitive impairment indicated by an ECAS score below 81.92 (ALS patients) or a MoCA score between 18 and 25.
- Physical conditions that significantly limit the use of the upper limbs (e.g., severe concomitant orthopedic disorders limiting shoulder movements).
- Current or recent participation (within the previous three months) in other rehabilitation programs or interventions that could influence the study outcomes.
- Unstable health conditions that could make the use of the device unsafe or inappropriate, such as unstable medical conditions or severe visual impairment.

STUDY ENDPOINTS

Primary Endpoints

Device safety for patients and staff will be assessed through evaluation of the incidence of adverse events by analyzing the frequency of adverse events reported by the patient or detected by the operator at the end of each session and recorded on a dedicated form. Usability and feasibility will be evaluated through:

• SUS (System Usability Scale): administered at the end of the study.

• QUEST 2.0: administered at the end of the study.

• Anxiety and stress levels – Self-reported scales (e.g., STAI, PSS) will measure changes in anxiety and stress related to the activities performed during device use.

• The TARPP-Q questionnaire evaluates usability, which can be defined as the ability of a system to enable users to perform tasks safely, effectively, and efficiently while enjoying the experience.

Secondary Endpoints

Motor performance will be assessed at the beginning and at the end of the study through:

• QuickDASH

• Fugl-Meyer Assessment

• ABILHAND Scale

• ARAT

• MAS

• Disease-specific scales: Bradykinesia Scale (Parkinson's disease), ALSFRS-R (ALS)

• Perceived quality of life will be assessed at the beginning and at the end of the study through:

• EuroQol-5D (EQ-5D)

For the assessment of the psychosocial impact of the system on the patient's life, the following will be used:

• PIADS Scale (Psychosocial Impact of Assistive Devices Scale)

Cognitive performance will be assessed at the beginning and at the end of the study through:

• Trail Making Test A

• Stroop Test

• Digit Span Test

SCALES	**Session 1**	**Sessions 2-11**	**Sessions 12**
SUS (System Usability Scale)			X^3
QUEST 2.0			X^3
STAI, PSS	X^3		X^3
(TARPP-Q)			X^3
Quick DASH	X		X

ABIL-HAND scale	X		X
Bradykinesia scale	X[1]		X[1]
ALSFRS-r	X[2]		X[2]
MAS	X		X
ARAT	X		X
test Fugl-Meyer	X		X
EuroQol-5D (EQ-5D)	X		X
Scala PIADS			X[3]
Trail Making Test A	X		X
Stroop Test	X		X
Digit Span Test	X		X
Adverse Events Reporting	X	X	X

Table 1: assessment scales administered during the various study sessions.

1) only for patients with Parkinson's disease, 2) only for patients with ALS, 3) only subjects in Group A

SUS (System Usability Scale) is a widely used instrument for evaluating system usability. The SUS consists of a series of 10 questions answered by users using a 5-point Likert scale ranging from "strongly disagree" to "strongly agree." The questions are designed to assess various aspects of usability, such as ease of use, complexity, user satisfaction, and other related dimensions.

QUEST 2.0: This questionnaire is used to assess user satisfaction with assistive technologies and related services. "QUEST" stands for *Quebec User Evaluation of Satisfaction with Assistive Technology* and was developed to measure users' perceived satisfaction with assistive devices and associated services. Version 2.0 is an updated version of the original questionnaire, designed to be more comprehensive and suitable for different healthcare settings.

STAI (State-Trait Anxiety Inventory), a psychometric questionnaire used to assess anxiety levels in adults. Two forms of the questionnaire are available: one measures state anxiety (temporary, situational anxiety) and the other measures trait anxiety (stable, dispositional anxiety).

PSS (*Perceived Stress Scale)*: a scale used to measure self-perceived stress levels. It consists of questions assessing thoughts and feelings related to stress experienced during the month preceding questionnaire completion. The PSS is designed to evaluate the extent to which life events are perceived as unpredictable, uncontrollable, and overwhelming.

TARPP-Q: a series of questions that users rate according to their experience using the system. The questions may address various aspects of usability, such as ease of learning, efficiency of use, usefulness of system functions, and overall user satisfaction.

QuickDASH: The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire is a 30-item questionnaire that evaluates a patient's ability to perform specific upper-limb activities. The QuickDASH is a shortened version of the original DASH measure. It is a self-administered questionnaire that measures an individual's ability to perform tasks, absorb forces, and the severity of symptoms. The QuickDASH instrument uses a 5-point Likert scale from which the patient selects the number corresponding to his or her level of severity or functional ability.

ABILHAND Scale: evaluates the perceived ability of an adult individual with upper-limb functional impairments to perform movements and activities related to daily living.

The Bradykinesia Scale is applied to patients with Parkinson's disease and evaluates the components of bradykinesia, namely speed, amplitude, and rhythm of limb movements. For the upper limbs, the assessment focuses on hand movements, including grasping, hand pronation-supination, and finger tapping.

The MAS (Modified Ashworth Scale) is a subjective clinical assessment scale widely used in clinical practice to quantify muscle spasticity in different patient populations. It consists of six response categories with scores ranging from 0 to 4, indicating the degree of resistance perceived during passive mobilization of the joints being tested. The modified version of the Ashworth Scale adds an additional score category (+1) to indicate resistance present through less than half of the range of motion.

The ARAT (Action Research Arm Test) is an observational assessment composed of four upper-limb subtests that evaluate motor performance with regard to coordination and accuracy in functions such as grasping and holding an object, touching with a finger, and performing gross arm movements (e.g., bringing the hand above or behind the head).

The ALSFRS-R is an assessment scale consisting of a patient questionnaire used to evaluate disability and functional status in individuals with amyotrophic lateral sclerosis. In the revised version, the assessment of respiratory function has been incorporated.

The Fugl-Meyer Assessment (FMA) evaluates motor function, sensory function, and balance in individuals with stroke or acquired brain injury.

The EuroQol-5D (EQ-5D) is a questionnaire that assesses health-related quality of life across multiple dimensions and includes a visual analogue scale for evaluating current health status.

The PIADS Scale (Psychosocial Impact of Assistive Devices Scale) is an instrument used to evaluate changes in functional abilities, perceptions of self-efficacy, and levels of participation in daily activities among individuals with disabilities. It consists of 26 items assessing three main dimensions: competence, adaptability, and self-esteem. The scale is widely used in rehabilitation settings to evaluate treatment effectiveness and improvements in patients' quality of life.

The Trail Making Test (TMT) evaluates executive functions and planning abilities and is used to assess cognitive functions, particularly attention, concentration, cognitive flexibility, planning abilities, and response inhibition. It consists of two main parts:

- Part A: The subject is required to connect consecutive numbers in ascending order as quickly as possible.
- Part B: The subject is required to alternate between numbers and letters, connecting them in ascending sequence (1-A-2-B-3-C, etc.).

Stroop Test: A psychological test used to measure concentration ability and cognitive flexibility. In the Stroop Test, participants are presented with a series of words printed in different colors. The task is to name the color of the ink in which each word is printed while ignoring the meaning of the word itself. For example, if the word "red" is printed in blue ink, the participant should respond "blue" rather than "red."

The Digit Span Test evaluates working memory and attention by requiring the participant to repeat sequences of numbers.

VARIABLES

Assessment Phase

During the assessment phase, the system automatically recognizes the beginning and end of the movement in each of the prescribed directions. During the execution of these movements, the following data are collected:

- movement duration;
- end-effector velocity at each time point;
- end-effector position at each time point;
- force exerted on the end-effector at each time point;

- distance between the target point reached and the desired target point;
- body joint angles at each time point.

Rehabilitation Phase

The above-mentioned data are also collected during the rehabilitation phase while performing the CO-PTP task combined with the cognitive exercise.

During the execution of trajectory-tracking exercises, the following information is collected:

- end-effector position at each time point;
- end-effector velocity at each time point;
- distance from the desired trajectory at each time point;
- mean squared error of the position with respect to the desired position;
- body joint angles at each time point;
- time required to complete the trajectory;
- force exerted on the end-effector at each time point;
- number of times the robot intervenes in assistive mode to guide the patient back to the desired trajectory.

Exposure Factors (Risk or Protective Factors):

- Use of the AS-ULDAR system.

Predictors:

- Type of chronic neurological condition (stroke, Parkinson's disease, ALS, MCI).
- Patient age.
- Severity level of the neurological condition.

Potential Confounding Factors:

- Patient's previous level of physical activity.
- Presence of other neurological or medical comorbidities.
- Use of medications affecting cognitive or motor abilities.

Effect Modifiers:

- Patient's level of motor and cognitive engagement.

- Adherence to and frequency of training sessions with the robotic rehabilitation system.

Data Sources and Measurement Methods:

- Use of the robotic system: automated recording of AS-ULDAR system usage data during sessions.
- Chronic neurological condition: patient medical history and clinical data obtained from medical records.
- Patient age: patient demographic records.
- Severity level of the neurological condition: clinical data obtained from medical records.
- Previous level of physical activity: clinical interview and self-assessment questionnaire.
- Neurological or medical comorbidities: patient medical history and clinical data obtained from medical records.
- Medication use: clinical interview and review of the patient's pharmacological treatment.
- Level of motor and cognitive engagement: clinical evaluation by the specialist physician.
- Adherence to and frequency of training sessions: attendance records from training sessions.

Strategies to Minimize Missing Data:

- Use of electronic data collection tools (eCRFs) to ensure accurate and complete data collection.
- Implementation of additional strategies to retrieve missing information during the retrospective study phase.

Measures to Minimize Systematic Errors:

- Use of standardized protocols for data collection and conduct of assessments.
- Appropriate training and supervision of interviewers and researchers.
- Continuous quality control throughout study execution.
- Regular data review to identify and correct potential errors or discrepancies.

SAMPLE SIZE

The sample of patients eligible for enrollment in this multicenter interventional study is structured as follows:

- 10 patients with upper-limb motor functional impairment, as measured by the QuickDASH scale with scores ranging from 20 to 90, resulting from chronic neurological diseases (Parkinson's disease and ALS) or post-acute neurological conditions (stroke sequelae), and 5 patients with or without upper-limb motor functional impairment but affected by mild cognitive impairment (MCI), who will use the study device in addition to conventional rehabilitation therapy.
- 10 patients with upper-limb motor functional impairment, as measured by the QuickDASH scale with scores ranging from 20 to 90, resulting from chronic neurological diseases (Parkinson's disease and ALS) or post-acute neurological conditions (stroke sequelae), and 5 patients with or without upper-limb motor functional impairment but affected by mild cognitive impairment (MCI), who will undergo conventional rehabilitation therapy only.

As this is a pilot feasibility study involving a technological device, a formal sample size calculation was not performed. The proposed sample size is based on empirical rules and similar experiences reported in the literature [13] [14], which indicate that a minimum of 12 participants is acceptable. Based on these considerations, taking into account the number of pathologies included in the study and the planned comparison with a control group, a total enrollment of 30 participants has been planned.

RECRUITMENT PROCEDURE

Patients will be enrolled following direct referral by their treating physicians and physiotherapists, according to the chronological order of admission to inpatient rehabilitation or outpatient/MAC rehabilitation services.

FOLLOW-UP PROCEDURES

No follow-up visits are planned after completion of the study.

DEFINITION OF STUDY COMPLETION

For each individual participant, the study will be considered completed at the end of the 12 sessions specified in the protocol. Overall, the study will be considered completed after the twelfth session of the last enrolled participant. Upon completion of all sessions, data analysis activities will be finalized and

STATISTICAL ANALYSIS PLAN

Descriptive analysis: processing of data collected with the robotic system

In patients selected for robotic therapy, during both phases of exercise execution (assessment and rehabilitation), the indices calculated to represent patient performance (e.g., movement fluidity and accuracy) will be subjected to an initial descriptive statistical analysis to evaluate their distribution, different measures of central tendency, and dispersion. This will also be carried out using graphical tools such as boxplots and histograms.

Association analysis: variables measured by the system and scores on standard clinical scales

To evaluate the correlation between the indices provided by the system and the scores on standard clinical scales assigned by clinical staff, Pearson's correlation coefficient and its square (R^2) will be calculated to assess the percentage of variability in clinical scale scores explained by the linear relationship with the computed indices. However, these measures allow one to establish dependence between variables only if it is linear. To evaluate more complex relationships, the use of more advanced regression models, such as regression and classification trees or neural networks, will be considered.

Comparative analysis: pre- and post-rehabilitation patients undergoing robotic therapy

To assess the impact of rehabilitation with the robotic system, statistical analysis will be based on the scores obtained in the scales reported in the study endpoints chapter. First, the distribution of at least interval-level data will be evaluated using a goodness-of-fit test (e.g., the Kolmogorov–Smirnov test). If it cannot be statistically demonstrated that the data deviate from normality, a parametric test for paired data, such as the paired t-test, will be used. Otherwise, a non-parametric test for paired data, such as the Wilcoxon signed-rank test, will be applied.

Comparative analysis: traditional therapy vs. traditional therapy integrated with robotics

To assess the existence of a statistically significant difference between patients treated only with traditional rehabilitation and patients treated with both traditional and robotic rehabilitation, several statistical tests will be employed. The comparison between the two groups will be based on variables chosen to represent upper limb motor abilities, cognitive status, and quality of life.

These variables can be mainly divided into two categories:

- Ordinal variables
- At least interval-level variables

For ordinal variables, the Friedman test for repeated measures will be used. The difference will be analyzed between subjects treated with and without robotic therapy, while the secondary factor considered will be pathology (PD, ALS, MCI, post-stroke outcomes). For

interval-level variables, a multi-factor ANOVA will be used. In this case as well, the difference between subjects treated with robotic therapy and those receiving only traditional therapy will be investigated, while the secondary factor in the test will be pathology.

Non-parametric analyses

Where the distribution of the variables under study is non-normal or in cases of very small sample sizes, non-parametric tests will be used for group comparisons and regression analyses (Mann–Whitney U test, Kruskal–Wallis test, or Friedman test, depending on the objective, as well as quantile regression).

These statistical considerations aim to ensure that the study is conducted with robustness and that the analyses are appropriate for evaluating the specific objectives of the study in an accurate and comprehensive manner.

As this is a pilot usability and feasibility study of a technological device, a formal sample size calculation was not performed. The sample size considered is based on empirical rules and similar experiences in the literature, which suggest a minimum of 12 subjects as acceptable. Based on these considerations, in relation to the number of pathologies included in the study and comparisons with a control patient group, a total enrollment of 30 subjects has been planned.

Data Collection

Anamnestic data and information related to medical history will be collected through access to the clinical records documented at the time of admission to the Institutes in the medical chart.

The assessments to be performed include validated scales and measurements that are routinely used in clinical practice, although not all of them are included in the standard protocols adopted by the Institutes.

Data Management and Storage

All study-related data will be carefully collected and documented using electronic Case Report Forms (eCRFs), which comprehensively capture all phases of the study. Data management and storage will comply with privacy regulations and will be subject to strict oversight.

Data will be collected and stored electronically and will be used exclusively for scientific research purposes. In accordance with Italian Legislative Decree No. 196/2003, articles 11–12–13 on the protection of individuals with regard to the processing of personal data, access to acquired data will be protected by the investigator. No information that could in any way identify participants will be disclosed.

All participants will be assigned an anonymous code by the researchers. Research data will be retained for 5 years after the completion of the project.

Safety Management

Participants are free to withdraw from the study at any time without any negative impact on the quality of the healthcare they receive. The reason for withdrawal will be requested and recorded in the Case Report Form (CRF). Furthermore, the study may be discontinued if the physician observes adverse effects or other conditions that justify suspension in the best interest of the patient. A detailed risk analysis related to the use of the system under investigation is provided in the relevant table.

Foreseeable Risks (Probability) and Mitigation Actions

Foreseeable risk (probability)	**Actions taken**
The subject has difficulty wearing the sensors (medium).	The operator must assist the subject in correctly wearing the sensors.
The subject interacts incorrectly with the robot, holding it improperly, which may lead to potentially dangerous movements for their joints (medium).	The operator must instruct the patient on how to properly grasp the handle attached to the end-effector.
The subject has difficulty using the device with standard parameters, or the exercise difficulty is not adequate to the patient's clinical condition (medium).	The operator may adjust the parameters to make the activity with the robotic system easier and less fatiguing, and may disable certain functionalities if necessary.
Prolonged use of the monitor may cause visual fatigue and discomfort (low).	The operator must position the monitor at an appropriate distance from the subject's eyes, and regular breaks must be taken during rehabilitation sessions.

Foreseeable risk (probability)	Actions taken
Lack of communication between hardware and software components of the proposed solution (low).	The software will send an error message to the therapist or user. The experiment can be interrupted via software or hardware by pressing the emergency button. The platform control system implements emergency stop procedures in case of malfunctions.
The subject experiences difficulty and requests immediate interruption (low).	Both the patient and the operator have an emergency button that allows immediate interruption of the test.
The subject has difficulty grasping the end-effector handle (medium).	The operator may provide the patient with an adjustable anti-spasticity glove and attach it to the handle.
The subject exerts excessive force on the robot, performing sudden movements (low).	The robotic system automatically stops when the speeds detected by internal sensors exceed predefined thresholds.

Table2: Foreseeable Risks Associated with the Use of the System and Risk Mitigation Measures

Each adverse event will be managed according to standardized procedures implemented within the Centers for the handling of adverse events during rehabilitation activities, based on the type of access to the facility (inpatient admission or MAC/outpatient setting). The presence of medical staff will be ensured during all activities foreseen by the study protocol.

Administrative aspects – Study funding

The study will be conducted using funds provided under the National Recovery and Resilience Plan (PNRR) within the Fit4Med Project for the Department of Engineering of the University of Pavia and for the Scientific Clinical Institutes Maugeri.

ETHICAL CONSIDERATIONS

Submission to CTS and Research Ethics Committees

The research project involves an intervention using technological equipment alongside conventional rehabilitation treatments. The project will be submitted to the Maugeri Scientific Technical Committee (CTS) and, through the coordinating center (ICS Maugeri Montescano), with any modifications deemed appropriate by the CTS, to the Regional Ethics Committee of Lombardy.

Compliance with international guidelines

The study protocol has been developed in accordance with the European Good Clinical Practice (GCP) guidelines and the latest revision of the Declaration of Helsinki, ensuring compliance with fundamental ethical principles in clinical research.

Ethical approval

The study will only begin after approval by the competent Ethics Committee, ensuring that the research is conducted in an ethically appropriate manner and that participants' rights, safety, and well-being are protected.

Insurance

Specific insurance coverage is planned for patients for assessments and interventions additional to those included in routine clinical and rehabilitation care related to their underlying condition. The sponsor will be responsible for providing the necessary insurance coverage, as outlined in the attached insurance request.

Appropriate standards of care and protection for study participants will be ensured.

In summary, the protocol ensures that the study is conducted in compliance with the highest ethical standards, guaranteeing data integrity, participant protection, and transparency in the communication of results.

Informed consent and data processing

To be enrolled, participants must sign a consent form in accordance with Legislative Decree No. 196/03 on personal data processing and privacy protection.

Informed consent for the use of personal and clinical data for research purposes is an integral part of the activities of the Maugeri Centers and is routinely collected on the day of admission to the ward.

For patients unable to provide consent due to communication or cognitive impairments, consent will be obtained from a designated family member or legal representative.

A copy of the privacy information sheet and the signed consent form for personal data processing, collected at admission to the Institute, are attached to the project. A specific informed consent form for participation in the study will be used for both healthy subjects and patients. Consent forms will be stored in a locked archive within a secured office at the Institute where the patient is enrolled.

Conflict of interest

The researchers involved in the participating Centers declare no conflicts of interest.

Responsibilities and publication policies

Role of sponsor and investigators

The sponsor is responsible for the overall design and organization of the study, including obtaining ethical approvals and managing funding. The sponsor also oversees the overall progress of the study and ensures its scientific integrity. The sponsor will provide, as study sponsor, the technology required to conduct the study.

Investigators contribute substantially to the study concept and design and are responsible for the practical implementation of the study protocol. This includes data collection, interaction with study participants, implementation of treatment procedures, and accurate recording of information. Investigators will strictly adhere to the established protocol to ensure consistency and reliability of the collected data. Together, the sponsor and investigators collaborate to ensure the success of the study and to obtain valid and meaningful results that can contribute to advances in rehabilitation research.

Investigators from the Department of Engineering of the University of Pavia will be responsible for training healthcare personnel on the procedures and tools used, in order to prevent errors and ensure safe use of the equipment.

Each researcher will have a role in the various research activities:

1. Substantial contribution to study concept and design;
2. Data acquisition;
3. Data analysis and interpretation;
4. Manuscript drafting;
5. Literature review and integration into the text;
6. Critical revision of the manuscript;
7. Submission to a scientific journal;
8. Responsibility for communication with the publisher and revisions.

Data ownership and dissemination of results

As an independent study under Ministerial Decree 17 December 2004, data ownership generally belongs to the study sponsor (Ministerial Decree 17 December 2004, Art. 1, paragraph 2, letter c). The sponsor ensures that ownership of the results derived from this research, as well as publication rights and authorship, is attributed to researchers who have made a significant contribution to the study, subject to approval by the Principal Investigator (PI).

Data transmission or dissemination, through scientific publications and/or presentations at congresses, conferences, seminars, and participation in multicenter studies, will occur exclusively after statistical processing of the data or in fully anonymized form.

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