CLINICAL INVESTIGATION PLAN
Drafted according to MDR 2017/745

1. General Information

STUDY TITLE:	Evaluation of the impact of a rehabilitation intervention based on cycling with Virtual Park on training motivation in adult patients
STUDY CODE:	VirtualPark-Adults
PROTOCOL VERSION:	4.0
HISTORY OF PREVIOUS VERSIONS:	n/a
DATE:	16.03.2026
SPONSOR/PROMOTER:	CNR-STIIMA - Institute of Intelligent Industrial Systems and Technologies for Advanced Manufacturing, Via Alfonso Corti, 12, 20133 Milan (MI) VAT No.: 02118311006 Tax Code: 80054330586
CONTACT PERSON OR LEGAL REPRESENTATIVE OF THE SPONSOR/PROMOTER:	c/o CNR-STIIMA
MANUFACTURER:	Via G. Previati 1/E 23900 Lecco (LC)
METHOD OF FINANCING THE CLINICAL TRIAL AND DESCRIPTION OF THE CONTRACT BETWEEN SPONSOR AND SITE:	Registered office: CNR-STIIMA, Via Alfonso Corti, 12, 20133 Milan (MI)

LIST OF PARTICIPATING CENTERS

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ANY OTHER CENTERS INVOLVED

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APPROVAL OF THE PROTOCOL

The Investigators:

- approve this Protocol;

- declare that the study will be conducted in accordance with the provisions of this Protocol.

This Protocol is duly signed by the investigators representing the participating centers on separate signature pages.

Center: CNR-STIIMA - Institute of Intelligent Industrial Systems and Technologies for Advanced Manufacturing

Investigator: Marta Mondellini

Date 18.02.2026 Signature

Center: Istituti Clinici Scientifici Maugeri IRCCS Montescano

Investigator: Dr. Cira Fundarò

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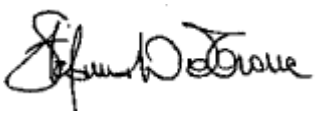
Date 18.02.2026



Center: Istituti Clinici Scientifici Maugeri IRCCS Telese

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Date 20.02.2026 Signature

Center: Istituti Clinici Scientifici Maugeri IRCCS Pavia

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Date 18.02.2026 Signature

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Investigator: Prof. Carmelo Chisari

Date 20.02.2026 Signature

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Date 22.02.2026 Signature

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1. Summary

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2. SUMMARY OF THE CLINICAL INVESTIGATION

This study is a prospective, exploratory, multicenter, randomized, crossover clinical trial in the pilot phase.

Figure 1 shows the flowchart summarizing the study phases, which are described in detail below.

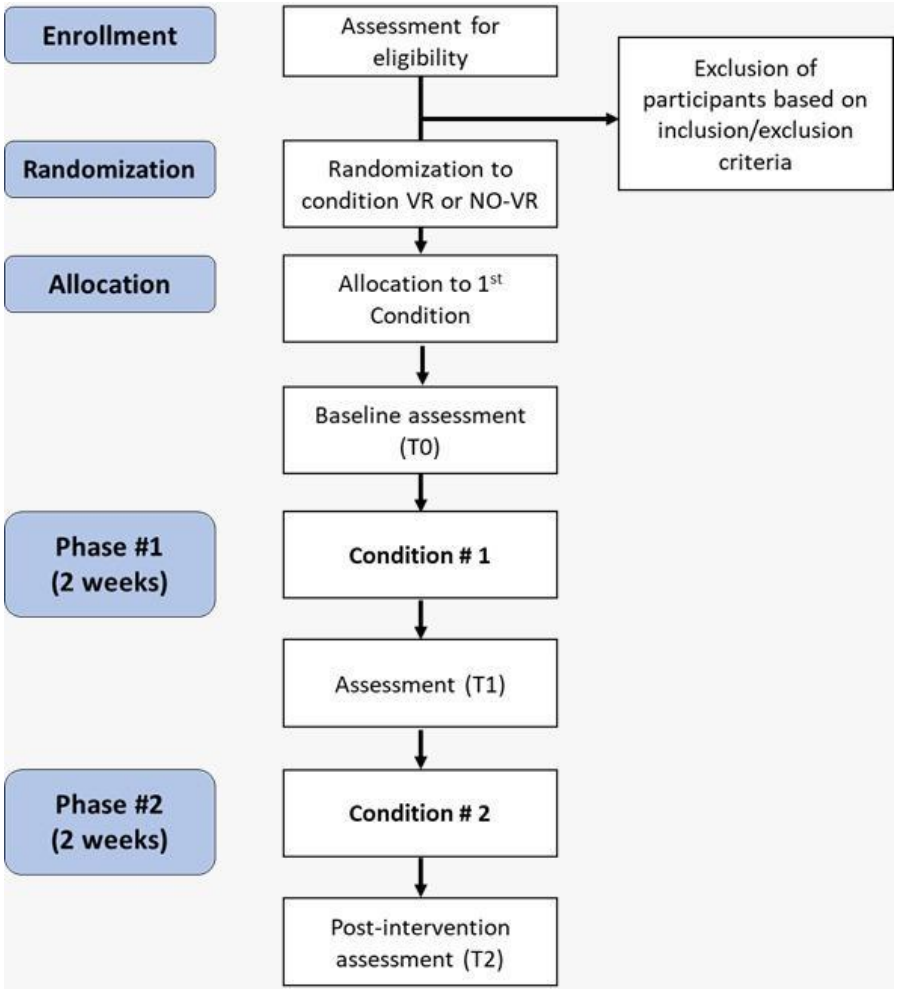

Figure 1: summary of the phases of this study

2. DEVICE INFORMATION

2.1 Device name

VirtualPark

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2.2 Device Description

The device consists of a virtual reality (VR) environment designed to support dual-task training for individuals with disabilities. The device provides a series of cognitive tasks and is designed for use in combination with a cycle/arm-ergometer (hereinafter referred to as the "ergometer"), to combine physical exercise with cognitive stimulation. The VR application is developed by CNR-STIIMA, manufacturer of the VirtualPark device; it offers cognitive tasks contextualized to the pedaling activity in virtual reality scenarios that simulate real-life situations. The ergometer that can be integrated with VirtualPark is a commercial device (THERA-Trainer tigo), certified as a medical device, which allows for passive or active pedaling exercises, including assisted pedaling, with upper or lower limbs. The VirtualPark software also allows for the integration of two Bluetooth buttons to allow interaction with the VR environment—even while pedaling—to perform cognitive exercises.

2.3 *Intended use and population for which the device is intended*

The VirtualPark device is designed for indoor multimodal dual-task training. Its compact design makes it easily transportable and usable by both operators and end users. The device is intended for use by patients over 6 years of age and adults with disabilities and/or comorbidities. In this study, the target population for the device is adults, at least 18 years of age and up to 85 years of age. The pedaling exercise can be performed with both the upper and lower limbs. Cognitive training includes four exercises, each focusing on a specific domain: attention, inhibition, working memory, and navigational skills.

2.4 Fabbricante

Institute of Intelligent Industrial Systems and Technologies for Advanced Manufacturing of the National Research Council (CNR-STIIMA)

The manufacturer's address is:

Registered office: CNR-STIIMA, Via A. Corti 12, 20133 Milano (Italy)

Operational headquarters: CNR-STIIMA, Via G. Previati 1/E, 23900 Lecco (Italy)

2.5 Indications for the traceability of the experimental product

Each device is equipped with a label containing the main device data and a serial number that uniquely identifies each device. Details on the label are provided in the attached user manual (Appendix H).

2.6 *Materials that come into contact with the human body*

The materials that come into contact with the user's body are: the THERA-Trainer ergometer and the buttons. In both cases, contact is superficial and non-invasive; all components and accessories are designed to comply with current biocompatibility directives, provided they are used within the specified timeframe.

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2.7 Medical or surgical procedure related to the use of the device

For a detailed description of how to use the device, please refer to the instructions for use in the VirtualPark User Manual (Appendix H).
Clinical monitoring of the patient will be performed by a clinician. Furthermore, appropriately trained healthcare personnel will be present during patient use of the device.

2.8 *Training and experience required to use the device*

Prima dell'inizio della sperimentazione il personale tecnico di CNR-STIIMA effettuerà una adeguata formazione per istruire il personale clinico dei centri all'utilizzo del dispositivo VirtualPark. Verranno forniti e lasciati a disposizione i manuali d'uso dei singoli dispositivi e del sistema integrato. Non è richiesta alcuna competenza o esperienza aggiuntiva rispetto a quanto già previsto per lo svolgimento dell'attività riabilitativa.

2.9 Analysis of the related *literature*

The VirtualPark system has already been validated in previous CNR-STIIMA research projects. Specifically, several versions of the system designed for different patient populations have been validated. All previous versions use the same ergometer: the medically certified COSMED E100-E5 model. The VR application and associated interaction and physiological response detection devices differ depending on the context of use.

An initial version of the system (Goji Aging Interest Project, later included in the Young Researchers Project GR-2013-02356043) designed for older adults with mild cognitive decline offered a semi-immersive experience using a large wall-mounted screen. The virtual environment consisted of two scenes: a park where navigation was based on actual pedaling speed, and a scenario in which the user had to cross roads, slowing down when appropriate. The physiological response was detected via a sensorized t-shirt worn by the patient. A third scene, set in a supermarket, was dedicated to cognitive training. The system was the subject of a pilot study (n=10, Goji) and a randomized clinical trial (n=80, GR) at the Santa Lucia Foundation in Rome, both of which were found to be acceptable and enjoyable for the older adults involved. In the Goji Project, following 6 weeks of physical and cognitive training, older adults in the experimental group reported slight improvements on neuropsychological tests and a significant increase in the concentration of biological markers of oxidative stress and, consequently, cognitive decline (Mrakic-Sposta et al., 2018). In the second study, it was found that the groups (n = 40) that performed physical activity, either alone or in combination with cognitive training, showed improvements in neuropsychological tests after 12 weeks, which were maintained at follow-up (Arlati, 2020).

A second version of the prototype was designed for endurance training for older adults with chronic respiratory diseases in collaboration with the IRCCS INRCA in Casatenovo (Lecco). Similar to the first version, the virtual environment was projected onto a wall-mounted screen placed in front of the COSMED cycle ergometer. The system also integrated a medically certified wrist pulse oximeter to measure oxygen saturation during exercise. A group of 14 older patients with chronic obstructive pulmonary disease used the system as part of a 3-week in-clinic rehabilitation program. Patients experienced improvements in endurance

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in line with traditional rehabilitation protocols. The subjective experience was positive, and engagement remained high throughout the treatment (Colombo et al., 2023).

Two immersive versions of this system were also developed, in which the patient's virtual environment while pedaling was displayed via a virtual reality headset. The first involved using a cycle ergometer for a dual-task exercise. In a Cave Automatic Virtual Environment (CAVE), installed at the Istituto Auxologico Italiano, the elderly user was tasked with pedaling through a virtual park and identifying a series of target objects/animals that appeared along the route among various distractors. The system was validated from a usability perspective by enrolling frail elderly individuals, demonstrating acceptability and user-friendliness (Pedroli et al., 2018). The second system, however, implements a training protocol for post-COVID patients. A preliminary study conducted at the MSWiA Specialized Hospital in Głuchołazy involved 22 adult post-COVID patients. Motivation and the state of flow (which is defined as the optimal experience a person has during a certain activity) increased over time (3 weeks), demonstrating how the use of virtual reality is perceived as motivating and engaging and has a positive impact on the rehabilitation experience (Mondellini et al., 2023).

Finally, a version for home use was created and tested (ARTEDIA project). In this case, the virtual environment is displayed on a tablet mounted to the cycle ergometer, ensuring a compact, easy-to-transport setup. In addition to navigation in the park, the virtual environment also offers a cognitive task, based on the Go-no Go task. The user must, via a button on the cycle ergometer's handlebars, recognize certain stimuli and identify them by pressing the button. To enable home use, the application was integrated into a commercial tele-rehabilitation platform (Khymeia VRSS) (Colombo et al., 2022). The feasibility study, in this case, involved post-stroke patients (9), children and adolescents with neurological disorders (13) and post-COVID patients (6). The entire system was judged positively by all patient groups, who demonstrated good adherence to the intervention protocol and appreciated the possibility of performing rehabilitation activities at home. In some cases, the perceived effort required to use the system was high due to an unstable internet connection and updates to the tele-rehabilitation platform that temporarily limited access to rehabilitation programs.

2.10 Current state of the art and advantages proposed by the new device

The new device, the subject of this study, was designed based on previous versions for use by adults with stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), frail elderly patients with comorbidities, mild cognitive impairment (MCI), spinal cord injury, and multiple sclerosis (MS). The modifications primarily concern the software in terms of content and connectivity and data exchange with hardware devices, particularly the ergometer.

- The virtual reality environment includes two scenarios, one naturalistic and one urban;
- The cognitive tasks coupled with the physical pedaling task were specifically designed with the needs of adult users with disabilities and frailties in mind.
- There are four tasks and they focus on: attention, inhibition, navigation, and working memory.
- The tasks have different difficulty levels, allowing the therapist to best adapt the difficulty of the exercise to the patient's age and cognitive abilities.

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- The hardware device that can be integrated with the VirtualPark version discussed in this document is the TheraTrainer Tigo (10.4" or 7" models). Compared to the previous version, this ergometer allows:
    - o the patient is seated in a chair or wheelchair
    - o the ergometer is adaptable to different heights by adjusting the seat, pedals, and handles, ensuring its use even by children and adolescents;
    - o the device is used with both the lower and upper limbs, making it suitable for patients with limited lower limb mobility;

3. RISKS AND BENEFITS

The risk analysis is reported in document Annex L. The risk analysis was prepared in accordance with the ALARP (As Low As Reasonably Practicable) principle. The risk analysis reported in this document specifically concerns the risks associated with combining the cycle/armor ergometer with the virtual reality application. A specific risk analysis associated with the use of the cycle/armor ergometer was not conducted as it is a medical device with CE medical certification that is used in accordance with its intended use. Furthermore, it is specified that the ergometer's operation is not controlled by external software and cannot be modified by it in any way.

4. RELEVANCE OF CLINICAL INVESTIGATION IN THE STATE OF THE ART

Numerous studies have shown that physical activity (Xu et al., 2019; Han et al., 2017; Nuzum et al., 2020; Meng et al., 2020) improves overall health, motor performance, and cardiorespiratory function, and can have a positive effect on cognitive functions, especially executive function, and the psychological state of patients with stroke, PD, ALS, frail elderly individuals with comorbidities, MCI, MS, and spinal cord injury.
The use of VR combined with dual-task motor training is gaining increasing attention as a potentially effective treatment for rehabilitation in MCI, although the heterogeneity of the studies conducted does not allow us to define the magnitude of the effect and the role of the level of immersion (Tortora et al., 2024; Papaioannou et al., 2022).
In motor rehabilitation for stroke patients, the effectiveness of VR has been extensively studied, with promising results for motor function, range of motion, muscle strength, and activities of daily living (Fernández-Vázquez et al., 2022).
In PD, numerous studies conducted using a dual-task intervention model (aerobic motor training with virtual reality) have shown improvements in cognitive/executive, attentional, and visuospatial functions (Pelosin et al., 2022; Yu et al., 2023), motor skills, daily living functions, and quality of life.
Initial evidence of the effect of motor training combined with virtual reality on upper limb function has also been observed in patients with ALS (Trevizan et al., 2018).
In frail elderly subjects, virtual reality interventions have shown potential to improve both motor (gait, balance, fall prevention, pain management) and cognitive functions; however, their usability and acceptability merit further consideration.
In multiple sclerosis (Galperin I et al. 2023), combining virtual reality with treadmill gait training has shown effects not only on motor skills but also on cognitive skills.

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The use of virtual reality in the aftermath of spinal cord injuries is Still to be extensively explored, although it shows promising evidence for both walking and balance.
These promising results highlight the need to further investigate other aspects of the intervention, focusing on specific parameters such as motivation, usability, and user experience. This study will also evaluate the effect of the dual task on cognitive and motor performance, functional abilities, and perceived and tolerance to effort during training.

5. OBJECTIVES OF THE CLINICAL INVESTIGATION

The primary objective of this clinical study is to evaluate the level of motivation to train induced by interaction in a virtual environment using the VirtualPark device. This system offers a multimodal rehabilitation intervention for adult patients with stroke, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frail elderly patients with comorbidities and mild cognitive impairment (MCI), multiple sclerosis (MS), and spinal cord injury. The device offers an innovative approach based on virtual reality combined with the use of an ergometer, with the aim of encouraging active involvement in rehabilitation training.
Additional objectives of the study include evaluating the usability of the device by different clinical populations, investigating the user experience in various patient groups, and the effect of dual-task training on improving cognitive and motor functions.

6. INFORMATION RELATING TO THE CLINICAL INVESTIGATION

6.1 Duration of the trial

The trial will last 4 weeks for each participant; specifically, this period is divided into 2 weeks of use of the ergometer with VR and 2 weeks without VR. The order of exposure to the condition used first (with/without VR) will be randomized among participants. A washout period is planned between the first two weeks and the last two, during which the patient participates in the standard rehabilitation activities provided by their center.
The total duration of the trial is 8 months; participant recruitment will begin at months 1 and 6, and the study will last from months 2 to 7. One month is planned for the final statistical analyses (month 8).

6.2 General information

This study is:

- Exploratory: The aim of the study is to test for the first time the applicability and effects of a multimodal rehabilitation protocol in a population of adult patients with stroke, PD, frail elderly patients with comorbidities, ALS, MCI, spinal cord injury, and MS;
- Non-first-in-human: The study uses a medical device (ergometer) integrated with a non-immersive virtual reality system (Virtual Park) previously tested on human subjects;
- Multicenter;
- Prospective: It involves the administration of a rehabilitation intervention and the evaluation of cases over time;

- Pilot: The study applies a protocol to a small sample of patients for each condition;
- Crossover: Each participant receives both treatments at different times;
- Randomized: Participants are randomly assigned to treatment groups.

6.3 Endpoints and Variables to Measure

Primary endpoint:

To measure intrinsic motivation in relation to the addition of virtual reality to traditional ergometer-based motor training. This investigation aims to obtain participant feedback on the overall experience and to understand whether the proposed technology is suitable for implementation in real-world clinical settings.

Variables measured: Motivation via questionnaires:

The Intrinsic Motivation Inventory (IMI): a self-administered, multidimensional questionnaire used to assess various aspects of intrinsic motivation across activities. For this study, the Interest/Pleasure scale, considered the measure of intrinsic motivation, was used. The IMI is widely used in psychological and educational research to analyze how engaging and rewarding an activity is for participants. The Interest/Pleasure scale consists of seven items rated on a seven-point Likert scale (McAuley et al., 1987).

The Situational Motivation Scale (SIMS) will be used to measure motivation. This self-report questionnaire consists of 16 items rated on a seven-point Likert scale and investigates four factors: intrinsic motivation, identified regulation, external regulation, and amotivation. This instrument has been validated in English (Guay et al., 2000). It will be back-translated into Italian, and the scales' internal reliability indices will then be evaluated. The addition of this instrument to the interest/pleasure scale is necessary to assess the various motivational aspects that can be placed along the amotivation-intrinsic motivation continuum identified by Self-Determination Theory (Deci & Ryan, 1985).

Secondary end-points:

- Endpoint 2: Evaluation of the usability of the ergometer device combined with virtual reality.
- Variables measured: System Usability Scale (SUS).

The System Usability Scale (SUS) was defined by Brooke in 1996 as "a quick and dirty tool to measure the perceived usability of a system." It is a post-study questionnaire consisting of 10 questions answered on a 5-point Likert scale. The SUS results in a score ranging from 0 to 100, allowing not only the evaluation of a system's usability but also its comparison with other systems. For each statement, participants are asked to provide a level of agreement on a scale of 1 to 5, where 1 equals "strongly disagree," and 5 equals "strongly agree."

- Endpoint 3: Measurement of user experience in relation to the adoption of the proposed technology.
- Variables measured: Technology-Assisted Rehabilitation Patient Perception Questionnaire (TARPP-Q).

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The instrument consists of 29 items and explores the following factors: perceived usability, positive emotions, feelings of obstacle/difficulty, and feelings of stress. The instrument was developed in Italian, and its reliability has been initially tested (Fundarò et al., 2023).

- Endpoint 4: Assessment of COGNITIVE FUNCTIONING
- Variables measured: Pre-/post-intervention changes using the Trail Making Test A–B (TMT), Stroop test, FAB, and Corsi tests.

Trail Making Test A-B (Siciliano et al., 2019) is designed to assess selective, sustained, and divided attention, as well as any deficits in visuo-motor coordination. In Trail Making Test A, the subject must match all 25 numbers on the sheet of paper in ascending order as quickly as possible. If the subject is able to complete the first part of the test, Trail Making Test B can be administered. It is administered in the same way, but the subject must match numbers and letters alternating between them as quickly as possible. This test allows for an assessment of psychomotor speed, visuo-spatial search ability, selective memory, and selective attention. The score is calculated based on the number of seconds the task is completed.

Short Stroop Test (Caffarra et al., 2002) is one of the most commonly used tests to assess prefrontal functions such as cognitive flexibility and the control and inhibition of automatic responses. It is a timed test divided into three parts: in the first part, the subject must name the color of the squares presented to them; in the second part, they simply read the words written on the board (color names); in the third part, they are asked to name the color of the ink the words are written in (the board presents a series of color names, each printed in a different color than the one indicated by the name). The third part is reported by subjects as the most difficult. The Stroop effect emphasizes the interference that automatic word processing generates on the color-naming task, which is more demanding in terms of mental effort. Two scores are calculated: one relating to the time taken and one relating to the errors made.

The Frontal Assessment Battery (FAB) (Dubois et al., 2000; Italian validation Aiello et al., 2022) is a screening test that assesses the presence and severity of a dysexecutive disorder affecting both cognition and motor behavior. The test consists of six subtests that explore, in order: the ability to conceptualize and abstract categories, mental flexibility, motor planning ability, sensitivity to interference, inhibition control, and environmental autonomy. The total score is the sum of the scores obtained for the individual subtests and ranges from 0 to 18 (cut-off 13.50/18).

Corsi Forward – Backward (Monaco et al., 2013) is a test designed to assess working memory and visuospatial short-term memory. The examiner places a board of nine cubes in front of the subject, which the subject will touch in sequences of increasing length. The subject must reproduce the sequence in the same order (Forward) or in reverse (Backward). Starting with a sequence of three cubes, the number of cubes the subject must memorize gradually increases.

- Endpoint 5: Assessment of MOTOR FUNCTION.
- Measured variables: Parameters obtained from the ergometer

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The ergometer enables the acquisition of objective data on motor performance, both in the lower and upper limbs. This data includes the overall pedaling duration, load or level of assistance, meters traveled, and the symmetry of the push on each pedal (for pedaling with the lower limbs only) as an average value.

- Endpoint 6: Improvement in functional capacity.
- Variables measured: Modified Barthel Scale.

The Modified Barthel Index (MBI) is a clinical tool used to assess independence in activities of daily living (ADLs) in patients with physical disabilities. The scale consists of 10 items covering activities such as: personal hygiene, bathing/showering (washing), feeding, dressing, bowel continence, urinary continence, bed or chair transfers, toileting, stairs, walking, and wheelchair use (alternative to walking). Each activity is rated on a numerical scale, with higher scores indicating greater independence. The sum of the scores provides a final score ranging from 0 (total dependence) to 100 (complete independence).

- Endpoint 7: Improved exercise tolerance and perception of effort.
- Variables measured: In-session heart rate and oxygen saturation measured with a finger pulse oximeter using medically certified devices; Borg RPE (Rating of Perceived Exertion, 6-20) scale: ranges from 6 (minimal effort) to 20 (maximum effort) and is often used to assess the intensity of effort in sports and rehabilitation settings. This scale is widely used in the medical and sports fields to monitor patients' perceived exertion during rehabilitation exercises or physical activities (Borg, 1982).

- Endpoint 8: Device Safety
- Measured Variables: The number and description of any adverse events related to the use of the device will be collected. Adverse events will be monitored according to MDR 2017/745, with events reported to Office V of the Ministry of Health and the relevant EC.

The assessments will be conducted by a healthcare professional to ensure the accuracy and completeness of the information collected. They will be conducted at three time points:

- T0 at the start of the study;
- T1 at the end of the first two weeks of training;
- T2 at the end of the rehabilitation intervention;
- T3 follow-up 1 month after the end of the intervention, for cognitive aspects only.

Table 1 reports the outcome measures and evaluation points for each of these

Tabella 1. Misure di outcome e timing di valutazione

Outcome	Measurement Tool	Timing (T0, T1, T2, T3)	Category

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Motivation for training	Intrinsic Motivation Inventory (IMI), Situational Motivation Scale (SIMS)	T1, T2	Primary outcome
Device usability	System Usability Scale (SUS)	T2 (RV only)	Secondary outcome
User experience	TARPP-Q	T2 (RV only)	Secondary outcome
Cognitive function	Trail Making Test A-B, Stroop test, FAB, Corsi	T0, T1, T2, T3 (follow-up 1 month)	Secondary outcome
Motor function	Objective data from the ergometer (load or level of assistance, meters traveled, thrust symmetry)	During each session	Tertiary outcome
Functional capabilities	Modified Barthel Index (MBI)	T0, T1, T2	Tertiary outcome
Exercise tolerance	Pulse Oximeter (HR, SpO2), Borg RPE Scale	During and after each session	Tertiary outcome
Device security	Number and type of adverse events related to the use of the device	During and after each session	Tertiary outcome

6.4 Information on the device under investigation and any comparison products

Object device: Virtual Park. No comparison devices will be included.

6.5 Information on the subjects

The clinical study will recruit patients with stroke, PD, frail elderly patients with comorbidities, ALS, MCI, and spinal cord injury from participating centers.
Study subjects will be identified as follows:

- General criteria: patients will be identified from the clinical database of the facilities involved among subjects diagnosed with stroke, PD, ALS, frail elderly, MCI, spinal cord injury attending the facility with outpatient access, MAC, or inpatient status.

They will be selected based on the following criteria:

a) inclusion: informed consent to the study, subjects > 18 years and <85 years, diagnosis of MCI according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders VTh Edition (DSM V TR American Psychological Association 2013), detection of ischemic stroke within 6 months preceding the study, frail elderly subjects (Gobbens RJ et al. 2010), subjects affected by idiopathic Parkinson's disease according to the MDS-PD criteria (Postuma et al., 2015), affected by possible, probable and definite ALS

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according to the revised El Escorial criteria (Brooks Br, et al. 2000), subjects affected by MS according to the McDonald criteria (2017) with disability measured with the EDSS (Expanded Disability status Scale) <= 8, patients with spinal cord injury of different etiology with incomplete spinal cord injury AIS (ASIA impairment scale) grade C and D, MMSE >18, naïve subjects compared to to the use of VR, no therapeutic changes or rehabilitation interventions in the month prior to inclusion in the study, no ongoing behavioral disorders.

b) Exclusions: other concomitant neurological pathologies in addition to the one being studied, presence of visual impairments that prevent access to the experimental virtual reality protocol, presence of impaired cardiorespiratory function or other organic instabilities that contraindicate ergometer training, severe osteoporosis.

6.6 Measures to minimize bias and management of potential confounding factors

Motor function and neuropsychological analyses will be conducted by disease subgroups to limit confounding factors related to different pathogenic processes. All procedures will be standardized to ensure repeatability. The collection of subjective patient responses will be conducted by a healthcare professional to ensure the accuracy and completeness of the information collected and to address any concerns participants may have regarding the questions.

6.7 *Procedures related to clinical investigation*

a) Expected time for each participant and study setup:

Subjects enrolled in the study will undergo an initial assessment according to the study's outcome measures (T0). The study is a within-subjects design.

Two conditions are defined:

- **NO-VR Condition**: Patients will follow the ergometer-based rehabilitation program without virtual reality in addition to standard care (outpatient or inpatient rehabilitation);
- **VR Condition**: Patients will follow the ergometer-based rehabilitation program + VirtualPark in addition to standard care (outpatient or inpatient rehabilitation).

The sequence of the NO-RV and RV conditions will be randomized, and patients will participate in the study according to the following schedule:

- **Weeks 1 and 2** (Phase 1, T0-T1): Participants will follow the rehabilitation program in one of the two RV or NO-RV conditions.
- **Weeks 3 and 4** (Phase 2, T1-T2): Patients will follow the rehabilitation program based on the RV or NO-RV condition, which will be different from that followed during Phase 1.

Randomization will be done in blocks, so the order of the two conditions will be alternated equally between participants. 50% of participants will perform Condition A first, followed by Condition B. The remaining 50% will perform Condition B first, followed by Condition A. This approach ensures balance between participants and reduces the risk of order effects.

b) Training description

The Virtual Park device allows for the administration of motor tasks (training via ergometer) and neuropsychological tasks (training on attention, inhibition, working memory, and navigational skills).

- The Virtual Park intervention involves 3 sessions per week;
- Each session consists of: a warm-up phase of approximately 5-10 minutes (passive), a 20-minute central phase (active or active-assisted), and a 5-10-minute final phase (passive); breaks can be taken during the central phase, if necessary.
- Cognitive tasks are performed during the central training phase, which involves the introduction of VR.
- The motor task (active phase) or level of assistance (active-assisted phase) is manually set by the operator via the ergometer screen.

c) Characteristics of the virtual environment and cognitive tasks

VirtualPark is an application with two 3D scenarios: a park and a city. The pedaling speed on the ergometer is converted into virtual speed to move a bicycle along a predefined trajectory.
The initial graphical interface allows the therapist to create and upload patient profiles, select cognitive exercises, and configure their parameters. During training, the patient views performance data and can interact via two buttons mounted on the ergometer's handles. The operator can pause the exercise with the STOP button on the THERA-Trainer.
The scenarios include ambient sound effects and audio feedback for correct or incorrect answers, increasing realism and engagement.

Cognitive Tasks

1. Attention (scenario: park)

Go–No Go task to train visual attention, inhibition, and cognitive flexibility. The patient must identify specific targets along the path, avoiding non-targets. The therapist can decide the frequency of the stimuli (15s, 10s, 5s), and there are four modes of increasing difficulty:

- Mode 1: Target and non-target without distinguishing colors.
- Mode 2: Target with a red aura to be hit.
- Mode 3: Target with a blue aura to be hit.
- Mode 4: The rule changes dynamically, and the patient must adapt.

2. Working Memory (scenario: park)

The patient must remember a list of target objects and collect them along the way, avoiding distractors. Two modes are available: a graphical one (list of images) and a textual one (list of names).

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The difficulty increases with the number of objects and the presence of similar elements (e.g., oranges vs. apples).

3. Inhibition (scenario: city)

The patient chooses the direction at intersections by pressing buttons. There are three difficulty levels:
- Level 1: Follow the arrow.
- Level 2: Choose the opposite direction.
- Level 3: Follow the arrow or do the opposite based on the color (yellow = follow, blue = opposite).

4. Navigation (scenario: city)

   The patient first follows a guided route, then repeats it, choosing the correct turns. The difficulty increases with more turns and landmarks. Goals include reaching specific locations (e.g., school, playground), broken down into progressive steps.

d) Motor training

The cycle ergometer allows for upper and lower limb training; it allows for the following settings: training duration, speed, and assistance level for both upper and lower limbs.

The patient will be asked to maintain the most comfortable speed (self-selected speed), which can be adjusted during training.

The duration of active or actively assisted training will be 20 minutes.

The therapist will assess the need for and level of assistance based on the patient's motor skills and can be adjusted during training.

All settings and their modifications can be recorded for each individual session.

e) Procedures required for each participant:

Patients who meet the inclusion and exclusion criteria among the potential study participants are contacted. Patients are informed of the study's procedures and, if they agree to participate, sign the written informed consent and data processing information. Patients are explained that clinical monitoring will be performed by a clinician, while a trained healthcare professional will assist them throughout the study.
Participants then undergo an initial assessment (T0) of cognitive (TMT A and B, FAB, Corsi, Stroop) and functional (MBI) abilities.

Participants are randomly assigned to one of two training modalities (with or without virtual reality).

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Participants then use their assigned training modality three times a week for two weeks.
At the end of the two weeks, motivation (IMI, SIMS) for performing the activity, cognitive functions (TMT A and B, FAB, Corsi, Stroop), and functional abilities (Borg, MBI) are measured (T1).

Participants then use the previously untested training modality for the remaining two weeks. At the end of this period, motivation (IMI, SIMS), cognitive functions (TMT A and B, FAB, Corsi, Stroop), and functional abilities (T2) (Borg, MBI) are measured.

At the end of the two-week period in which participants use the ergometer with VirtualPark in virtual reality (VR condition, at T1 or T2 depending on the participant), questionnaires regarding device usability (SUS) and user experience (TARPP-Q) will be administered.

Subjective questions are asked to the patient, assisted by a healthcare professional, both to address any unclear questions and to ensure that all questions are answered.

During each training session, objective performance parameters are also collected through data recorded by the ergometer, the participant's heart rate, and oxygen saturation.

One month after completing the study, patients will be re-assessed for cognitive aspects (TMT A and B, FAB, Corsi, Stroop) (T3).

6.8 Monitoring plan

The study will be monitored in accordance with the institutes' procedures for monitoring research projects. The investigator undertakes to ensure that the planned procedures and actions comply with the Code of Good Clinical Practice (GCP) and applicable regulations. The clinical study will be conducted in compliance with the principles of the Declaration of Helsinki.

6.9 *Enrollenment*

Enrollment in the clinical study is voluntary and subject to informed consent from participants. If the patient has a legal representative, this person will be required to sign the consent form.

Recruitment will take place at the IRCCS ICS Maugeri (Montescano, Milan Camaldoli, Telese, Bari, and Pavia locations), at the Pisana University Hospital, and at the Villa Beretta Rehabilitation Center at Valduce Hospital.

7. STATISTICA

The collected data will be analyzed using specialized statistical software.

For training motivation (IMI, SIMS), a comparison between T1 and T2 will be performed using dependent-samples t-tests or nonparametric tests (Wilcoxon) in the case of non-normal distribution. Device usability (SUS) and user experience (TARPP-Q) will be analyzed exclusively for the VR condition at T2 using descriptive

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statistics and, if necessary, nonparametric tests to assess individual variability. Cognitive functions (TMT A-B, Stroop, FAB, Corsi), functional capacity (MBI), and exercise tolerance (heart rate, SpO2, Borg Scale) will be analyzed using a repeated-measures ANOVA (or equivalent nonparametric tests), comparing values at T0, T1, and T2 to observe any effects of training and the VR condition over time. For cognitive functions only, a repeated measures ANOVA will be performed considering T3 to assess the persistence of the effects one month after the end (follow-up). For motor function, the objective data collected by the ergometer (load, meters traveled, push symmetry) will be analyzed using descriptive statistics and regression models to identify any patterns of improvement and relationships with other variables. All analyses will be conducted at a significance level of $p < .05$.

The number of subjects was calculated based on a similar study that measured intrinsic motivation after cycling outdoors, indoors with an immersive headset, and indoors with a non-immersive virtual reality display (Poli et al., 2024). The study uses the Intrinsic Motivation Inventory questionnaire and reports, compared to this instrument, an Eta squared = 0.627 across the three conditions, and an effect size of 0.627 for the two conditions (display/outdoor).

The original study, which reported an ES = 0.627, proposed the use of the immersive VR device and outdoor cycling only once. We expect the effect size to be lower in the current study, which involves participation for a total of 4 weeks. Therefore, we set an ES = 0.4 (medium effect size). The calculation is estimated with G-power. Considering a power of 90%, an alpha of 0.05, and an ES of 0.4 for one group with two measurements (T1 and T2), the result is 70.

8. DATA MANAGEMENT AND STORAGE

Data, particularly personal and health data, will be processed only to the extent necessary for the purpose of the trial in accordance with EU Regulation 2016/679 (GDPR) and Legislative Decree No. 101 of August 10, 2018.

When collecting data, whether obtained from standardized clinical assessments or from the device report, the Data Controllers will pseudonymize the collected data, identifying the recruited subjects with codes, or adopt other solutions compliant with point 5.4 of the Italian Data Protection Authority's Provision No. 146/2019. The use of encryption techniques allows the data subject's information to be stored and processed in a form that prevents identification by anyone outside the Center. Only the Project Manager of each center and authorized personnel will be able to link each code to the participant's name.

Subjects, if they wish, may be informed of what information will be archived and how. Access to the data will be granted only to personnel authorized by the center involved in the trial. Upon individual subject's request, at the end of the research, the study results, both general and specific, may be communicated to them.

Data will be processed as follows:

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- Each clinical center is designated as a joint controller of the pseudonymized personal data of patients enrolled at its facility, under a joint controllership agreement with the other centers involved in the study.
- Personal data will be available only to the individual clinics, which are responsible for recruiting patients and conducting therapy sessions. Data previously held by the clinics (e.g., medical records) remain the exclusive property of the individual clinics.
- Each clinic will be responsible for the pseudonymization process of the data collected during the trial and for ensuring the security of the pseudonym mapping table.
- Each clinic will appoint designated personnel who have authorization to access the pseudonymization table.
- The methods of storing and processing personal data will be the responsibility of the individual centers.
- Instrumental data collected via the device during the trial will be identified only by the pseudonym. No personal data will be stored within the device.
- The personal data collected by each center will be transmitted to the other centers involved in the study exclusively in pseudonymized form.
- The pseudonymized data will be shared on a cloud platform by the specific centers with the study sponsor and the other centers. Sharing will take place via a secure cloud platform, with access limited to authorized personnel of the participating centers and the sponsor, in compliance with the security measures required by the GDPR. Access to the data will be granted to authorized personnel with appropriate read and read/write rights.
- The data collected in the study will be managed using cloud services provided by Microsoft. In this context, Microsoft operates exclusively as a technical infrastructure provider, with no decision-making role regarding the purposes of the processing. Therefore, pursuant to Article 28 of the GDPR, Microsoft is a data processor for data hosting and storage under a specific Data Processing Agreement (DPA) signed with the Sponsor.
- Access to the systems containing the data will be granted exclusively to authorized personnel appointed by the centers involved in the study. Access will require two-factor authentication to reduce the risk of unauthorized use. The data will be stored on secure servers within the European Union, and no international transfers are planned.
- The Sponsor is the joint controller of the pseudonymized data received from the centers. The legal basis for the processing is the explicit consent given by the data subject for the specific purposes of the Study pursuant to Article 6, paragraph 1, letter a) and Article 9, paragraph 2, letter a) of the GDPR.
- Only anonymized data will be made public.

9. INTELLECTUAL PROPERTY

Each research institution involved in the project remains the independent data controller of its data subjects, using independently defined processing tools. The results achieved during the study will be jointly owned by the centers participating in the study.

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The methods of exploitation of intellectual property will be defined through specific agreements entered into by the centers. The results of the study will be the property of all the centers involved. The methods of exploitation of intellectual property will be defined through specific agreements entered into by the centers.

10. INFORMATION ON POSSIBLE CHANGES TO THE CLINICAL INVESTIGATION PLAN

Any proposed changes to the clinical trial will be submitted to the National Ethics Committee for Experimentation by Public Research Bodies (CEN-EPR) and other national public bodies and notified to the Ministry of Health.

11. FOLLOW-UP POLICY AND MANAGEMENT OF ANY DEVIATIONS FROM THE EXPERIMENTATION PLAN

If changes are made that could significantly impact the safety, health, or rights of participants or the robustness or reliability of the data obtained from the study, the Ethics Committee will be notified within one week of the reasons and nature of such changes, including an updated version of the relevant documentation.
Changes to the relevant documentation will be clearly identifiable and reported in the "Information on any changes to the trial plan" section of this document.
Notification of substantial changes will be accompanied by a previously requested opinion from the Ethics Committee.

12. DEVICE LIABILITY

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13. ETHICAL CONSIDERATIONS

The proposed Clinical Investigation Plan was drafted in accordance with the European Union's Good Clinical Practice standards, in accordance with the Helsinki Declaration. Approval is required from the National Ethics Committee for Trials of Public Research Institutions (EPR) and other national public bodies.

14. METHODS FOR OBTAINING INFORMED CONSENT

Eligible subjects will be identified in accordance with the inclusion and exclusion criteria above.

Voluntary participation in the research will be possible only after patients have had a comprehensive interview with the study investigators and have carefully read the informed consent document, which provides detailed information about the planned procedures and the medical devices used. The study investigators will ensure that the consent form is properly signed and dated by the patients and that there are no doubts regarding the procedures before any procedure required by the study protocol is performed. However, each subject may request any information or clarification, and the healthcare personnel will be available at any stage of the trial.

The patient may withdraw from the study at any time without penalty. Current and future care at the reference clinical center will not be compromised, and the same care and assistance will be guaranteed. Any changes to the clinical protocol will be promptly communicated to participants.

15. ADVERSE EVENT MANAGEMENT

Pursuant to EU Regulation 2017/745 and the MDCG 2020-10 Rev 1 guidelines on Safety reporting in clinical investigations of medical devices under Regulation (EU) 2017/745, all incidents and serious adverse events that may occur during the clinical investigation must be reported to Office V (Medical Device Vigilance) of the Directorate-General for Medical Devices (DGDFSC) of the Ministry of Health and to the competent EC. Since this is a clinical trial, serious adverse events may also be forwarded to Office VI of the Ministry of Health for information.

16. CRITERIA AND PROCEDURES FOR THE FOLLOW-UP OF SUBJECTS FOLLOWING THE TERMINATION, TEMPORARY INTERRUPTION OR EARLY TERMINATION OF THE TRIAL AND FOLLOW-UP OF SUBJECTS WHO HAVE WITHDRAWN THEIR CONSENT OR ABANDONED

In the event of suspension or early termination of the trial, the Ethics Committee will be notified. The notification will include detailed information on the suspension or early termination date, the centers involved, and the reasons for the suspension or interruption of the trial.
Furthermore, patients may withdraw from the study at any time without penalty. Current and future care at the reference clinical center will not be affected, and the same care and assistance will be guaranteed.

17. DATA DISCLOSURE POLICY

The results obtained at the end of this clinical trial will be presented at national and international conferences and will be submitted to specialized international peer-reviewed journals.

18. TECHNICAL AND FUNCTIONAL CHARACTERISTICS OF THE DEVICE

The VirtualPark device is a virtual reality application. The VR environment is a Windows application developed in Unity by CNR-STIIMA. The application is installed on a Windows PC equipped with a screen positioned in front of the patient, at a distance of approximately 1.5 m. The application includes four

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cognitive tasks, each focusing on a specific domain (attention, inhibition, working memory, and navigational skills), set in two scenarios. The scenarios represent a park and a city. The user navigates within the scenarios using the actual speed detected by the ergometer and sent via Bluetooth.

The device interfaces with an ergometer and two buttons that constitute the user interface. The integration of these elements enables the creation of a dual-task training system that combines physical and cognitive training.

- **The ergometer** is a commercial device produced by THERA-Trainer. Specifically, the THERA-Trainer tigo model with a 7" color screen is a lower limb device combined with an upper limb device module, allowing training in both modes. The THERA-Trainer tigo is a Class IIa medical device. The device is motorized and allows passive, assisted, and active training. The training mode and exercise parameters (duration, assistance level, etc.) can be set for each session directly from the THERA-Trainer panel.
- **The user interface** consists of Puck.js buttons through which the user interacts in performing the cognitive task. Specifically, pressing a button corresponds to an action in the VR environment that differs depending on the exercise being performed. For example, the user presses the button to indicate the identification of a target. The buttons are positioned on the cranks so as to allow their use during training of both the upper and lower limbs.

Please refer to the device's user manual (Appendix H) for further technical details.

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