Evaluation of usability and safety of the self-balancing walking system Atalante in patients with Multiple Sclerosis

Protocol

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30.03.2022	Draft Version2: Comments applied MARS, IG, RS
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1 Justification

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS), affecting more than 2 million people worldwide,1 It's a chronic and degenerative disease that selectively affects the central nervous system represents the leading cause of non-traumatic disability in young adults. The age of onset of the disease is usually between 20 and 40 years. The prevalence of MS in Spain fluctuates between 40 and 125 cases per 100,000 inhabitants, with an incidence of 3-4 new cases per 100,000 inhabitants and year 2

Clinically, the disease initially presents in more than 80% of cases in a relapsing-remitting form, that is, in the form of outbreaks or exacerbations in one or several locations with periods apparently stable between two of these episodes. In most of these patients, after a variable period of time, but on many occasions related to with age, a progressive deterioration appears usually associated to important accumulation of disability. The symptoms of the patients are very variable and differ from one patient to another in topography and intensity. Thus, we can find visual, sensory symptoms, loss of strength, sphincter and sexual alterations, coordination problems, balance problems, cognitive alterations and fatigue among others. 3

Gait and balance disturbances in MS are already common even in the early stages of the disease. Half of the patients already refer some alteration in the quality of their gait within the first month after diagnosis, reaching 90% at 10 years of evolution. [4] [5] Furthermore, it is the symptom that patients give the most importance to [6], both those with less than 5 years of evolution and those who have more than 15 years and the one that most conditions their activity and participation. [7]
The causes of gait disturbance are multifactorial and it is influenced by different aspects such as muscle strength, balance, coordination, proprioception, vision, spasticity, fatigue and even cognitive aspects.[4]
There are multiple interventions, including aerobic, resistance, yoga, and combined exercise training, that have shown significant improvements in walking endurance regardless of outcome measures (6MWT, 2MWT). [8]

Some impairments arise in the clinical and social context of each patient, including fatigue, limitations for basic daily activities, high risk of falls or high disability, to participate in activities or therapies to improve balance, fatigue, strength and gait characteristics.[7] This would support the development and application of rehabilitation strategies for mitigating the energetic penalties of gait abnormalities during ambulation, and possible approaches for this might involve Robot-assisted gait training. At the last 5 years have appeared a lot of robotic solutions that offers both strategies of support in the daily living and rehabilitative devices, that have shown effectiveness in patients whit neurological diseases. Some studies have shown how people with multiple sclerosis and severe gait impairment participating in Robot-assisted gait training (RAGT) achieved significant improvement in lower limb muscle strength and increase in walking speed, yet the effect was not long-lasting.[9]

In the last years the evidence around the robot-based rehabilitation in people whit multiple sclerosis PwMS has been growing, actually there are more than 5 devices approved for use in gait rehabilitation in neurological diseases. Yeh et al. concluded that Robotic locomotor training limitedly affects motor functions of multiple sclerosis, but improves fatigue and spasticity, it is safe and well-tolerated for PwMS and less demanding for physical therapists.[10] Bowman et al. concluded that Robotic-Assisted Gait therapy (RAGT) improves balance and gait outcomes in a clinically meaningful way in PwMS, RAGT seems more effective if compared to unspecific rehabilitation, while it shows similar effects if compared to specific balance and gait training in studies with level 2 evidence.[11] RAGT has several advantages in terms of patient motor assistance, intensity of training, safety, and the possibility to combine other therapeutic approaches and should be promoted for PwMS with severe disability in a multimodal rehabilitation context as an opportunity to maximize recovery.[11] In this context is needed a further larger-scale, better-designed RCTs with a longer training duration and more studies evaluating the satisfaction, usability and effectivity of RAGT.[10] [12] [13] [11]

The Atalante exoskeleton is composed of an external, powered, motorized orthosis that is placed over a person's paralyzed limbs to provide self-ambulation functions without the use of crutches or other technical aids. The main feature of the exoskeleton is that it is fully actuated with 12 actuated degrees of freedom: three at each hip, one at each knee, and two at each ankle. [14] [15]

Usability of assistive technology has been described as the interaction between the user, the device, the context or environment, and nature of the activities in which the user engages with the device.[16 17] A model described by Fuhrer et al.[18] to guide thinking about optimizing use of assistive technology devices is relevant in the analysis and future comparative of outcomes. The framework for Assessment of the Usability of Lower-Extremity Robotic Exoskeletal Orthoses (FUREO)[19] includes the principals five major components of the Fuhrer model and develop some data-set useful to compare devices, protocols and possible structural o personal limitations. The main points are: the functional problem that device is intended to impact; critical device features responsible for addressing the problem; characteristics of individuals (personal factors) that make them successful device users; other elements not intrinsic to the device but closely linked, for example, access to the technology; and expected changes in user status, especially those alterations related to continued and regular use of the device.

The FUREO modules may be used at an individual level to help guide the clinical prescription of robotic Hip Knee Ankle Foot Orthoses (HKAFOs) and to predict the functional applications of a given robotic exoskeleton for a particular person. Additionally, the collection and analysis of FUREO data for groups of individuals can provide insight into the resources associated with training and the level of independence that persons with a range of impairments can attain with robotic HKAFOs. Within the Activities module, FUREO includes suggested thresholds for describing levels of functioning and mobility (community, household, or exercise only) yet to be validated, which can help predict functional outcome. Such data on varied samples of users also can provide insight as to what features should be modified in future generations of robotic exoskeletons. [19]

2 Aims

2.1 Primary Aim:

To describe **usability** of Robotic-Assisted Gait therapy (RAGT) using the Atalante self-balance exoskeleton for persons with multiple sclerosis (PwMS) and explore patient characteristics related to this feature.

Defining usability as a quality attribute that evaluates the ease of use of user interfaces, evaluating the perspective of patients by the Satisfaction Quebec user Evaluation of Satisfaction with assistive technology (QUEST) score and a questionnaire specific to the use of Atalante device.

We have defined high Usability as: Obtaining a positive score greater than or equal to 70% of the total possible score on the Satisfaction Quebec user Evaluation of Satisfaction with assistive technology (QUEST) score.[20]

2.2 Secondary Aims:

To describe **safety** of Robotic-Assisted Gait therapy (RAGT) using the Atalante self-balance exoskeleton for persons with multiple sclerosis (PwMS).
We consider safety as the low occurrence or not appearance of adverse effects.

- Defining a low occurrence as the appearance of an adverse effect related to the rehabilitation program in less than 10% of the reported patients. Defining an adverse event later in the chapter on instructions for reporting adverse events
- The occurrence of pressure ulcers more than grade 1 in more than 10% of reported patients. Not taking into account the pressure zones that can be considered as an acceptable effect within the program as long as it is reversible in minutes after the program.[15]

To describe the effect at the functional level of RAGT using the Atalante self-balance exoskeleton for improving **Balance outcome**, **Walking speed**, **quality of life**, **depression**.

- Balance: We will assess the effect of RAGT at the balance outcome measured by the Berg scale, considering a clinically relevant change for improvement in balance as measured by BBS was +3 points, meaning that PwMS are likely to perceive that as a reproducible and clinically important change in them balance performance.[21]

- Walking speed: We will assess the effect of RAGT at the walking speed measured by the 10 meters walking test, considering a clinically relevant change as an improvement of 20% of the score with respect to the baseline assess.[22]

- Physiological Changes: We will observe the effect of RAGT at the bowel function using the Neurogenic Bowel Dysfunction Spanish version, (NBD) and Patient Global Impression of Improvement (PGI-I). considering a clinically relevant change of +3 points at NBD.[23]

To describe the effect at the self-perception and psychological level of RAGT using the Atalante self-balancing exoskeleton to improve quality of life and depression.

- Using the Multiple Sclerosis Quality of Life-54 (MSQoL 54 Health Survey Spanish version)[24] and Hospital Anxiety and Depression Scale (HADs) considering a clinically relevant change of 1.7 points at HADs[25]

3 Materials And methods

3.1 Design:

This study is prospective, open label, non-randomized, non-comparative and observational.
This study protocol includes 12 one-hour training RAGT sessions during 4 weeks three times per week, under the supervision of qualified rehab team.
Informed consent will be obtained from patients prior to inclusion in the study, which will be carried out in accordance with the Declaration of Helsinki.

3.2 Inclusion and exclusion Criteria

Subjects will be evaluated for their eligibility from neurorehabilitation and neurology outpatient clinics at the Multiple Sclerosis Center of Catalonia (Cemcat).

3.2.1 Inclusion criteria

- Male or female, between 18 and 65 years of age
- Confirmed diagnosis of MS
- EDSS from 6.0 to 7.0
- Able to verticalize on a daily basis
- Stable course of disease-modifying therapy over the past 6 months
- Clinical comorbidity asymptomatic (i.e., no underlying cardiovascular disease)
- Height: between approximately 1.60 and 1.90 m.
- Willingness to visit the Multiple Sclerosis Center of Catalonia (Cemcat) for testing and training.
- Gait disorder conditioned by paresis or hemiparesis associated with ataxia or sensory problems
- Patient having given written consent
  Atalante is able to accommodate the following limb lengths:
- Thigh: 380-460mm
- Distance between the ground and the joint space of the knee (to be measured while wearing the shoes they intend to wear with Atalante):
  - 457–607mm for patient with an ankle dorsiflexion ≥ 16°
  - 457–577mm for patient with an ankle dorsiflexion between 13° et 16°
  - 457–567mm for patient with an ankle dorsiflexion between 10° et 13°
  - 457–557mm for patient with an ankle dorsiflexion between 0° and 10°
- Hip with less or equal to 460mm when seated
- Maximum weight:90 kg

3.2.2 Exclusion criteria

- Pregnancy
- Starting or switching from fampridine (Fampyra®) in the last 4 weeks
- Height and weight outside the secure standard of safe use, described in the safety guides
- Contraindications to training with Atalante (eg, bone instability, history of osteoporosis or osteoporotic fractures)
- Subjects under Corticosteroids treatment or relapse

- Changes in disease-modifying and symptomatic therapy for MS during the study period
- Subjects with psychiatric or cognitive comorbidities that may interfere with the trial
- Whose joint centers cannot be aligned Atalante's
- Ranges of motion below:
    - Knee: 5° extension, 110° flexion
    - Ankle: 0° dorsiflexion, 9° plantar flexion, 18° inversion and eversion
    - Hip: 115° flexion, 15° extension, 17° abduction, 10° adduction, 10°
    - medial rotation, 20° lateral rotation
- Severe spasticity (greater than Ashworth 3) or uncontrolled clonus
- Severe concurrent medical diseases: infections, circulatory, heart or lung, pressure sores
- Active implantable medical device

3.3 Enrollment and Screening

Subjects will be evaluated for their eligibility from neurorehabilitation and neurology outpatient clinics at the Multiple Sclerosis Center of Catalonia (Cemcat).

Potential subjects will be referred to the study via Cemcat Physicians. A member of the research team will screen the referral and confirm they meet the necessary inclusion and exclusion criteria. Following confirmation of criteria, potential subjects will be contacted by phone to schedule an initial visit for consent and baseline assessment.

Prior to all testing, each of the 20 selected participants will have time to read the consent form and ask questions (see Draft Informed Consent). The consent process will take place at the Multiple Sclerosis Centre of Catalonia (Cemcat, Vall d'Hebron Barcelona Hospital Campus, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona).

3.4 Assessments

The following information will be collected for all patients: age, gender, weight, height, type of MS, years from the diagnosis, Expanded Disability Status Scale (EDSS) and type of support device.
For the correct evolution of the training sessions will be assessed the Arterial pressure and the heart rate before each training session. As well as the level of global fatigability by Modified fatigue scale (MFIS) and the physical effort of each session by means of the scale of perception of the effort R.P.E of Borg at the end of each training[26 27]. We will also monitor the appearance of pain in any part of the body related to the RAGT at end of each training session using a pain registry (type of pain, location, intensity)[28].
To reduce the incidence of any type of muscle injury the physical therapist before each RAGT session will assess the level of spasticity using the modified Ashworth scale[34] and the Penn spasm frequency scale.

We will to report the process metrics: the rate of potential candidates referred, do not meet device-related criteria (height, weight, or leg length segments), The rate of patient rejection of the device or protocol, Ratio of assistance and missed sessions and expectative of patients at begin of this study.

We will use a FUREO framework for Assessment of the Usability of Lower-Extremity Robotic Exoskeletal Orthoses to facilitate futures comparatives whit other robots strategies [19 18], using some modules as health outcomes module, device module, external and internal factor module, adding patients and professional acceptability modules, furthermore assessing cognition disability and type of personality.

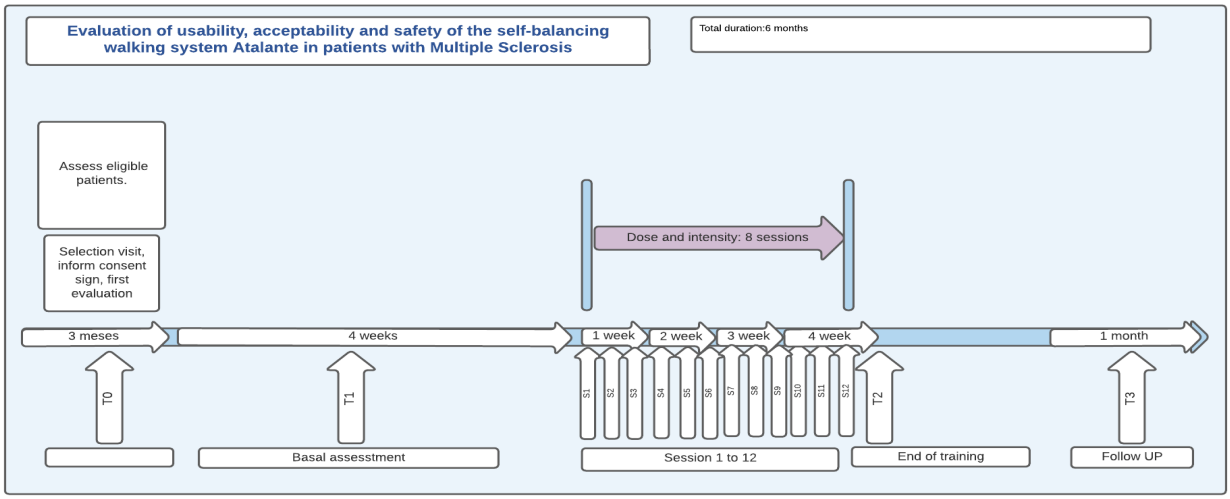
A record of any unexpected Serious Adverse Events (SAE) within trial episodes will be keep. These are defined as death, a life-threatening adverse event or an event occurring as a result of the use of the device that requires medical intervention.

Type outcome	Test		Baseline (T1)		RAG Session 1-12 (S1-S12)		end of training (T2)	
			CRO	PROMs	CRO	PROMs	CRO	PROMs
Pain	1	Pain registry		x		x		x
Physiologic indicators	2	Heart rate	x		x		x	
	3	Arterial pressure	x		x		x	
Bowel function	4	Neurogenic Bowel Dysfunction NBD score Spanish version (NBD)	x				x	
Effort	5	Rating perception exertion The Borg R.P.E scale				x		
Fatigue:	6	Modified fatigue scale (MFIS)		x				x
Depression	7	Hospital Anxiety and Depression Scale (HADs)		x				x
User satisfaction	8	Gagnon questionnaire score user Evaluation of Satisfaction with assistive technology (QUEST) score		x			x	
	9	Satisfaction Quebec user Evaluation of Satisfaction with assistive technology (QUEST)						x
Health-related quality of life	10	MSQoL 54 Health Survey	x					x
Mobility	11	Rivermead Mobility Index	x				x	
Disability	12	Expanded Disability Status Scale (EDSS) de Kurtzke	x				x	
Balance	13	Berg scale test	x				x	
Spasticity	14	Ashworth assess by physiotherapist at start of each training day	x				x	
	15	Pen spams scale	x		x		x	
IC, Informated consentiment; Patient-Reported Outcome Measures (PROMs), Clinic report, CRO;								

3.4.1 Schedule

Following completion of day 1 assessments, all subjects will be scheduled for the intervention phase of the study, each participant will receive 12 sessions of RAGT scheduled ideally for three times a week for 4 weeks. If a subject cancels a treatment session, it will be counted as missed session. If a subject misses three consecutive treatment sessions, they will be dropped from the study due to inconsistency in treatment carryover. Cancellations and changes in patient scheduling represents a true clinical environment and represents normal clinical patient management.

At the end of RAGT, a new exploration will be carried out to evaluate the initial parameters. A follow-up will be carried out 4 weeks after the rehabilitation protocol has ended.



3.5 Device

3.5.1 Description

Atalante is the first exoskeleton designed and developed by Wandercraft. Atalante is intended to perform ambulatory functions, mobility exercises and adapted physical exercises, hands-free for individuals having lower limb and trunk disability in rehabilitation centers, city cabinets or adapted physical exercise centers under the supervision of a trained operator.

The device is available with one unique model and allows for length mechanical adjustment of specific parts so that patients with different physical characteristics can undergo care sessions with the same unit of Atalante - after it has been adjusted to their own set of measurements.

Figure 1 shows the main parts of the device.

Figure 1: Atalante main parts

Atalante is an exoskeleton composed of:

- **Two operated legs** made up of articulated parts: thigh, leg, and foot. These parts can move thanks to 12 actuators comprised each of an electric motor, a position sensor (encoder), and a motor controller board to process related data. Figure 2 shows the location of each of the actuators. In addition, the thighs and legs are adjustable in length to allow adaptation to different patient morphologies. The lower structure is made of aluminium alloy, parts of which are covered by plastic shells.
- **A back**, made of composite material, which links the lower limbs together and supports the upper body of the patient.
- **A vest**, made of fabric, and equipped with an inertial sensor (IMU) to detect the intention of the patient inside the exoskeleton based on the motion of his chest. The vest is available in two sizes: small (S) and large (L).
- **Five additional inertial sensors** located in the back, legs and feet for orientation estimation of different parts of the exoskeleton.
- **Force sensors** placed in the feet for contact state estimation.
- An **embedded computing system** (Wanderbrain and Wanderneuron software) to retrieve data from all sensors and boards, and coordinate motion - determining commands for the actuator blocks.
- A **set of plastic wedges** to adapt to the patient morphology. The wedges compensate for a less than 16° dorsal flexion of the ankle and/or increase the distance between the patient's knee and Atalante's foot. They exist in 8 different sizes in terms of inclination (between 0 and 16°) and height and they are placed on Atalante's feet, if needed.
- A **battery system** consisting of two pluggable and rechargeable packs of Lithium-Ion cells enclosed in plastic casings and located each on the thighs.

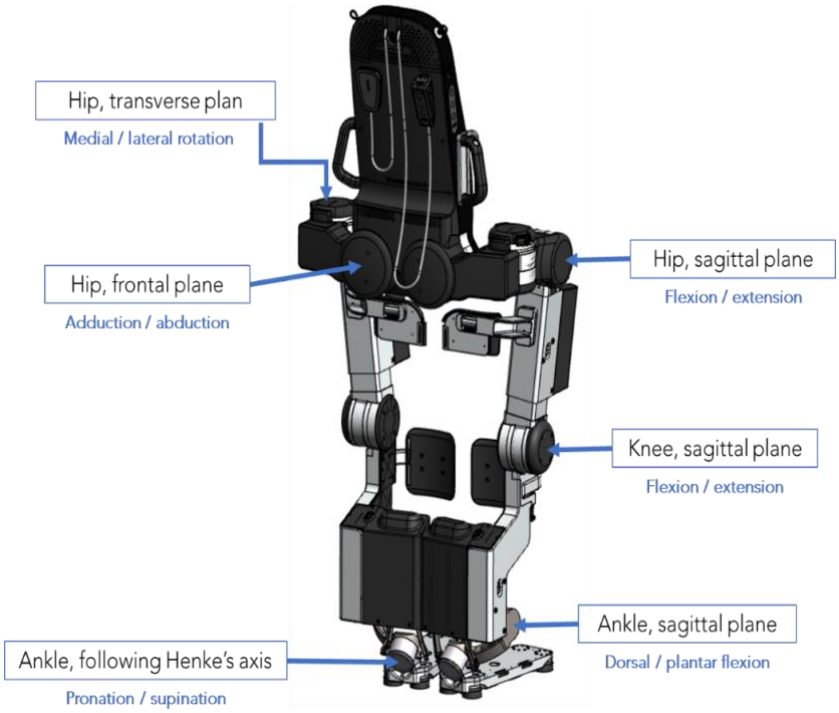


Figure 2: Atalante joints

The ranges of motion of the 12 joints are constrained by mechanical stops and supplemented by software stops to protect the patient's joints from exceeding motion limits. Atalante is attached to the patient in 3 locations per leg (thigh, leg, foot) plus at the abdomen level thanks to the vest's belt. These interfaces are made of rigid shells covered with foams and equipped with adjustable straps that maintain the patient and facilitate transmission of the system movements to the patient, all while ensuring their comfort. The rigid shells are located at the back of the patient's thigh and at the front of the leg.
Atalante is controlled (Figure 3) by its user thanks to:

- Sensors, especially a motion sensor (i.e., the IMU) placed on the back of the vest which triggers the movement.
- Two keyboards, one for the operator (physio controller) leading the care session and one remote intended for either the operator or optionally the patient.

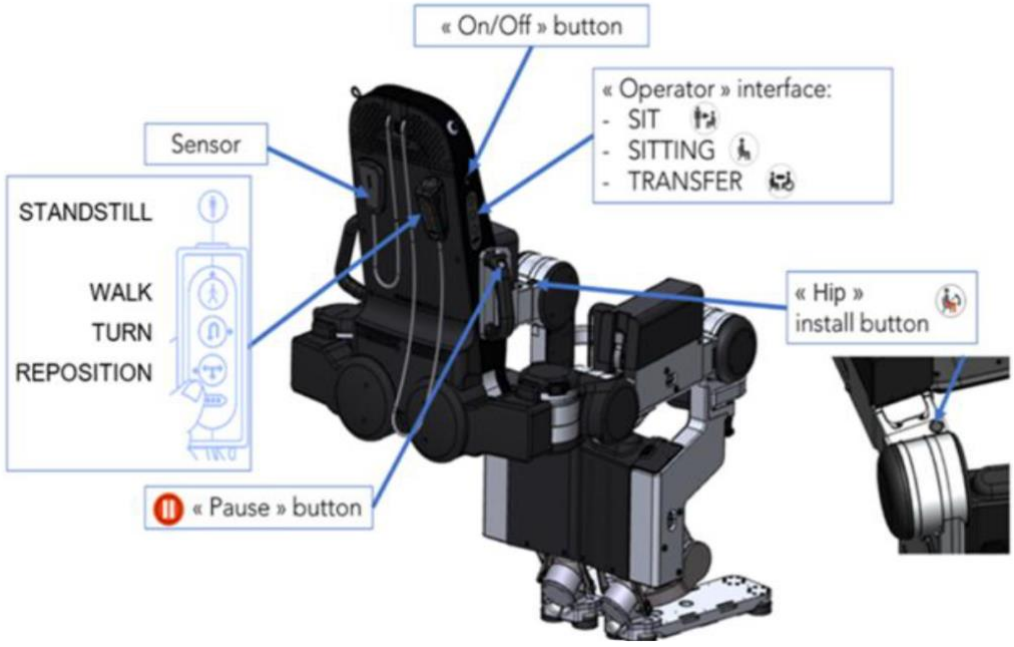


Figure 3: Control interface of Atalante

As Atalante is destined to be used in healthcare facilities, city cabinets or adapted physical exercise centers with several patients in a day, the angular amplitudes of each articulation have been designed to allow a broad range of patients to be included into the exoskeleton.
Furthermore, the device is equipped with mechanical adjustments allowing the length of the legs and the thighs to be regulated in the range 40-49 cm and 38-46 cm respectively, according to the dimensional measurements of the patients. The angular amplitudes of the 12 motorized articulations and the mechanical adjustment ranges are shown in the figure below.

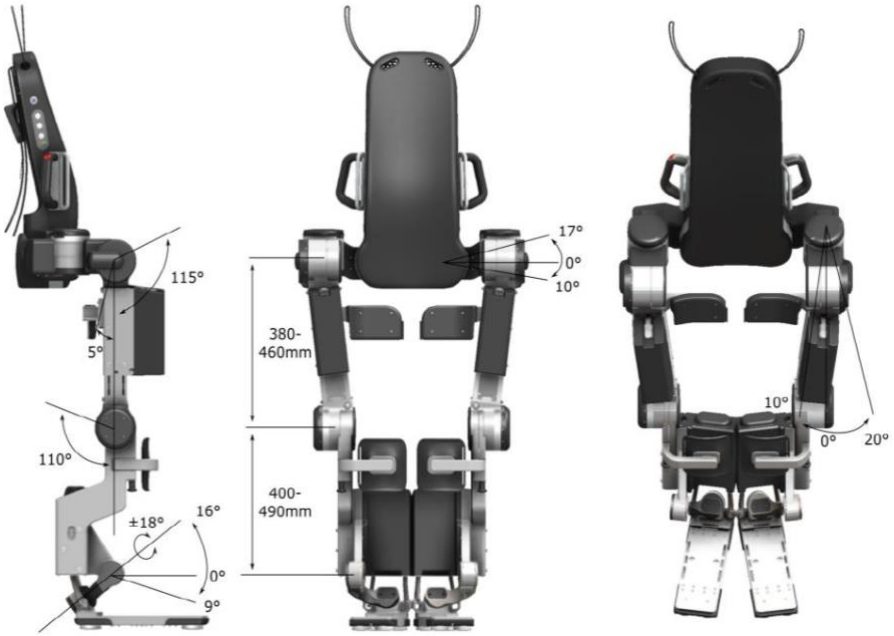


Figure 4: Angular amplitudes and mechanical adjustments of the V5 exoskeleton

Atalante exoskeleton is part of a system (Figure 5) composed of:

- **DataGen**: a dynamic adaptation of the algorithms is performed by a computation software running on a server called DataGen. It takes as input the patient measurements and computes a model of Atalante and the patient, as well as patient-specific trajectories for standing, sitting, walking, repositioning, and turning. All these outputs are transmitted to the exoskeleton.
- **AGUI (commercial name WanderTouch**): an application running on a portable device, called AGUI, offers a way to communicate with the exoskeleton using Bluetooth communication, as well as with DataGen using Wi-Fi. Data flows from AGUI to DataGen (patient measurements) and back from DataGen to AGUI to Atalante exoskeleton (algorithm outputs). AGUI also allows for real-time configuration and monitoring of a session, by fine tuning the gait pattern, and by selecting the level of assistance (ActiveGait) provided by Atalante to the patient while performing walking steps. Gait can be resistive (ActiveGait up to -25%), fully supported by the patient (ActiveGait 0%), assisted by Atalante at a chosen level per leg (ActiveGait up to 100%), or fully passive where Atalante provides all the necessary effort to perform the gait. Additional indicators are collected and available on AGUI per session and per patient.
- **Bluetooth dongle**: plugged in the back of Atalante and used to establish the communication between the AGUI and the exoskeleton.
- **Battery charger** for the removable battery packs that power the exoskeleton.
- **Dynamometric screwdriver** to adjust the thighs and legs.
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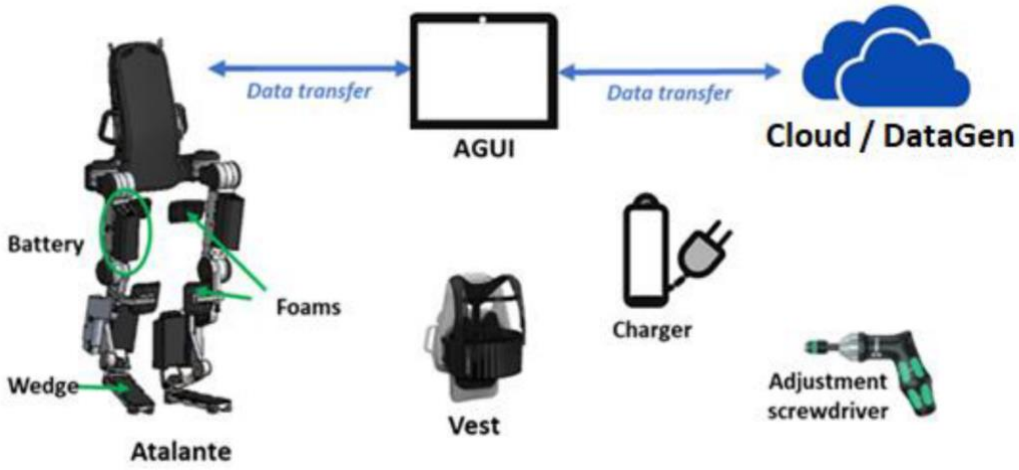

Figure 5: Atalante system

In addition, the Atalante system is used in combination with

- a seat with the following characteristics:
  - A minimal depth of 40 cm,
  - A minimal width of 65 cm,
  - A height in the range 40-55 cm,
  - Able to support at least 200 kg,
  - Be covered with a cushion.
- an electrical safety rail having the following characteristics:
  - Legally marketed medical device intended to support or lift people (compliance with ISO 10535 “Hoists for the Transfer of Disabled Persons - Requirements and Test Methods” standard or equivalent).
  - Stable and installed in accordance with the manufacturer instructions.
  - Able to support at least 200 kg.

The electrical safety rail and the seat are not distributed by Wandercraft. Only the swivel to link the safety rail to Atalante is provided with its protection. An example of safety rail without the protection is shown in Figure 6 below.

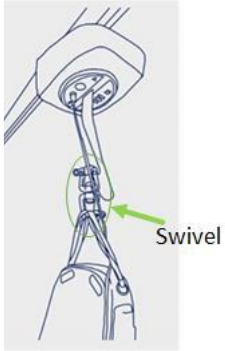

Figure 6: Atalante fixation to a safety rail without the protection

The exoskeleton is handled by the remote control, the “operator” interface located on the right-hand side of Atalante’s back and the sensor and an installation button located on Atalante's thighs at knee level at each side. The patient or the healthcare or the adapted physical activity professional select a mode or transition by pressing the relevant button. Then, the patient moves the bust; the sensor placed on the patient’s back detects the patient’s intention and trigger the movement.

The various modes and transitions are listed below:

- SITTING position: stable and comfortable sitting position.
- STANDING position: stable and comfortable standing position. The STANDING button also allows to switch to "exercise" mode, to stand up and to stop the motion.
- SITTING DOWN transition allows the patient to switch from standing up to sitting down.
- WALKING mode allows the patient to walk with Atalante.

- ROTATION mode allows the patient to turn with Atalante to the left or right.
- REPOSITION mode allows the patient to perform side and back steps with Atalante.
- INSTALLATION mode allows the patient to be transferred from his/her wheelchair to Atalante, or vice versa.

3.5.2 Regulatory approval

The Atalante system including its parts and accessories is considered as a Class IIa medical device following Rule 9, according to the annex VIII, according to the regulation (EU) 2017/745 and is covered by a EU certificate N° MDR 727 876 R000 issued by BSI on May 26th, 2021.

3.6 Intervention

The intervention will be delivered through the Neurorehabilitation Cemcat team.
Participants will receive a Atalante gait training, delivered 3 times per week, intensity 40 to 60 minutes, and duration over 4-weeks. Progression will occur by increasing the session intensity weekly. Training intensity will be monitored and standardized using the Borg Rating of Perceived Exertion scale, and will progress from 'fairly light' to 'somewhat hard'. This prescription is consistent and appropriate for individuals with MS with mobility impairment and low fitness levels. Progression will occur by increasing the intensity of the session increase the number of steps in each session and decrease the level of assistance. Sessions will not exceed 60 minutes. We will record all training parameters.

Atalante Gait training: Using the Atalante System, participants will be secured with the appropriate sized harness and attached to an overhead body-weight support system. Each session will begin with a 3–5 minute warm-up in the continuous passive mode (cadence ~40-45 steps/minute). The participant will then be transitioned into the adaptive training phase for practicing repetitive floor walking for up to 30 minutes. During this phase, the force produced by the robot is modulated to support the effort of the patient in producing a typical walking pattern.

4 Statistical considerations

The sample size calculation was based on the observed success rate (70%) in a previous evaluation of safety and performance of the self-balancing walking system Atalante in patients with spinal cord injury (i.e., 10 mWT with continuous walking mode)[15]
A sample size of 15 patients had been deemed necessary to demonstrate the performance with an alpha risk of 5% and a statistical power of 80% (Two-sided test).

Descriptive statistics (i.e., mean, standard deviation) will be calculated for quantitative data (demographics and clinical characteristics and outcome measures). Frequencies will be calculated for qualitative variables. For the proportions, binomial proportion confidences will be calculated using the Wilson formulae. Proportions will be compared using the Newcombe formulae
The Wilcoxon bilateral matched-pairs test will be used to compare repeated measurement on a single sample (mean, standard deviation).

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