Active Report

Title of the research project (in English):

A multicenter single-blind pilot study for evaluating the activity and the efficacy of ASSISTarmMS, an exoskeleton, on upper-limb related ADL in MS patient.

Titolo del progetto ricerca (in italiano):

Studio pilota multicentrico singolo cieco per valutare l'attività e l'efficacia dell'ASSISTarmMS (esoscheletro) sulle ADL correlate all'arto superiore in pazienti con SM.

Type and duration of Project

☐ 1 year - Research Project

☐ 2 years Research Project

☐ 3 years Research Project

☒ 1 year - Pilot Project

Multicentric Study

☒ Yes

☐ No

Name of applicant

First name: MARCO

Last name: CAIMMI

Funds awarded FISM Call 2018, Research Project 2018, € 29925.00

Summary of the original project (max 3000 characters)

An adequate upper-limb function is essential to interact with the environment. Upper-limb impairments can occur in patients with Multiple Sclerosis (MS) with different disorders involving hand sensation, strength, tactile sensibility, active range of motion, tremor, and difficulties in inter-joint coordination. These impairments lead to reduced manual dexterity and difficulties in carrying out Activities of Daily Living (ADLs). Nevertheless, much attention has focused on impaired mobility in MS, while upper-limb impairment is understudied (Kraft et al. 2014). Several pilot studies demonstrated the positive effect of robotic programs on upper-limb impairment reduction in MS. Specifically, the effectiveness of upper-limb weight- support seems to be promising as preliminary demonstrated in a rehabilitation program based on the use of an exoskeleton to assist patients during the execution of virtual tasks (Gijbels et al. 2011). The aim of this project is to preliminary verify on a group of 26 MS patients with a high level of upper-limb impairment whether an intervention based on the use of an exoskeleton (ASSISTarmMS), which supports the upper-limb weight allowing the execution of complex functional movements, could be beneficial for MS patients. The rehabilitative program is made of 12 sessions of 45 minutes (3 times a week for 4 weeks). At each session, patients will perform functional tasks involving reaching and manipulation of real objects, (e.g., bottles, jars, padlocks, keys, small containers, pegs, beads, coin slots) taken from typical activities of daily living. Bimanual tasks will also be considered. Once results would show the efficacy of the proposed intervention and the benefits of using ASSISTarmMS in MS, a randomized, double-blind control trial involving a larger group of patients will be done.

Summary of the research performed (max 3000 characters)

The researchers conducted the study following the protocol presented in the submitted project. However, they decided to re-evaluate the people who had not undergone the intervention 4 weeks after the previous evaluation to confirm that the possible gains in the treated group are not random but actually due to the intervention.

List of the participants involved in the project and their role
(max 2000 characters)

STIMA-CNR (coordinator)

Marco Caimmi (Eng, PI): coordination of the activities, analysis of the results, and reporting.

Matteo Malosio (Eng): in charge of ASSISTarmMS design and functioning.
Tito Dinon (Technician): in charge of ASSISTarmMS maintenaince

Alberto Mora (Eng): technical support during the intervention, data elaboration, data analysis

Department of Rehabilitation Mons. Luigi Novarese.

Claudio Solaro (MD): chief of the Department of Rehabilitation Mons. Luigi Novarese
Grange Erica (OT): patients recruitment, assessment and treatment
Di Giovanni Rachele (OT): patients recruitment, assessment and treatment

IRCCS Don Gnocchi Foundation

Davide Cattaneo (PT, PhD): head of "LaRiCE" Lab, in charge of the activities at the Don Gnocchi Foundation

Thomas Bowman (PT, MSc): patients recruitment, assessment and treatment

Alessandro Torchio (PT, Bsc): patients recruitment, assessment and treatment

Rachele Agazzi (PT, MSc): assessment, intervention, and analysis of the results

Clear explanation of the research performed underlying the most important results. Describe in detail the results of your research even when they are negative. Avoid inadequate repetitions (max 20.000characters)

For the sake of clearness, the material and methods are briefly reported.

Study design

Subjects were screened for pre-selection, assessed at T0 for selection for the study, submitted for the 4-week intervention, and, finally, re-evaluated at T1, just after the intervention. The immediate device ortotic effect and training effects were evaluated (see Figure below).

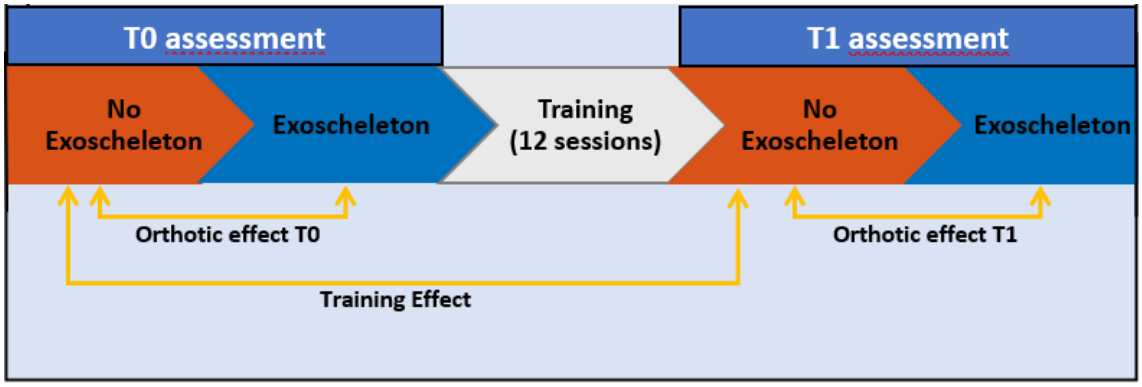

Figure. The study protocol, the orthotic effect, and the training effect

Screening

The databases of the two clinical centers were screened to pre-select PwMS for the study.

Subject assessment

Pre-selected subjects were clinically and instrumentally evaluated (Instrumented ARAT, Carpinella et al. 2014) at T0 to investigate whether ASSISTarmMS could be used and its immediate benefit (orthotic effect). Both arms were clinically evaluated to define the subject's clinical picture and find the most impaired arm. The most impaired arm was finally tested with the support of ASSISTarmMS.

The assessment consisted (both arms) in:

- Manual Ability Measure (MAM-36)

- Fatigue Severity Scale (FSS)

In addition, the following tests were performed with and without ASSISTarmMS (selected arm – most impaired):

- IstrumentedAction Research Arm Test (ARAT)

- Nine-Hole Peg Test (9HOLE)

- Box and Block test (BBT)

- BBT_fatigue

The last is a modified BBT test, designed to investigate patients on fatigue. The test lasts 180 sec, and the final score is the number of displaced blocks as in the original test.

PRIMARY OUTCOME MEASURES

- the orthotic effect is defined as:
Exo_Effect = T0_ARAT_WithExo - T0_ARAT_NoExo
to assess the immediate effect of the weight support provided by the exoskeleton;

- the Intervention effect is defined as:

INT_effect = T1_ARAT_NoExo – T0_ARAT_NoExo
to assess the efficacy of the intervention performed with ASSISTarmMS;

Intervention

Subjects having proper inclusion and exclusion criteria were assessesd at baseline. Those with orthotic effect at T0 ≥ -1 were further selected for the intervention or to be included in the preliminary control group (assessment with the device after 4 weeks without intervention)

It consisted of 12 sessions of 45 minutes (3 times a week for 4 weeks). At each session, subjects performed functional tasks involving reaching and manipulating actual objects (e.g., bottles, jars, locks, keys, small containers,

pegs, beads, coin slots) typical of daily life's mono and bimanual activities. Using the MAM-36 activities as a reference, each patient chose the activities of everyday life most suited to their interest to be exercised during the intervention. These activities were assessed at the beginning and the end of the 12 treatments, with and without exoskeletal support. The performance satisfaction was evaluated by a Visual Analog Scale (VAS).

Results

Elaboration and analysis of the data are in progress. In this report, the preliminary clinical assessment results are presented. Two cases are provided beside the group data results, which exemplify the group and result heterogeneity.

Considering the low number of participants and the explorative nature or the study, an alpha error lower than 0.1 was considered to be statistically significant (Ganesh 2018)

Group results

One hundred and seventeen (117) patients were screened for eligibility. Data are presented as mean (min value – max value).

Eighteen subjects (age 58 years (51÷82), 7 females) participated in the study. The group was highly heterogeneous: EDSS 7.3 (2.5 ÷ 8) points, ARAT: 27 (4 ÷ 50) points.

Eight people were tested at T0 but had no advantage in using ASSISTarmMS. according to the ARAT scores at baseline (*Exo_Effect=-6.9±6.2 points)*. The group was higly heterogeneus: EDSS 7 (4 ÷ 8) points, ARAT: 30.5 (4 ÷ 56) points, BBT 20.5 (7-44) blocks, BBT fatigue 31 (5-126) blocks, 9HPT 102 (28-300) seconds.

The other 10 people reported feeling an advantage in function from the ASSISTarmMS weight support. In this subgroup, the orthotic effect (the improvement in ARAT using ASSISTarmMS at T0) was statistically significant (*Exo_Effect= 4.1±4.3 points, p<0.02).* In the same group, the difference in BBT_fafigue (BBT test performed in 180s at T0) was statistically significant (*+6.8±8.1 blocks).* Figure 1 and Figure 2 show this group's ARAT and BBT fatigue with and without the exoskeleton, along with the interval of confidence and the statistics.

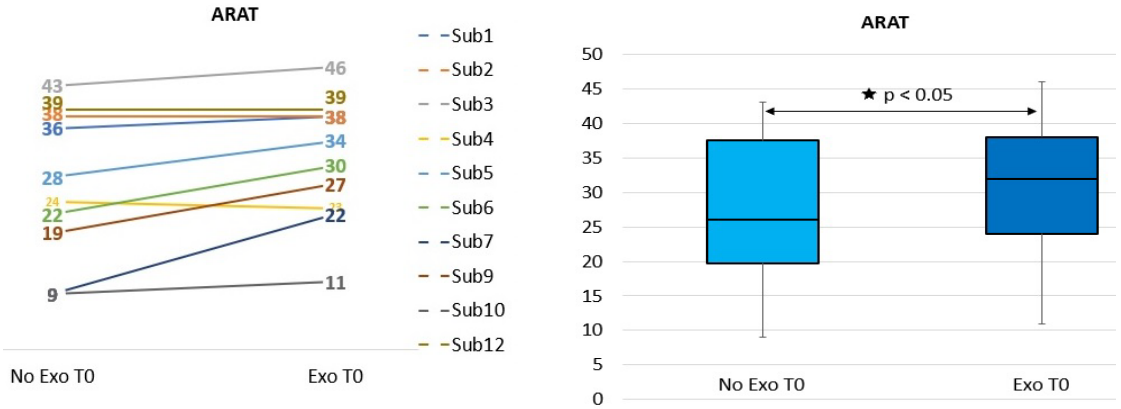

Figure 1 ARAT scores and statistics in the group of responders (orhotic effect group, 10 subs)

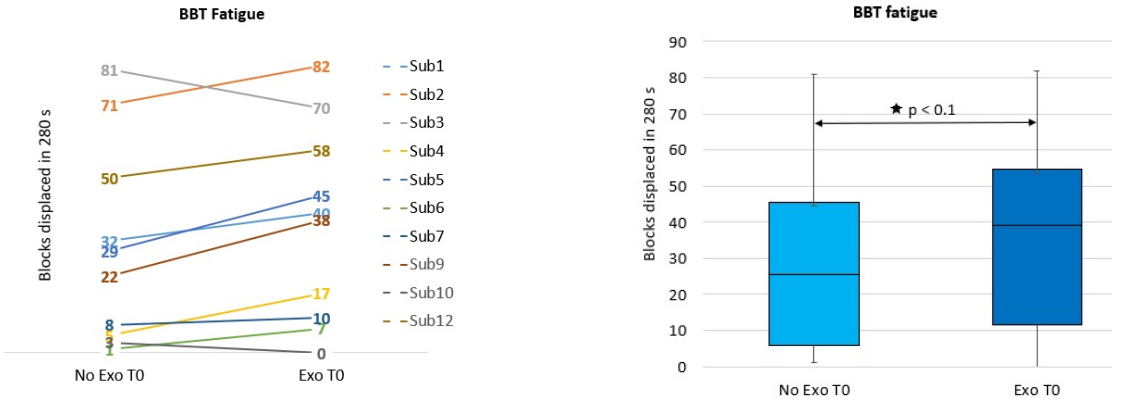

Figure 2 BBT fatigue scores and statistics in the group of responders (orhotic effect group, 10 subs)

Out of these 10 people responders to the orthotic effect at baseline, 7 accessed the four-week ASSISTarmMS intervention (12 sessions, 3 a week) while the others (3 subjects) were randomized as control with a 2:1 ratio. In the intervention subgroup, the orthotic and the treatment effect (the last defined as the ARAT improvement at T1 compaed to T0) were statistically significant. Figure 3 and Figure 4 show this group's ARAT and BBT fatigue with and without the exoskeleton at T0 and T1, along with the statistics.

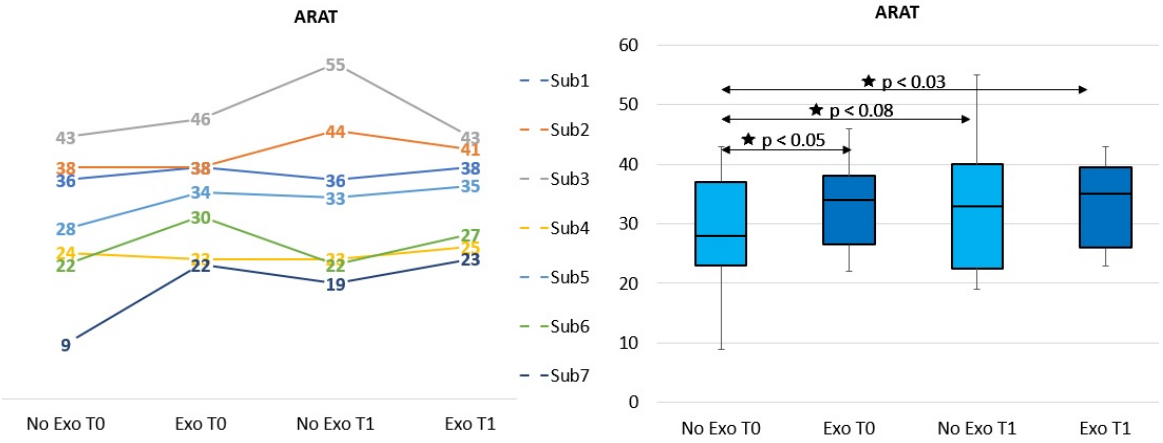

Figure 3 ARAT scores and statistics (intervention group, 7 subs) with and without ASSISTarmMS at T0 and T1

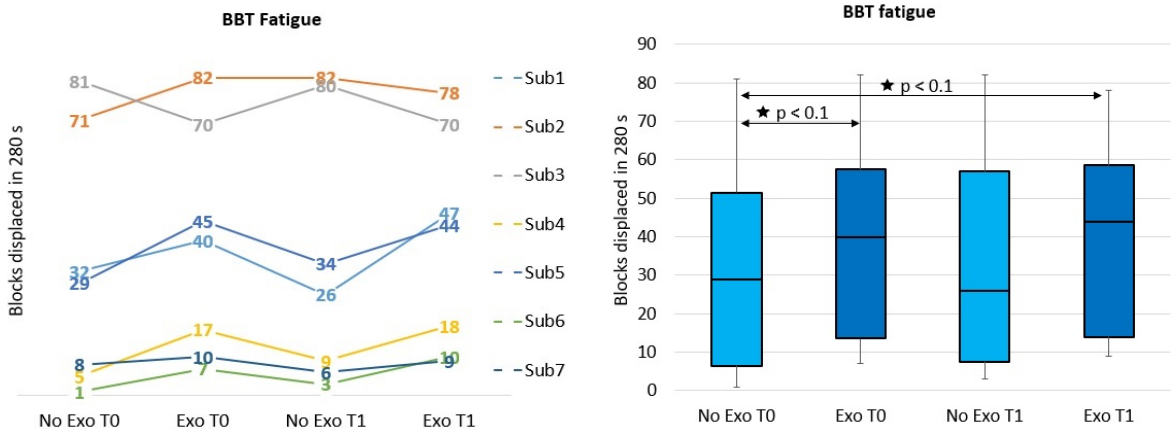

Figure 4 BBT fatigue scores and statistics (intervention group, 7 subs) with and without ASSISTarmMS at T0 and T1

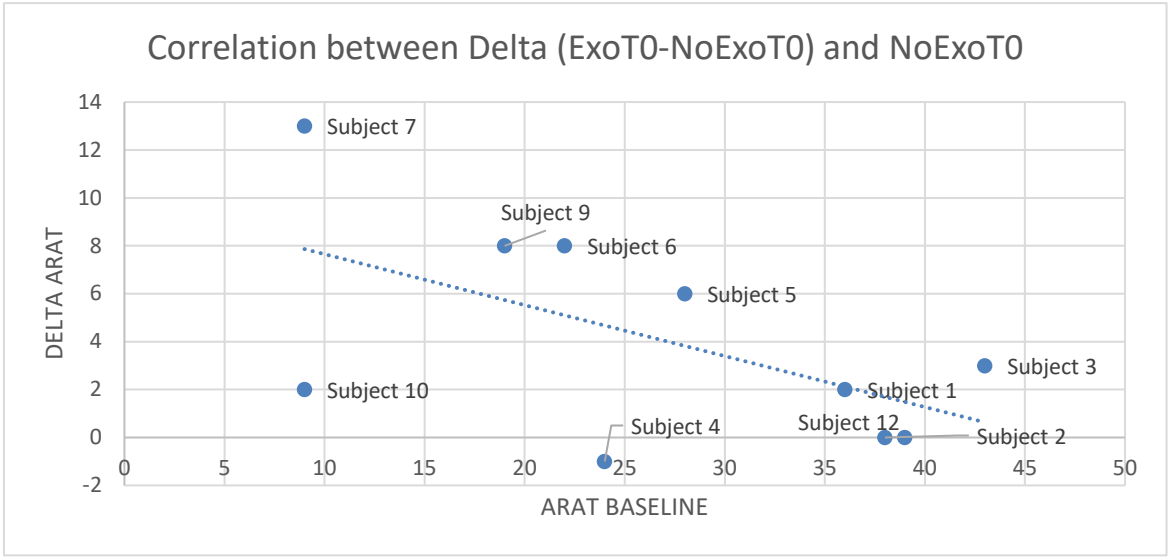

Figure 5 Correlation between Delta (ExoT0-NoExoT0) and No Exo T0

Spearm correlation= -0,57; $p < 0.05$

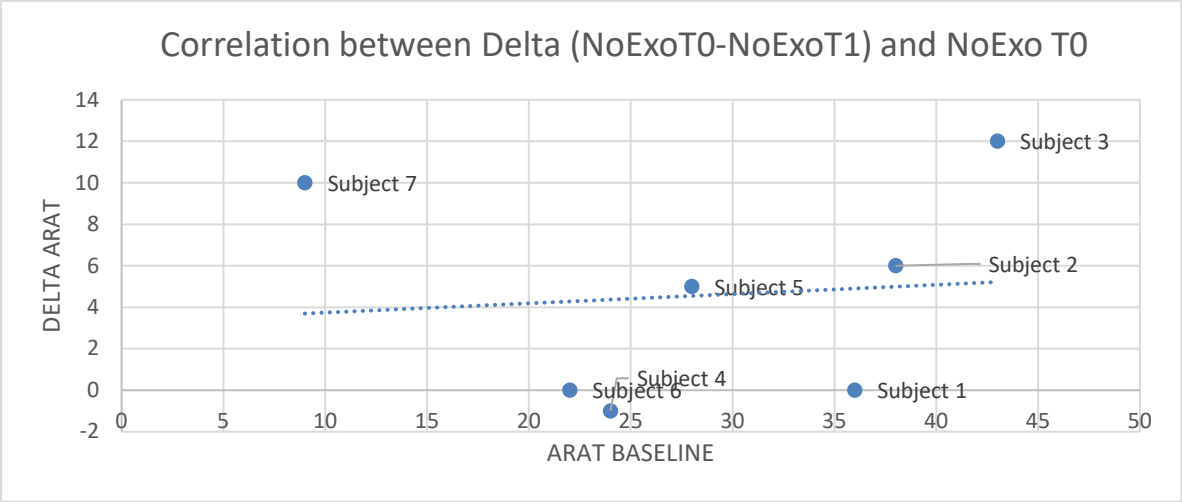

Figure 5 Correlation between delta ARAT and ARAT at baseline

Spearm correlation= 0,34; p = 0.46

Control group results:

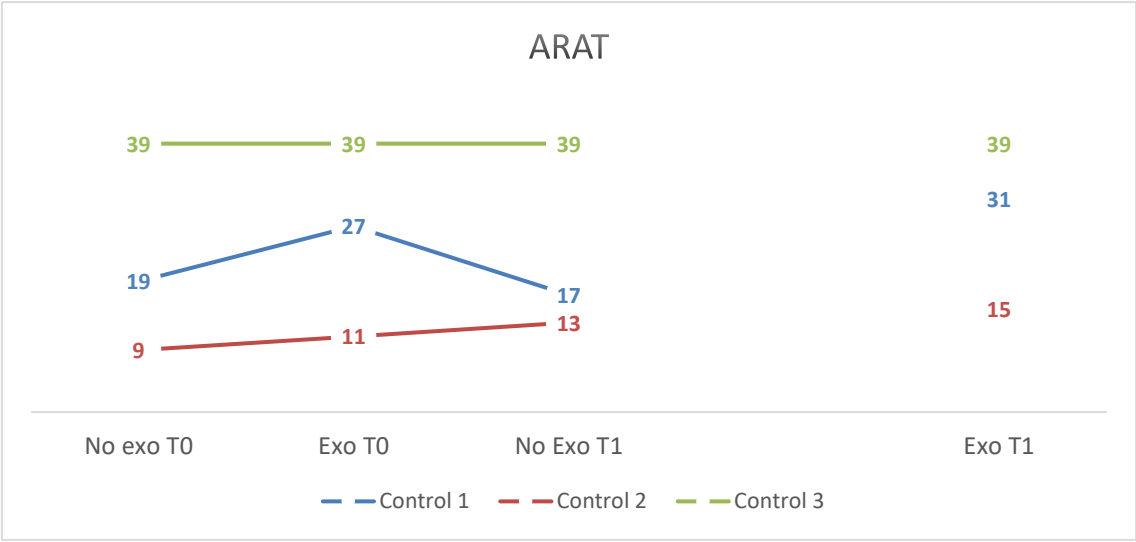

Figure 6ARAT scores and statistics (control group, 3 subs) with and without ASSISTarmMS at T0 and T1

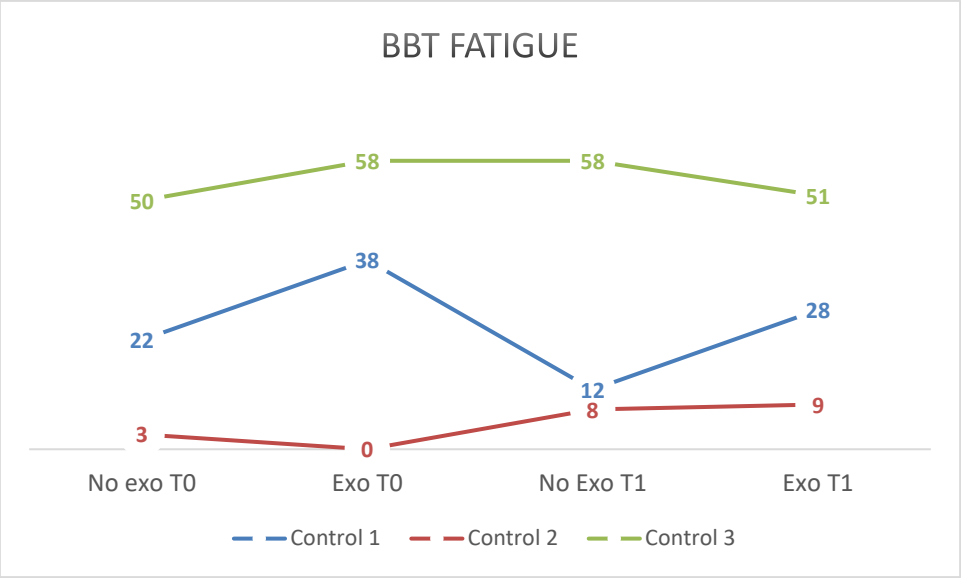

Figure 7 BBT fatigue scores and statistics (control group, 3 subs) with and without ASSISTarmMS at T0 and T1

For example, we further report two single cases showing two typical behaviors, the one demonstrating the orthotic effect and the other the treatment effect.

Subject 1 female, 65-year old, 30 years from the disease onset.

She is in a wheelchair, still able to make simple transfers, although with difficulty. She still leads an active life. Regarding the upper limb, she has a tremor, proximal muscle fatigue, impaired proximal force, and reasonable control of the hand and fingers (EDSS=7.5/10; MAM36=78/144; FSS=56/63; SDMT=17/110).

Orthotic effect

No *vs.* with ASSISTarmMS at T0: BBT_fatigue from 32 to 40 blocks (+8, +25%); ARAT from 36 to 38 points (+2, +6%);

No *vs* with ASSISTarmMS at T1: BBT_fatigue from 26 to 47 blocks (+21, +81%); ARAT from 36 to 38 points (+2, +6%).

Effect of training

BBT 15 to 18 blocks (+3, +20%); BBT_fatigue 32 to 26 blocks (-6, -19%); 9HPT from 259 to 201 secs (-58sec -22%); ARAT from 36 to 36 points (+0, +0%).

The selected task was "write sentences": 1-point improvement at the VAS, from 2 points at T0 to 3 points at T1.

Write sentences (No *vs*. with ASSISTarmMS at T0): 4-point improvement, from 2 to 6;

Write sentences (No *vs*. with ASSISTarmMS at T1): 4-point improvement, from 3 to 7.

Subject 3, male, 50-year old, 11 years from the disease onset.

He can walk and drive and leads a fully active life. He has an impaired left dominant upper limb: impaired proximal force and adequate control of the hand and fingers (EDSS=2.5/10; MAM36=104/144; FSS=25/63; SDMT=58/?).

Orthotic effect

No vs with ASSISTarmMS at T0: BBT_fatigue from 81 to 70 blocks (-11, -14%); ARAT from 43 to 46 points (+3, +7%);

No vs with ASSISTarmMS at T1: BBT_fatigue from 80 to 70 points (-10, -14%); ARAT from 55 to 43 points (-12, 22%).

Effect of training

BBT 30 to 36 blocks (+6, +20%); BBT_fatigue 71 to 82 blocks (11, 15%); 9HPT from 75 to 62 secs (-13sec -17%); ARAT from 43 to 55 points (+12, +28%).

The selected task is "twist a towel": 1-point improvement at the VAS, from 5 points at T0 to 6 points at T1.

Twist a towel (No *vs.* with ASSISTarmMS at T0): 1-point improvement, from 5 to 6;

Twist a towel (No *vs.* with ASSISTarmMS at T1): 2-point improvement, from 6 to 8.

Discussion

The main study results report a double possible effect of ASSISTarmMS on the selected subjects' performance: an immediate effect, a kind of orthotic assistance (orthotic effect), which enables the subjects to perform tasks better and for a longer time when using the exoskeleton if compared with performing the same tasks without any assistance; a midterm effect, which is due to the training with the exoskeleton, which enables the subject to perform tasks, without ASSISTarmMS, better and for a longer time after the four-week intervention as compared to before the intervention (treatment effect). In general, not all the subjects recruited after the screening showed positive effects using the device at baseline, but the subjects who showed improvements already in the baseline session (orthotic effect) generally had also good results from the training

The improvements concern both the subjects' functional ability and dexterity and the reduced fatigue. The preliminary results show that the orthotic effect is more evident in the more impaired subjects (Figure 5:*e.g.,* subject 7), while, by contrast, there is trend, not statistically significant, that shows that the less impaired ones could benefit more from the intervention (e.g., subject 3) compared to the more impaired ones; in these subjects, who are still capable of using the arm in ADLs, the use of the exoskeleton may even worsen their performance. This result is not strange as ASSISTarmMS, like all exoskeletons, may hinder some movements and make the execution of some tasks slower, especially when the subject shows muscle weakness and fatigue. However, even in these subjects, the exoskeleton allows for longer upper-limb training sessions, which could not be performed for such a time without assistance.

The patient's selection is a crucial point to discuss; results showed that many subjects (8 out of 18) did not benefit from the use of ASSISTarmMS at the first assessment. Interestingly the group is highly heterogeneous, and it includes both the least and the most impaired subjects for the ARAT test.

Different reasons can account for this result.

We already discussed the case of highly functioning subjects who are still able to perform upper-limb ADLs in this phase. In these subjects, if ASSISTarmMS is not perfectly fitted, the advantage provided by the support for the arm weight is not worth the disadvantages of the movent hindrance. It should be investigated which is the limit where, in these subjects, ASSISTarmMS could allow for longer interventions focused on complex task requiring hand dexterity.

In the case of the most impaired subjects, the inability to use the hand could have affected the exoskeleton efficacy. In fact, even if the subjects could raise their arm and reach for objects, they were totally unable to fulfill most of the tasks. Proximal arm functionality is a prerequisite for hand use but is insufficient to drive functional hand use and improvement. ASSISTarmMS should be used jointly with hand functional assistance (e.g., provided by functional electrical stimulation) in these patients.

A third cause that could have limited the use of ASSISTarmMS, is the still low usability of the exoskeleton. Setup times are still too long and do not comply with the routine use of the system in a clinical setting. For instance, the time is too long to set up the system to be used on the contralateral arm (e.g., when you have to train a person's left arm after it has been used on the right arm). In addition, tests highlighted the difficulty of fitting the exoskeleton on small people with short and thin arms. A newly redesigned version of the system is needed before performing further studies.

Finally, the training and ability to use the ASSISTarmMS of the occupation and physical therapist play a significant role. The therapists who used the system the most could often overcome some of the fitting issues of the system.

In conclusion, attention must be paid to the patients' selection; some criteria were defined to select the patients who can benefit from ASSISTarmMS. Results are promising in selected PwMS, indicating an immediate orthotic effect, which enables to (better) perform complex 3D ADLs tasks for a longer time. Results also show that the intervention effect seems to be more evident in the less impaired PwMS. Considering recent findings on the importance of exercise in reducing inflammation in PwMS (Yuksel et al. 2022), it would be important to investigate in a more extensive study the efficacy of training with ASSISTarmMS. Anyway, before starting a new trial, a redesign of the system to improve fitting and reduce setup times must be considered in the future.

For the multicentric projects, clearly state the contribution of each collaborating center (max 6.000 characters)

STIMA-CNR (coordinator)

The role of STIIMA is to coordinate all activities.
As the owner of ASSISTarmMS, STIIMA-CNR is in charge of the functioning and maintenance of the exoskeleton, and technical support during the tests of the exoskeleton on the patinets.
STIIMA-CNR also participates in the elaboration and analysis of the data.

Department of Rehabilitation Mons. Luigi Novarese.

The role of Department of Rehabilitation Mons. Luigi Novarese is to recruit, assess and provide the treatment with the ASSISTarmMS in the MS population.

12 subjects with MS took part in the preliminary phase of assessing the usability of the ASSISTarmMS.

Eghty-five subjects have been screened for proximal and distal upper limb impairment, and 9 have been recruited and performed the baseline assessment.

The team also participates in the elaboration and analysis of the data

IRCCS Don Gnocchi Foundation

The role of IRCCS Don Gnocchi Foundation is to recruit, assess and provide the treatment with the ASSISTarmMS in the MS population.

Up to now, 32 patients have been screened, 13 have been recruited, 7 completed the study with the intervention, 6 have been recruited in the control group, 3 were assessed at T0 and T1, and 3 at T0.

The team also participates in the elaboration and analysis of the data

List of all peer-reviewed scientific publications, conference abstracts and invited lectureships. Include in preparation, in press and already submitted publications. Mention only publications that acknowledge FISM contribution including grant number. The bibliography must include a full title, a list of all authors, pages, and year of publication (max 10.000 characters)

Preliminary results of the project have already been presented in a Bachelor's degree thesis. Results were also presented to the FISM meeting, Rome 2021.

- *Rachele Agazzi. Utilizzo di un esoscheletro per il trattamento dell'arto superiore in soggetti con Sclerosi Multipla. Bachelor's thesis. Relatore: Davide Cattaneo, anno accademico 2020/2021, Corso di laurea: Fisioterapia*
- *Bowman T, Agazzi R, Carpinella I, Torchio A,Di Giovanni R, Grange E, Dinon T, Malosio M, Cattaneo D, Solaro C, Caimmi M, The orthotic and rehabilitative effect of an exoskeletal device on upper limb function and daily living activities in people with Multiple Sclerosis"; in preparation.*

List all patent applications submitted and granted

- IT1401979B1
- US8801639B2
- WO2012042471A1
- EP2621448A1