AWARD NUMBER: W81XWH-15-2-0068

TITLE: Ambulatory and Non-Ambulatory Benefits of Lower Limb Exoskeleton Use, with and without FES, in Clinical and Community Settings

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REPORT DATE: February 2021

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
February 2021	Final	30Sep2015-29Sep2020

4. TITLE AND SUBTITLE

Ambulatory and Non-Ambulatory Benefits of Lower Limb Exoskeleton Use, with and without FES, in Clinical and Community Settings

5a. CONTRACT NUMBER W81XWH-15-2-0068

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This research investigates the extent to which regular walking in an exoskeleton will provide mobility, health, and recovery benefits to individuals with spinal cord injury. The research was proposed as a series of three sub-studies. The first investigates prospective benefits while walking in an exoskeleton; the second investigates prospective additional benefits when the exoskeleton is supplement with lower limb functional electrical stimulation; and the third investigates prospective benefits during home and community use. At the conclusion of this project, the first and second studies have been completed, with respective final enrollments of 21 and 14, respectively. The third study was approved by the lead IRB, and was expected to enroll 3 participants, but the project ran out of time and funding before the third study could be initiated. Results from study 1 indicate promising benefits resulting from regular exoskeletal use. Results from study 2, which is basically the same as study 1 with supplemental FES, appear similar to those of study 1, perhaps indicating that, for the population involved here, supplementing an exoskeleton with FES may not have substantial benefits beyond those associated with using the exoskeleton without FES.

15. SUBJECT TERMS

spinal cord injury, paraplegia, exoskeleton, physical medicine and rehabilitation, rehabilitation research, legged mobility, neuromuscular impairment, neural and functional recovery

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT Unclassified	**b. ABSTRACT** Unclassified	**c. THIS PAGE** Unclassified	Unclassified	66	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION:

This research investigated the extent to which regular walking in an exoskeleton provides mobility, health, and recovery benefits to individuals with spinal cord injury. The research was proposed as three sub-studies. The first investigated prospective benefits while walking in an exoskeleton; the second investigated prospective additional benefits when the exoskeleton is supplemented with lower limb functional electrical stimulation; and the third was intended to investigate prospective benefits during home and community use. The research was conducted at three sites – Vanderbilt Medical Center, Mayo Clinic, and the Tampa VA – each of which conducted the same study protocol. The first two studies, each of which were conducted in a clinical setting, were completed at enrollments of 21 and 14 subjects, respectively. The third study was intended to enroll 3 subjects total (1 per study site), but was not started due to various delays in the study, including several approval delays, and also delays associated with COVID-19 mitigation.

2. KEYWORDS:

spinal cord injury; paraplegia; exoskeleton; physical medicine and rehabilitation; rehabilitation research; legged mobility; neuromuscular impairment; neural and functional recovery

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The following narrative provides a description of progress:

This research entailed three sub-studies. Studies 1 and 2 were the core investigations of the research. Study 1 investigated the potential health benefits of regular walking in an exoskeleton, while Study 2 investigated the potential added benefits of regular exoskeleton walking with supplement functional electrical stimulation (FES). Each of Studies 1 and 2 were originally intended to enrolled 24 subjects, each of whom walks for 24 walking sessions over an 8-week treatment period. Study 3 was intended as a follow-on exploratory pilot study originally involving 6 subjects, intended to inform the potential utility of an exoskeleton in the home and community, and to examine the potential health and mobility benefits associated with exoskeleton use in the home and community over a two-month usage period. Studies 1 and 2 were completed, although Study 1 at a somewhat lower enrollment than originally proposed, and Study 2 at a lower enrollment than originally proposed (mostly since the Tampa site was unable to complete Study 2 participants). Study 3 was not started, due to various delays incurred during the period of performance.

The following table outlines the major tasks there were scheduled to start and be in progress during previous reporting periods:

Task/Milestone	Description	Target Completion Date/Quarter	Status
Major Task 1	Finalize Protocol and Obtain IRB/HRPO Approval for Study 1	Apr 2016 or Y1Q3	COMPLETED
Major Task 2	Conduct Study 1	Jan 2018 or Y3Q2	COMPLETED (final enrollment of 21, relative to originally proposed enrollment of 24)
Major Task 3	Finalize Protocol and Obtain IRB/HRPO Approval for Study 2	Jan 2018 or Y3Q2	COMPLETED
Major Task 4	Conduct Study 2	Jan 2019 or Y4Q2	COMPLETED (final enrollment of 14, relative to originally proposed enrollment of 24)
Major Task 5	Finalize Protocol and Obtain IRB/HRPO Approval for Study 3	Jan 2019 or Y4Q2	COMPLETED
Major Task 6	Conduct Study 3	Sept 2019 or Y4Q4	NOT COMPLETED (ran out of time and resources to complete)

What was accomplished under these goals?

- Major activities:
  - Study 1 protocol drafted and approved
  - Study 1 conducted and completed
  - Study 1 data analysis conducted and paper drafted
  - Study 1 protocol drafted and approved
  - Study 2 conducted and completed
  - Study 2 data analysis conducted and paper drafted
  - Study 3 protocol drafted and approved

- Significant results or key outcomes:
  - Study 1 has been completed. See attached paper draft for Study 1 results. Facilitation of functional recovery for the n=7 poorly-ambulatory (PA) participants, in aggregate, between the baseline and treatment-end time points, participants improved mobility in all five mobility measures. The changes included a 17% median improvement in the 10MWT, corresponding to an increase in walking speed from 0.22 m/s at baseline to 0.26 m/s at treatment-end; a 19% improvement in TUG test time; 14% improvement in 6MWT; 20% improvement in FIM-G score; and 30% improvement in WISCI-II score. Further, these improvements generally persisted two months following the walking intervention. The average time-since-injury for the n=7 PA participants was 5.0 years and median was 6.1 years, so in aggregate participants were well within a chronic classification. As such, the treatment of exoskeletal walking appears to have had a consistent effect in improving mobility among PA participants, with a number of limitations as follows.
  - Study 2 has been completed. See attached paper draft for Study 2 results. Study 2 results were similar to those of Study 1, indicating that supplemental FES may not have additional benefits for this patient population beyond those of exoskeletal walking without FES.

What opportunities for training and professional development has the project provided?

Clinical staff at all study sites attended an initial 3-day course, and subsequently attend another 2-day course, and obtained training and certification to use exoskeletons with FES in clinical practice.

How were the results disseminated to communities of interest?

The results of Study 1 have been analyzed and drafted into a paper for publication. The paper is co-authored between the three institutions, and is currently in final stages of inter-institutional review prior to submission for publication. The results of Study 2 have also been analyzed and drafted into a paper for publication. That paper will undergo inter-institutional review following submission of the Study 1 manuscript.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Facilitation of functional recovery
For the n=7 poorly-ambulatory (PA) participants, in aggregate, between the baseline and treatment-end time points, participants improved mobility in all five mobility measures. The changes included a 17% median improvement in the 10MWT, corresponding to an increase in walking speed from 0.22 m/s at baseline to 0.26 m/s at treatment-end; a 19% improvement in TUG test time; 14% improvement in 6MWT; 20% improvement in FIM-G score; and 30% improvement in WISCI-II score. Further, these improvements generally persisted two months following the walking intervention. The average time-since-injury for the n=7 PA participants was 5.0 years and median was 6.1 years, so in aggregate participants were well within a chronic classification. As such, the treatment of exoskeletal walking appears to have had a consistent effect in improving mobility among PA participants, with a number of limitations as follows.

Effects on secondary health issues
Of the five secondary health issues examined in the study, 24% of participants indicated changes in pain during the study; 29% indicated changes in spasticity; 33% indicated changes in bowel habits; 33% changes in bladder habits; and 52% changes in mood. In aggregate, the median rating of all five secondary health issues for these participants at baseline was zero; namely, they indicated “no change” over the preceding month in the respective secondary health issue at the baseline measurement (i.e., at the study start). In aggregate, the median rating of all five secondary health issues for these participants at treatment-end changed by 1.2 points in a direction of improvement, where 3 is the maximum possible change. Namely, for pain and spasticity, participants indicated a decrease of one point (i.e., 1/3 of the maximum rating) over the preceding month; for bowel habits, participants indicated an increase in two points (i.e., 2/3 of the maximum rating); and in bladder habits and mood, participants indicated an increase of one point (i.e., 1/3 of the maximum rating). Thus, for individuals who indicated some change in a second health issue, the treatment of exoskeletal walking in aggregate had a uniformly beneficial effect on all respective secondary healthy issues. On average, 34% of participants responded to any given secondary health issue, and in aggregate, each issue was improved by 40% of the maximum possible improvement. The results for effects on bowel and bladder habits exceed a 5% confidence level, while p-values for other measures provide lower confidence of the differences in medians. These improvements washed out at the two-month follow-up measurement, indicating the putative benefits are associated with continuing use of the exoskeleton.

Subjective comments

In the questionnaire, participants were asked to elaborate on changes observed for each secondary health issue, if changes had occurred. Specifically, participants were asked "If your overall level of [pain/spasticity] over the past month has changed, please elaborate," or "If you have noticed changes in your [bowel habits/bladder habits/mood] over the past month, please elaborate." Subjective comments from participants in answer to these questions support the quantitative measures presented above. Specifically, with respect to pain, all comments indicated a decrease in pain, while no comments indicated an increase. Representative comments, each from a different participant, include: "Pain has stopped due to standing more and straight up"; "My lower back feels like it has loosened up since walking in the exoskeleton"; "My overall level of pain has decreased extremely due to exoskeleton use"; and "In the past month my pain has not been as intense as usual." With regard to spasticity, as the low statistical confidence indicates, subjective comments were less uniform, with 4/6 comments indicating a decrease in spasticity and 2/6 indicating an increase. Representative comments reporting a decrease in spasticity include "My tone has decrease noticeably in both knees"; "It has decreased extremely due to daily use of the exoskeleton"; "Sessions have decreased spasticity"; and "Not as much as before." Comments reporting an increase in spasticity include "In the past month my right leg has had a little more spasticity than usual" and "The more I do the more spastic the legs can be." Subjective comments regarding bowel habits, bladder habits, and mood were uniformly positive (i.e., no negative comments were recorded by participants). Representative comments regarding changes in bowel habits, each from a different participant, include: "Going BM everyday where before it was 3-4 days"; "I have been going more easily and more frequently"; "It seems that the increased movement has helped me have a more consistent bowel movement"; and "I am now having sensations prior to bowel movement. These sensations are providing me adequate time to use the restroom." Representative comments regarding changes in bladder habits, each from a different participant, include: "Less bladder accidents"; "I don't have any accidents. My bladder is holding longer and throughout the night"; "I have been able to feel more often when I need to empty my bladder"; " I now have sensations that provide a warning for urination"; and "Better, feel like it's really trying to come back." Finally, representative comments regarding changes in mood, each from a different participant, include: "I have been in a better mood overall physically and mentally"; "While i have been able to do [walking] therapy, it just makes me feel better and be happy"; "I have felt physically and mentally stronger, more motivated"; "Love walking"; and "My emotional and mental health in general has significantly improved. I looked forward to being in exoskeleton. Self-esteem and confidence went up. Felt better about being in social situations."

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Due to delays associated initially with study approval and subsequently with COVID-1, Study 3 was not conducted as originally proposed.

Actual or anticipated problems or delays and actions or plans to resolve them

Study 1 and 2 approval took longer than expected, after which the study schedule was well behind the original schedule. Once approvals were obtained, the studies proceeded well, with few problems relative to expectations (i.e., occasional minor equipment problems, and some subjects who had to withdraw due to non-study-related issues). Although all sites were able to complete Study 1 participants, the Tampa VA ran out of resources before they could complete any Study 2 participants. As such, while we completed 21 participants across all sites for Study 1 (8 at Mayo, 7 at Vanderbilt, and 6 from Tampa), due to excessive approval delays, Tampa was unable to complete any for Study 2. Further, one Vanderbilt Study 2 participant and two Tampa Study 2 participants had to withdraw as a result of study restrictions associated with COVID-19. Therefore, final completed enrollment for Study 2 was 14 participants – 8 at Mayo and 6 at Vanderbilt. Finally, we were unable to proceed with Study 3, due to a lack of remaining time and budgetary resources.

Changes that had a significant impact on expenditures

None significant. We were able to stretch our funds to last about 6 months longer than the originally proposed period, but at that point ran out of funds to continue the study.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

None to report.

Significant changes in use or care of vertebrate animals.

None to report.

Significant changes in use of biohazards and/or select agents

None to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

None yet to report. Two papers have been drafted, but remain in circulation within project personnel. The first paper is undergoing minor revisions, and should be submitted soon. The second paper was recently drafted, and will go through a revisions process before being submitted.

Books or other non-periodical, one-time publications.

None yet to report.

Other publications, conference papers, and presentations.

None yet to report.

- **Website(s) or other Internet site(s)**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

None yet to report.

- **Inventions, patent applications, and/or licenses**

  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

1. Goldfarb, M., Martinez-Guerra, A., and Lawson, B. A CONTROL METHOD FOR A ROBOTIC SYSTEM. Non-provisional patent no. PCT/US2019/030048. Filed 4/30/2018. Pending.
2. Ekelem, A. and Goldfarb, M. ELECTRICAL STIMULATION SYSTEM AND METHODS FOR LIMB CONTROL. Non-provisional patent no. PCT/US2019/017531. Filed 2/11/2019. Pending.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

None yet to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

None yet to report.

- **Technologies or techniques**

None yet to report.

- **Inventions, patent applications, and/or licenses**

None yet to report.

- **Other Products**

None yet to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Dr. Michael Goldfarb
Project Role: PI, Vanderbilt lead researcher
Researcher Identifier: ORCID ID 0000-0002-6622-095X
Nearest person month worked: 3
Contribution to Project: Dr. Goldfarb is coordinating the research effort.

Name: Ms. Sheri Dixon
Project Role: Vanderbilt study coordinator
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Ms. Dixon is the Vanderbilt study coordinator, has been assembling IRB and HRPO applications for Vanderbilt and all sites, has set up the REDCap database, and the overall project (i.e., multi-site) study coordinator.

Name: Ms. Christina Durrough
Project Role: Vanderbilt lead physical therapist
Researcher Identifier: n/a
Nearest person month worked: 3
Contribution to Project: Ms. Durrough has been assisting with design and assembly of the protocol and data recording notebooks, and is responsible for exoskeleton use and oversight.

Name: Dr. Kristin Zhao
Project Role: Mayo lead researcher
Researcher Identifier: ORCID ID 0000-0001-7598-8197
Nearest person month worked: 2
Contribution to Project: Dr. Zhao is leading the research effort at the Mayo Clinic.

Name: Ms. Megan Gill
Project Role: Mayo Clinic lead physical therapist
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Ms. Gill has been administering the study protocol on the two subject currently enrolled at Mayo.

Name: Mr. Tyson Scrabeck
Project Role: Mayo study coordinator
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Mr. Scrabeck has authored and assembled IRB and HRPO applications for the Mayo site.

Name: Mr. Daniel Veith
Project Role: PT
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to Project: Mr. Veith oversees treatment for some subjects.

Name: Mr. Michael Boyd
Project Role: PT assistant
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to Project: Mr. Boyd oversees treatment for some subjects.

Name: Dr. Walter Kremers
Project Role: Statistician
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Dr. Kremers is the study statistician.

Name: Mr. Zachary Pohlkamp
Project Role: PT assistant
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Mr. Pohlkamp oversees treatment for some subjects.

Name: Dr. Sam Phillips
Project Role: Tampa VA lead researcher
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Dr. Phillips leading the research effort at the Tampa VA.

Name: Mrs. Padmaja Ramaiah
Project Role: Tampa VA study coordinator
Researcher Identifier: n/a
Nearest person month worked: 1
Contribution to Project: Mrs. Ramaiah has authored and assembled IRB and HRPO applications for the Tampa site.

Name: Mrs. Anita Ramrattan
Project Role: PT
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to Project: Mrs. Ramrattan is the lead PT at Tampa.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There has been no significant net change in active support for the study PI or co-PIs.

What other organizations were involved as partners?

Organization Name: Mayo Clinic
Location of Organization: Rochester MN
Partner's contribution to the project (identify one or more)

- Collaboration: Mayo is one of the three study sites conducting the study protocol.

Organization Name: Tampa VA
Location of Organization: Tampa Bay FL
Partner's contribution to the project (identify one or more)

- Collaboration: Tampa is one of the three study sites conducting the study protocol.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

Quad chart attached.

9. APPENDICES:

Two appendices are included, which together summarize the results of this project:

1. Study 1 paper draft: "Prospective Effects of Regular Exoskeleton Walking on Individuals with SCI"

2. Study 2 paper draft: "Prospective Effects of Exoskeleton Walking with Supplemental FES on Individuals with SCI"

APPENDIX 1

Study 1 paper draft: “Prospective Effects of Regular Exoskeleton Walking on Individuals with SCI”

Prospective Effects of Regular Exoskeleton Walking on Individuals with SCI

Ver. 20NOV2020

1. Introduction

About 270,000 individuals in the United States currently live with spinal cord injury, and approximately 12,000 new injuries occur annually [National SCI Statistics Center]. One of the most significant impairments resulting from SCI is loss of mobility. Surveys of persons with SCI indicate that mobility concerns are among the most prevalent [Hanson and Franklin 1976], and that chief among mobility desires is the ability to stand and walk [Brown-Triolo et al. 2002]. In addition to limiting access to places inaccessible by wheelchair, the loss of legged mobility results in substantial secondary adverse health effects, among them increased incidence of pain and muscle spasticity, difficulty associated with bowel and bladder management, and depressive psychological impact [Phillips et al. 1987, Noreau et al. 2000, Ragnarsson 2007]. These secondary health effects can collectively result in a decrease in quality of life and increase in health care costs for individuals with SCI.

Recently, powered lower limb exoskeletons have emerged onto the landscape of rehabilitative interventions for people with SCI (e.g., see recent review [Dijkers et al. 2019]). These devices can provide some degree of upright legged mobility to individuals with substantial mobility impairment due to SCI (e.g., [Tefertiller et al. 2018]). In addition to their potential to provide legged mobility, regular exoskeletal walking may also provide secondary health benefits to non-ambulatory or poorly-ambulatory individuals with SCI, an assertion which is supported by a limited number of recent studies and/or reports on the topic, including those by [Tsai et al. 2020; Alamro et al. 2018; Kressler and Domingo 2019; Maher et al. 2020; Juszczak et al. 2018; Jansen et al. 2018; Chang et al. 2018; Chun et al. 2020; Cirnigliaro et al. 2018]. Specifically, Chun et al. report improvement in bowel function in the majority of enrolled participants (ten non-ambulatory individuals with chronic SCI) [Chun et al. 2020]. In a study of 45 non-ambulatory participants with chronic SCI, each of whom walked in an exoskeleton in 26 sessions over 8 weeks, Juszczak et al. report reduction in spasticity and pain among a subset of participants. In a study of eight participants with chronic SCI, each of whom walked in an exoskeleton for 100 sessions, Cirnigliaro et al. report a significant decrease in total body fat mass among participants. In separate studies of individuals with chronic motor-incomplete SCI, Jansen et al. and Chang et al. each report significant improvement in (unassisted) mobility following exoskeletal walking (with 21 and nine participants, respectively). Other associated potential secondary benefits were described by Alamro et al., who report increased activation of trunk muscle in a study of eight individuals with thoracic-level motor-complete SCI [Alamro et al. 2018]. A study of cardiometabolic responses involving ten participants with chronic SCI suggests the exertion associated with exoskeletal walking may be below that associated with cardiometabolic conditioning [Maher et al. 2020], although a separately-conducted case series suggests that higher metabolic challenge may be achievable for individuals with incomplete SCI walking in a partial-assist mode.

This paper presents the results of a study intended to supplement the collective inquiry of the previously cited studies regarding the potential effects of regular exoskeletal walking on secondary health issues associated with SCI. This study in particular focuses on non-ambulatory and/or poorly-ambulatory participants with chronic SCI. Twenty-one participants completed the treatment, which involved exoskeletal walking for 24 approximately one-hour sessions over an eight-week period. Outcome measures were intended to inform the prospective effects of regular exoskeletal walking on: 1) secondary health issues, and 2) unassisted mobility (for participants with motor-incomplete injuries). Regarding the first, the study was intended to inform potential effects on: pain, spasticity, bowel function, bladder function, and mood. Regarding the second, for individuals with motor-incomplete injuries, the study assessed changes in mobility when walking without the exoskeleton over the course of the 8-week treatment period. Primary measurement points were at the study start; after 12 walking sessions (i.e., at 4 weeks); after 24 walking sessions (i.e., at 8 weeks); and then again 8 weeks after the last walking session (i.e., a two-month follow-up). Primary measurement instruments were a self-report survey for secondary healthy effects, and standard mobility measures for the mobility effects.

2. Methods

2.1. Sites

The study occurred at three study sites: the Mayo Clinic (Mayo) in Rochester MN; the James A. Haley Veterans' Hospital (Tampa VA) in Tampa FL; and the Vanderbilt University Medical Center (Vanderbilt) in Nashville TN. Each site conducted the same study protocol, as described below. The protocol was approved at each site by its respective institutional IRB.

2.2. Participants

A total of 21 participants completed the protocol – 8 at Mayo, 6 at the Tampa VA, and 7 at Vanderbilt – although one of the 21 was unable to return for the two-month follow-up visit. Three participants withdrew from the study prior to completion due to non-study-related health issues that occurred during the course of their involvement. Participants were recruited by study staff at each respective study site. The study was listed on ClinicalTrials.gov, identifier NCT03082898. Inclusion criteria for the study were as follows: age 18 years or older; size and limb proportions capable of fitting in the exoskeletal device (e.g., body mass no greater than 114 kg or 250 lb); either non-ambulatory or poorly-ambulatory (discussed further below); sufficient upper extremity strength and coordination to balance using an appropriate stability aid, such as a rolling walker or forearm crutches, during exoskeleton walking; spinal cord injury at neurological injury level (NLI) C5 or lower, with AIS A, B, C or D (as per the International Standard for Neurological Classification of SCI); chronic SCI, defined as at least 6 months post-injury; sufficient bone health for walking with full weight-bearing without undue risk of fracture, as determined by each subject's personal medical doctor, and approved by each site's medical supervisor; passive range of motion (PROM) at shoulders, trunk, upper extremities and lower extremities within functional limits for safe gait and safe use of appropriate assistive device/stability aid; skin intact where interfacing with exoskeleton; Modified Ashworth Score (MAS) of 3 or less in lower extremities; blood pressure and heart rate within established guidelines for locomotor training (i.e., at rest: systolic 150 mmHg or less, diastolic 90 mmHg or less, heart rate 105 bpm or less; during exercise: systolic 180 mmHg or less, diastolic 105 mmHg or less, heart rate 145 bpm or less); and the ability to tolerate an upright standing position for 20 min, passive or active, without being lightheaded or having a headache.

Exclusion criteria included: heterotopic ossification that, in the opinion of the site medical supervisor, would place the subject at undue risk for fracture; inability to follow instructions; use of a colostomy bag; women who are pregnant or attempting to become pregnant during the course of the study; any disease, concomitant injury, or condition that interferes with the performance or interpretation of the protocol-specified assessments.

Note that participation was restricted to chronic injuries to better isolate the prospective effects of exoskeletal walking (i.e., to isolate the study results from potential spontaneous recovery). The classifications of "non-ambulatory" and "poorly" ambulatory were established to examine the potential effect of exoskeletal walking on functional recovery, for individuals who may have the capacity for such recovery. As such, for purposes of this study, “non-ambulatory” is defined as a person who cannot walk, or is classified with a Functional Independence Measure (FIM) Gait score 1, while “poorly ambulatory” is defined as a person with FIM Gait score between 2 and 6 (inclusive), who may be able to walk short distances with or without leg braces or a stability aid, or may be able to walk with assistance of one person, but whose primary means of mobility is a manual or power-operated wheelchair.

2.3. Exoskeletal intervention

The study employed the Indego exoskeleton (Parker Hannifin Corp), shown independent of a user in Fig. 1, and shown as used by a subject in Fig. 2. The exoskeleton incorporates four motors for powered movement of bilateral hip and knee joints in the sagittal plane, in addition to built-in ankle-foot-orthoses (AFOs) at both ankle joints to provide ankle stability and transfer the weight of the exoskeleton to the ground. The mass of the exoskeleton including the battery is approximately 12 kg (26 lb). The general configuration is similar to other commercially-available lower limb exoskeleton devices for SCI (e.g., ReWalk and Ekso), and thus is representative of the most common class of lower limb exoskeletal devices available for clinical use.

2.4. Study protocol

The timeline of study activity and primary assessments for each participant is shown in Fig. 3. The primary participant activity consisted of 24 “treatment” sessions, which were scheduled at a frequency of three days per week for a nominal treatment period of eight weeks (two months in Fig. 3). Each walking session consisted of approximately 1 hour of walking in the exoskeleton, with an additional 30 min scheduled to accommodate donning/doffing of the exoskeleton, measurement of vital signs, and pre and post walking skin checks. As shown in the figure, the 24 walking sessions were preceded in the study protocol by three fitting and training sessions (lasting approximately 1.5 hours each), which occurred over a one-week period preceding the start of treatment, during which participants were fit with the exoskeleton and trained to stand, sit, and walk in it. In addition to the 24 treatment sessions and three training sessions, the protocol included four assessment sessions (see Fig. 3 bottom), which occurred at the start of the study (baseline); after the first 12 treatment sessions (mid-treatment); after all 24 treatment sessions (treatment end); and finally two months following the end of treatment (follow-up). The assessments and corresponding outcome measures are described in the following section.

2.5. Outcome measures

The study included four primary measurement points: baseline, mid-treatment, treatment end, and follow-up. As indicated in Fig. 3, these measurement points occurred for each participant approximately at the study start; after one month of walking; after two months of walking; and finally, two-months after the end of treatment. The prospective effects of exoskeletal walking were assessed primarily by examining differences between outcome measures at baseline and treatment end. The mid-treatment measurement was employed as an indication of continuity between the baseline and treatment end measurements, while the follow-up measurement point was employed to provide an indication of persistence in a given effect.

For all participants, the prospective effects of the exoskeletal walking on pain, spasticity, bowel and bladder function, and mood were assessed by a written survey administered to each participant at each assessment time point. For each of these five categories (i.e., pain, spasticity, bowel function, bladder function, and mood), each participant was asked to rate an increase/decrease or improvement/worsening of each aspect on a scale of -3 to +3. For pain and spasticity, -3 corresponded to the greatest decrease, while +3 corresponded to the greatest increase; for bowel habits, bladder habits, and mood, -3 corresponded to the greatest worsening in each, while +3 corresponded to the greatest improvement.

For poorly-ambulatory participants, effects relating to the potential improvement of physiological (i.e., non-exoskeletal) walking function were assessed by a combination of walking assessments conducted without the exoskeleton, including: the Ten Meter Walk Test (10MWT); the Timed Up and Go (TUG) test; the Six Minute Walk Test (6MWT); the Functional Independence Measure gait score (FIM-G); and the Walking Index for Spinal Cord Injury II (WISCI-II).

In addition to these measures, the level of mobility while using the exoskeleton was assessed at various time points throughout the 24-session walking period. Specifically, 10MWTs were administered in walking sessions 7, 12, 19, and 24; TUG tests were administered in sessions 11 and 23; and 6MWTs were administered in sessions 12 and 24.

3. Results

Study results for various metrics are shown graphically in Figs. 4 through 17, and additionally enumerated in Tables 1 through 3. Each figure includes plots of both aggregate (top plot) and individual (bottom plot) data. The aggregate data plots show the median (using circled dots) and interquartile ranges (IQRs, extent of boxes), where the whiskers associated with each extend to +/- 1.5 IQRs beyond the 25th and 75th percentiles, such that 99.3% of the data would be contained within the whiskers if the data were normally distributed. Data points that fall outside the whiskers are marked as outliers (red crosses). The individualized plots on the bottom of each figure presents the corresponding data for each individual participant included in each aggregate plot.

3.1. Quantity and nature of exoskeletal walking during treatment

Figure 4 shows the number of steps taken during each of the 24 walking sessions for all 21 participants. Over the 24 walking sessions, patients took a median of 1108 steps per day, or a median total of 26,590 steps over the entire study. The maximum number of steps taken over the study was 39,022, while the minimum number was 15,867. Six of the sessions, shown in the gray bands, were used to conduct clinical assessments of exoskeleton walking (e.g., ten-meter-walk test, time-up-and-go TUG test, etc.), which reduced somewhat the number of steps (particularly in sessions 11 and 12, and sessions 23 and 24. The median number of steps taken in the first session was 860, while the median number taken in the 22nd session (last session of regular walking without assessments) was 1744.

The six sessions shown within the gray bands were used to assess exoskeleton mobility. In particular, ten-meter-walk tests (10MWTs) in the exoskeleton were conducted during sessions 7, 12, 19, and 24; timed-up-and-go (TUG) tests in the exoskeleton were conducted during sessions 11 and 23; and six-minute-walk tests (6MWTs) were conducted during sessions 12 and 24. The medians and IQRs from these tests are shown in Figs. 4 through 6. At the conclusion of the walking sessions, the median 10MWT was 32.8 s (IQR of 6.6 s); the median TUG was 86.0 s (IQR of 26.5 s); and the median 6MWT was 292 ft (IQR of 131.5 ft).

3.2. Effect on unassisted walking function

Seven of the 21 participants were poorly-ambulatory (PA), as per the definition listed previously. For these participants, at each of the four assessment time points, each PA participant completed three 10MWTs, two TUG tests, and one 6MWT. During the course of these tests, the attending physical therapist also assessed a FIM-G score and a WISCII-II score. The median data corresponding to all measurements for each of the PA participants at each time point is shown in Figs. 8 through 12. The medians and interquartile ranges (IQRs) corresponding to each measure at baseline (BL) and at treatment end (TE) are given in Table 1. The data were determined for each measure to be non-normally distributed, as per a Kolmogorov–Smirnov (KS) test, and as such is represented by median and IQR rather than mean and standard deviation. Differences in medians (between BL and TE) were tested using a Wilcoxon rank-sum test, and corresponding p values are given in Table 1 for each.

3.3. Effects on secondary health issues

All subjects answered survey questions regarding five secondary health issues: pain, spasticity, bowel function, bladder function, and mood. For each health issue, each participant was asked if a change had occurred, and to circle a numerical rating between -3 and +3 corresponding to the degree of change (i.e., responses were strictly integers). The questions associated with each secondary health issue, and the meaning and numerical scale associated with the corresponding numerical score are listed in Table 2. For the participants who indicated a change had occurred, the corresponding median numerical ratings at each of the four measurement time points are shown in Figs. 13 through 17. Table 3 lists the number of respondents for each secondary health issue (i.e., the number indicating a change had occurred), and the corresponding medians and IQRs corresponding to each numerical score at baseline (BL) and at treatment end (TE). Table 3 also lists the p-values corresponding to a Wilcoxon rank-sum test of differences in medians between the BL and TE time points. On average 34% of participants reported a change in any given secondary health issue, and in the aggregate, the reported effects of exoskeletal walking were beneficial in all cases, improving each respective secondary health issue by 1.2 points (i.e., 40% of the maximum scale).

4. Discussion

4.1. Facilitation of functional recovery

Table 1 summarizes the mobility measures, all taken without the exoskeleton, for the n=7 poorly-ambulatory participants. In aggregate, between the baseline and treatment-end time points, participants improved mobility in all five mobility measures. The changes included a 17% median improvement in the 10MWT, corresponding to an increase in walking speed from 0.22 m/s at baseline to 0.26 m/s at treatment-end; a 19% improvement in TUG test time; 14% improvement in 6MWT; 20% improvement in FIM-G score; and 30% improvement in WISCI-II score. Further, as indicated in Figs. 8 through 12, these improvements generally persisted two months following the walking intervention. The average time-since-injury for the n=7 PA participants was 5.0 years and median was 6.1 years, so in aggregate were well within a chronic classification. As such, the treatment of exoskeletal walking appears to have had a consistent effect in improving mobility among PA participants, with a number of limitations as follows.

Although in aggregate, exoskeletal walking improved mobility across outcome measures, the results considered on an individual basis indicates heterogeneous responses to the intervention, where some participants improved notably, while others either exhibited small improvements, or no clear improvement (although it is perhaps notable that no participant seems to have worsened). It should be noted that the use of median as a measure of aggregate improvement, and the indication of outliers in the box plots, both serve to reduce the effect of outliers on the aggregate results. Nonetheless, the individualized data shown in Figs. 8 through 12 demonstrate the heterogeneity of responses, and support the notion of responders versus non-responders, which is an aspect of the intervention also highlighted in several other studies investigating the effects of exoskeletal walking (e.g., Juszczak et al. 2018, Chun et al. 2020).

4.2. Limitations regarding functional recovery

First and perhaps most obviously, the confidence associated with the statistically significant differences in medians is low, particularly in the 6MWT, FIM-G, and WISCI-II measures. Given the relatively small number of PA participants and the heterogeneity of injuries, the relatively high p-values are not unexpected, although a study limitation nonetheless. Second, the study lacks a control treatment of equivalent time commitment, and thus the extent to which an alternate treatment may have provided similar improvements in unknown. Third, the clinical significance associated with the measured improvements is unclear. Some have asserted that a reasonable clinical goal for the 10MWT is 0.1 m/s improvement [Purser et al. 2005, Hardy et al. 2007]. The median improvement measured in this study was 0.04 m/s, which may or may not be clinically significant. In the case of the FIM-G, the median improvement was one point; most clinicians would consider this clinically significant, although as previously stated, given the small number of participants, the statistical confidence in that difference is low. Despite these limitations, the near uniformity of improvements indicates promise for the potential beneficial effects of exoskeletal walking with respect to facilitating functional improvements in PA individuals with chronic SCI. As previously indicated, the data indicates that subjects did not reach a plateau in the number of steps taken in a given session; extending the study duration would presumably have continued to increase the weekly dosing, which would likely amplify the results observed here.

4.3. Effects on secondary health issues

Table 3 summarizes the secondary health issue responses for the five secondary health issues (pain, spasticity, bowel management, bladder management, and mood) for the subjects who indicated a change had occurred associated with the respective health issue. Specifically, given the heterogeneity SCI, participants with different secondary health conditions are expected to respond differently to the walking treatment. For example, participants without chronic pain are not expected to necessarily be affected by a treatment that might affect pain, just as participants without spasticity are not expected to be affected by a treatment associated with spasticity. As such, the assessment of the effects of exoskeletal walking were treated in a compound manner by first considering, for each health issue, what proportion of participants were affected in some manner, and second considering the nature of the effect (e.g., positive or negative). Note that, by considering the effects on responders only, the analysis does not exclude negative effects, nor the possibility that a participant initially without a secondary health issue did not develop one during the study (e.g., does not exclude the possibility that a participant initially without pain could develop pain as a result of exoskeletal walking). Rather, the analysis considers if the treatment had any effect, the proportion of participants for which it had an effect, and the aggregate nature of that effect.

As summarized in Table 3, 24% of participants indicated changes in pain during the study; 29% indicated changes in spasticity; 33% indicated changes in bowel habits; 33% changes in bladder habits; and 52% changes in mood. In aggregate, the median rating of all five secondary health issues for these participants at baseline was zero; namely, they indicated “no change” over the preceding month in the respective secondary health issue at the baseline measurement (i.e., at the study start). In aggregate, the median rating of all five secondary health issues for these participants at treatment-end changed by 1.2 points in a direction of improvement. Namely, for pain and spasticity, participants indicated a decrease of one point (i.e., 1/3 of the maximum rating) over the preceding month; for bowel habits, participants indicated an increase in two points (i.e., 2/3 of the maximum rating); and in bladder habits and mood, participants indicated an increase of one point (i.e., 1/3 of the maximum rating). Thus, for individuals who indicated some change in a secondary health issue, the treatment of exoskeletal walking in aggregate had a uniformly beneficial effect on all respective secondary health issues. On average, 34%

of participants responded to any given secondary health issue, and in aggregate, each issue was improved by 40% of the maximum possible improvement. As indicated in Table 3, the results for effects on bowel and bladder habits exceed a 5% confidence level, while p-values for other measures provide lower confidence of the differences in medians. As indicated in Figs. 13 through 17, for all secondary health issues, the improvements washed out at the two-month follow-up measurement, indicating the putative benefits are associated with continuing use of the exoskeleton.

4.4. Limitations regarding secondary health benefits

Among the limitations of the secondary health benefits, the assessment relies entirely on the (subjective) numerical ratings indicated by each participant in the study questionnaire. Additionally, the questionnaire was developed for this study, and as such is neither uniformly accepted nor broadly validated as a measure. Further, the subjective nature of the measurement instrument, and the fact that the rating scale is not directly associated with a clinical outcome, renders it difficult to assess the clinical significance of the respective health benefits. Finally, the statistical confidence of differences between medians for pain and mood is lower than generally preferred, while statistical confidence in differences in means in spasticity is substantially lower than generally preferred.

4.5. Subjective comments

In the questionnaire, participants were asked to elaborate on changes observed for each secondary health issue, if changes had occurred. Specifically, participants were asked “If your overall level of [pain/spasticity] over the past month has changed, please elaborate,” or “If you have noticed changes in your [bowel habits/bladder habits/mood] over the past month, please elaborate.” Subjective comments from participants in answer to these questions support the quantitative measures presented above. Specifically, with respect to pain, all comments indicated a decrease in pain, while no comments indicated an increase. Representative comments, each from a different participant, include: “Pain has stopped due to standing more and straight up”; “My lower back feels like it has loosened up since walking in the exoskeleton”; “My overall level of pain has decreased extremely due to exoskeleton use”; and “In the past month my pain has not been as intense as usual.” With regard to spasticity, as the low statistical confidence indicates, subjective comments were less uniform, with 4/6 comments indicating a decrease in spasticity and 2/6 indicating an increase. Representative comments reporting a decrease in spasticity include “My tone has decrease noticeably in both knees”; “It has decreased extremely due to daily use of the exoskeleton”; “Sessions have decreased spasticity”; and “Not as much as before.” Comments reporting an increase in spasticity include “In the past month my right leg has had a little more spasticity than usual” and “The more I do the more spastic the legs can be.” Subjective comments regarding bowel habits, bladder habits, and mood were uniformly positive (i.e., no negative comments were recorded by participants). Representative comments regarding changes in bowel habits, each from a different participant, include: “Going BM everyday where before it was 3-4 days”; “I have been going more easily and more frequently”; “It seems that the increased movement has helped me have a more consistent bowel movement”; and “I am now having sensations prior to bowel movement. These sensations are providing me adequate time to use the restroom.” Representative comments regarding changes in bladder habits, each from a different participant, include: “Less bladder accidents”; “I don't have any accidents. My bladder is holding longer and throughout the night”; “I have been able to feel more often when I need to empty my bladder”; “ I now have sensations that provide a warning for urination”; and “Better, feel like it's really trying to come back.” Finally, representative comments regarding changes in mood, each from a different participant, include: “I have been in a better mood overall physically and mentally”; “While I have been able to do [walking] therapy, it just makes me feel better and be happy”; “I have felt physically and mentally stronger, more motivated”; “Love walking”;

and "My emotional and mental health in general has significantly improved. I looked forward to being in exoskeleton. Self-esteem and confidence went up. Felt better about being in social situations."

4.6. Dosage

The results presented here were obtained with a median of approximately 1100 steps per session, or a median of approximately 3300 steps per week over the 8-week treatment period. A greater dosage (i.e., number of steps) would presumably provide a greater effect size. Throughout the 24-session period, participants in aggregate continued to increase the number of steps taken per session, and continued to increase walking speed (as per 10MWT results), without either measure appearing to reach a plateau (see Figs. 4 and 5). Considering the rate of increase following the mid-treatment assessment, subjects would reach double the 24-session step average after 35 sessions. A 12-week treatment duration may therefore provide substantially greater dosing per session than an 8-week duration, due to proficiency of walking in the exoskeleton, and may therefore provide greater effect than reported here.

5. Conclusions

The authors report here on the results of a study intended to assess potential benefits of regular exoskeletal walking for individuals with SCI. The study included a total of 21 participants, all of whom had chronic SCI, 14 of whom were non-ambulatory, and 7 of whom were poorly ambulatory. The study intervention consisted of 24 approximate 1-hour sessions of exoskeletal walking conducted over an approximate two-month period, with major assessment time points at start, mid-treatment (i.e., after one month), treatment end (i.e., after two months), and finally in a follow-up two months after treatment end. For the subset of 7 poorly-ambulatory individuals, the study assessed potential benefits of exoskeletal walking on (non-exoskeletal) walking recovery, while for the entire set of participants, the study assessed potential benefits of the exoskeletal walking on secondary health issues such as pain, spasticity, bowel and bladder function, and mood. With regard to walking recovery, participants exhibited a 17% median improvement in the 10MWT; a 19% improvement in TUG test time; 14% improvement in 6MWT; 20% improvement in FIM-G score; and 30% improvement in WISCI-II score, although given the small number of subjects and heterogeneity in data, the statistical confidence associated with these changes is low. With regard to the effect of exoskeletal walking on secondary health issues, for individuals who indicated some change in a given secondary health issue, the treatment of exoskeletal walking in aggregate had a uniformly beneficial effect on all respective secondary health issues. On average, 34% of participants responded to any given secondary health issue, and in aggregate, each issue was improved by 40% of the maximum possible improvement. The statistical confidence associated with reported improvements in bowel and bladder habits exceeded a 95% confidence level, while the statistical confidence associated with changes in other secondary health issues was lower, particularly for changes in spasticity.

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Paper figures

Fig 1. Indego exoskeleton to be used in proposed study.

Fig. 2. SCI subject walking with exoskeleton, with assistance from physical therapist.

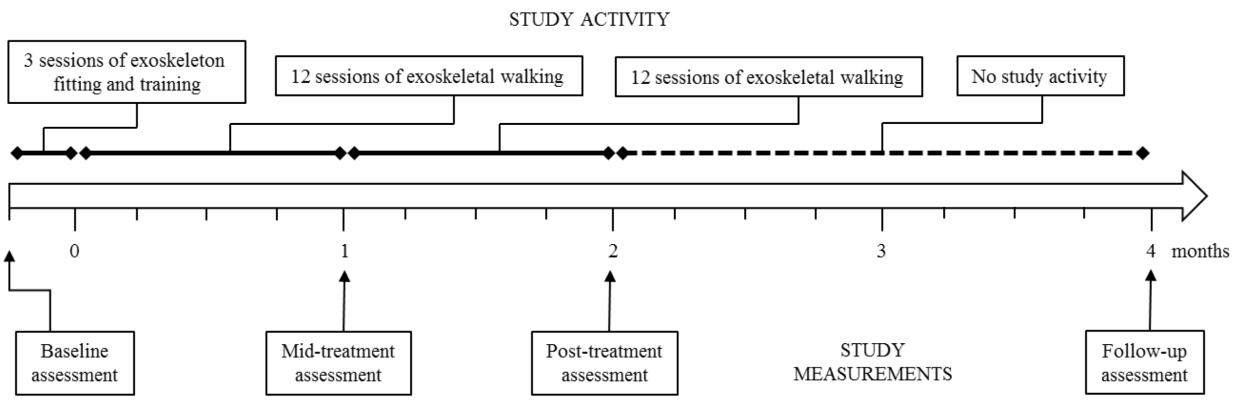


Fig. 3. Timeline of study activity and measurements for each participant.

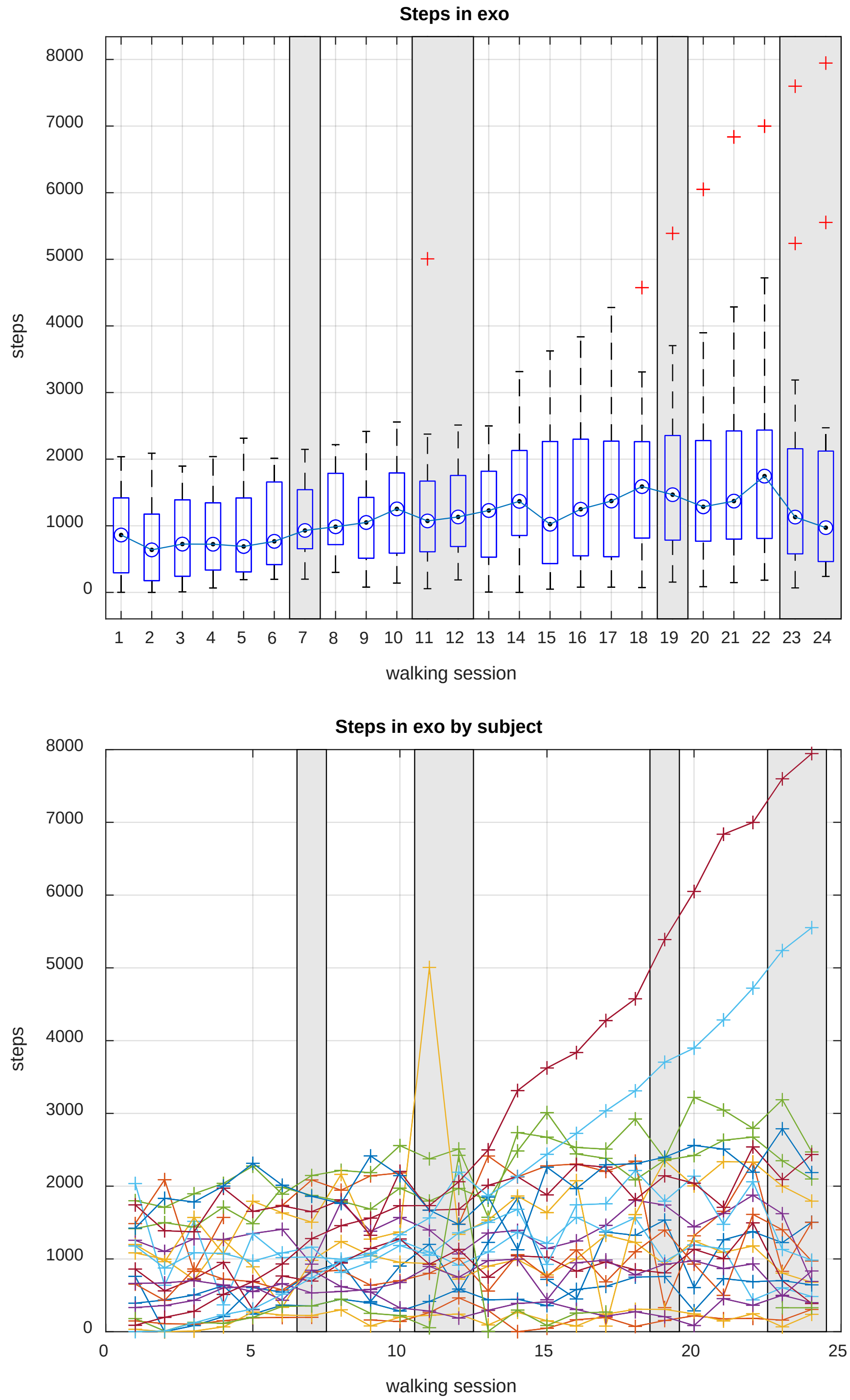


Fig. 4. Median number of steps in exoskeleton during the 24 walking sessions. The gray bands indicate sessions during which some assessments were performed.

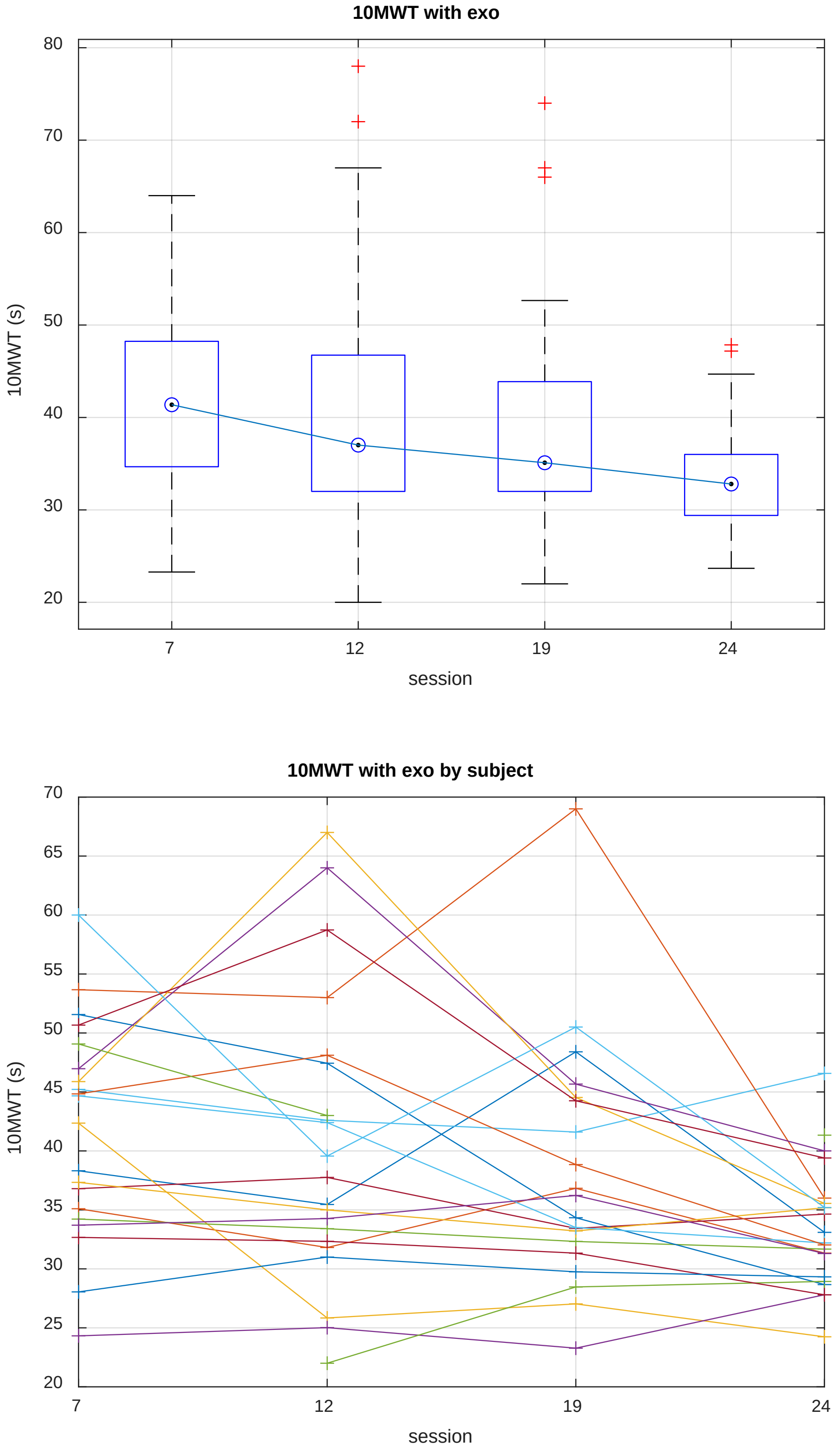
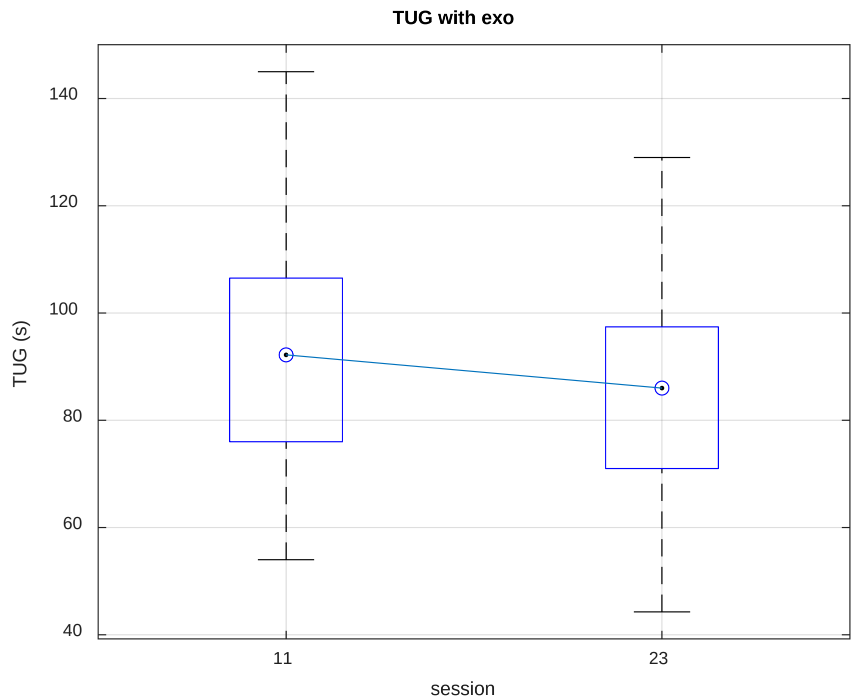


Fig. 5. Ten meter walk tests during the course of the study.


TUG with exo
TUG (s)
140
120
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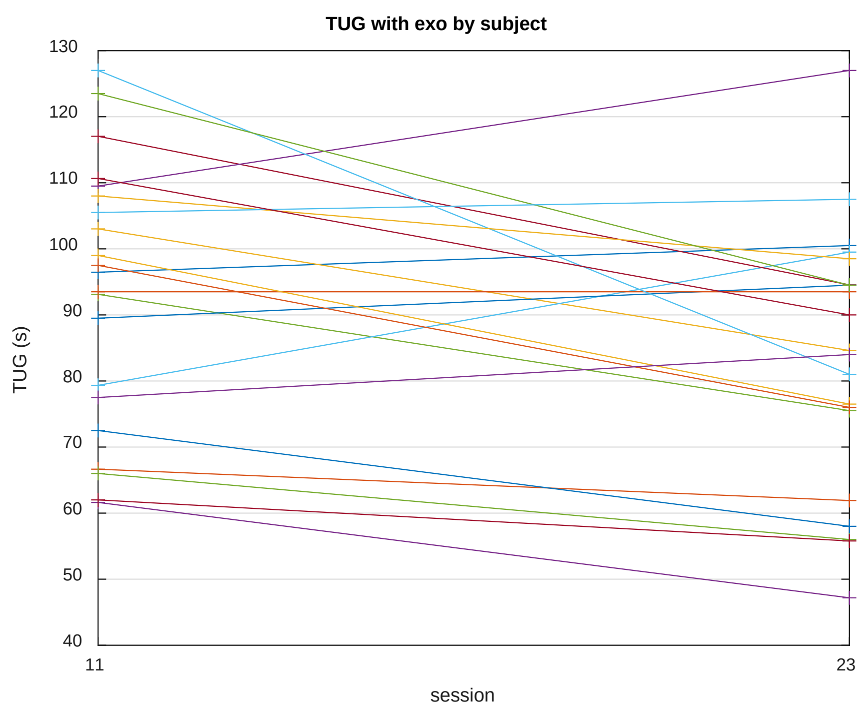
23
session


TUG with exo by subject
TUG (s)
130
120
110
100
90
80
70
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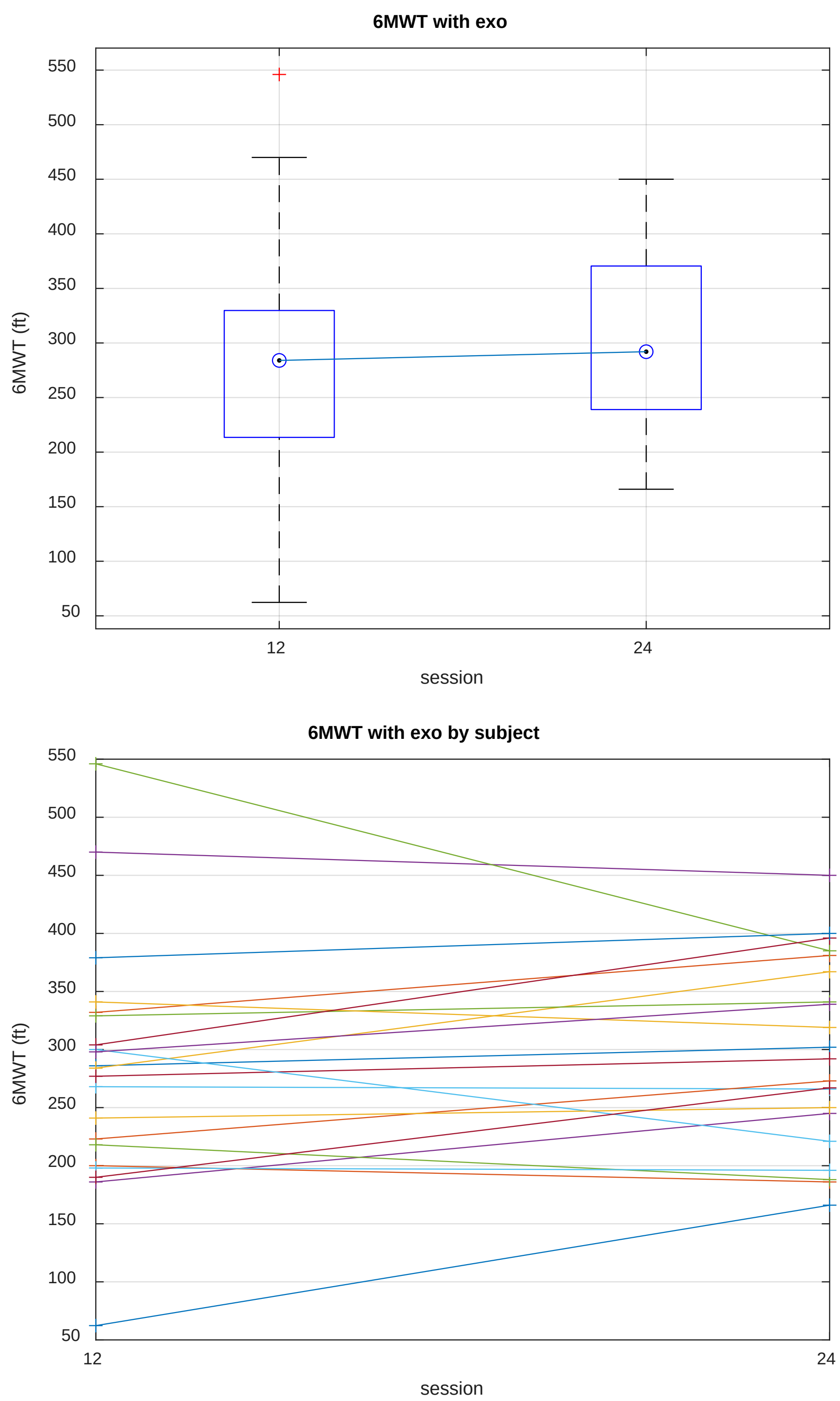
50
40
11
23
session

Fig. 6


6MWT with exo
6MWT (ft)
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250
200
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50
12
24
session
6MWT with exo by subject
6MWT (ft)
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350
300
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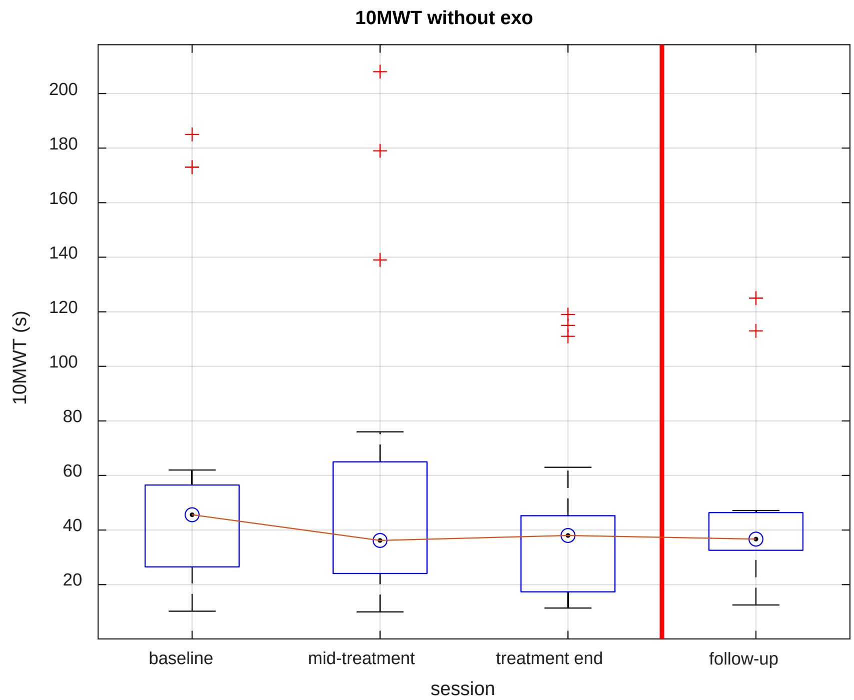
200
150
100
50
12
24
session

Fig. 7


10MWT without exo
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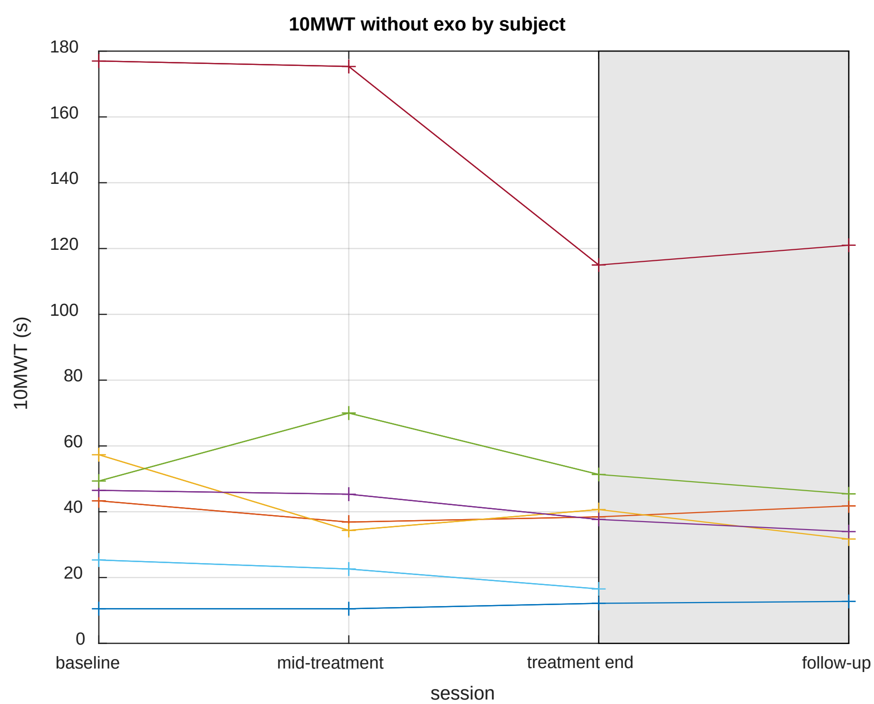
baseline
mid-treatment
treatment end
follow-up
session


10MWT without exo by subject
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baseline
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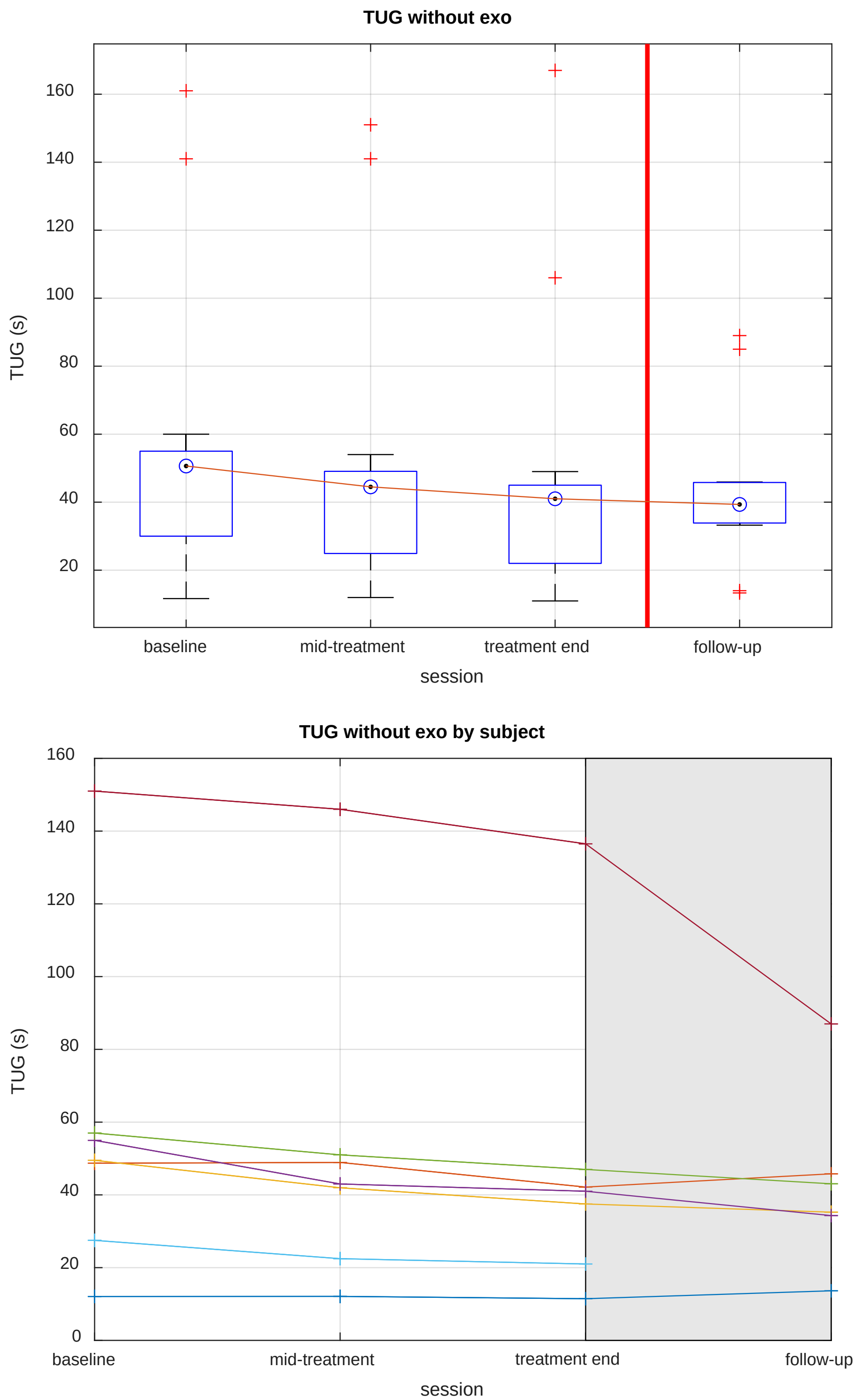
treatment end
follow-up
session

Fig. 8


TUG without exo
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TUG without exo by subject
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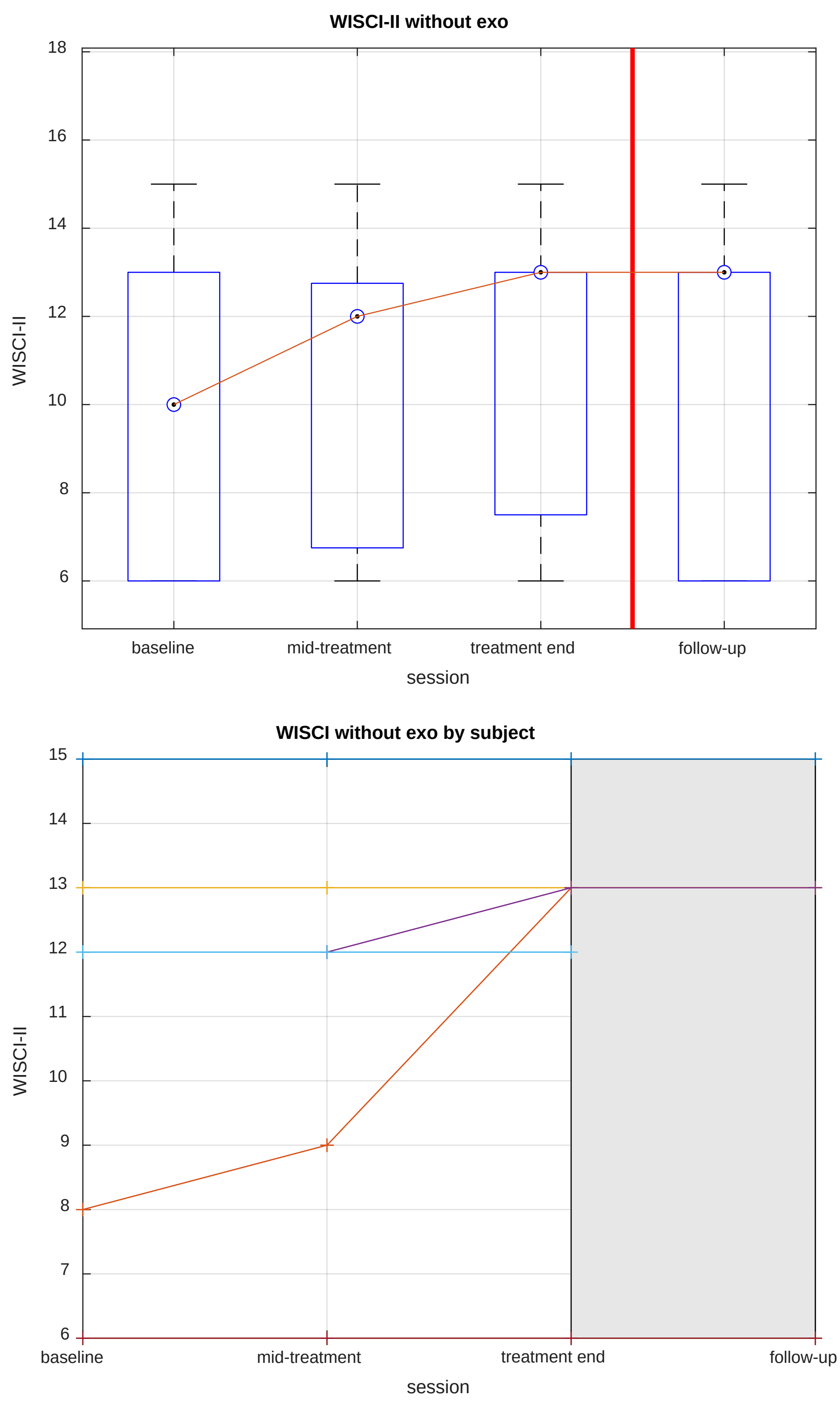
Fig. 9


WISCI-II without exo
18
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14
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WISCI-II
baseline
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follow-up
session
WISCI without exo by subject
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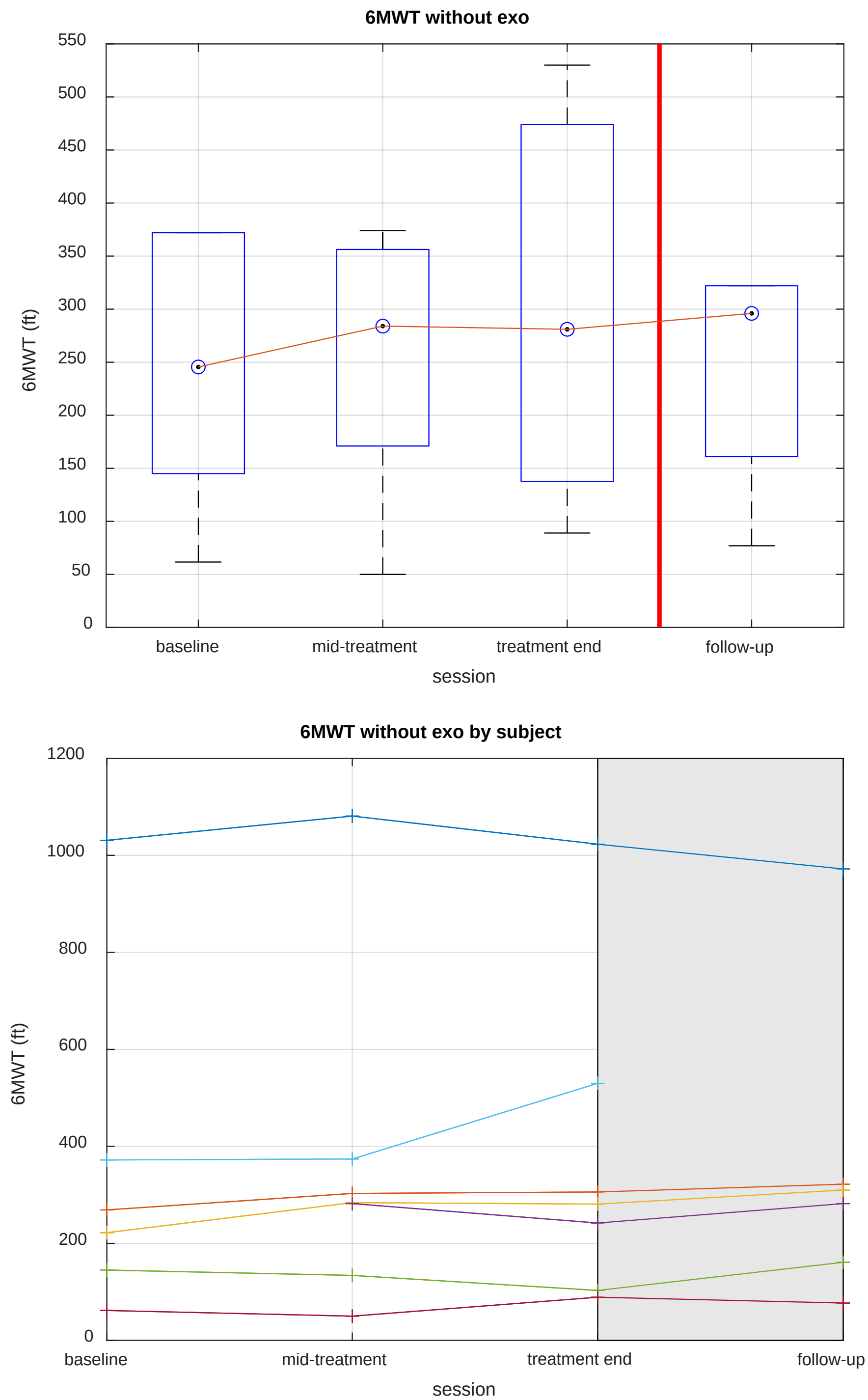
baseline
mid-treatment
treatment end
follow-up
session

Fig. 10


6MWT without exo
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6MWT (ft)
baseline
mid-treatment
treatment end
follow-up
session
6MWT without exo by subject
1200
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200
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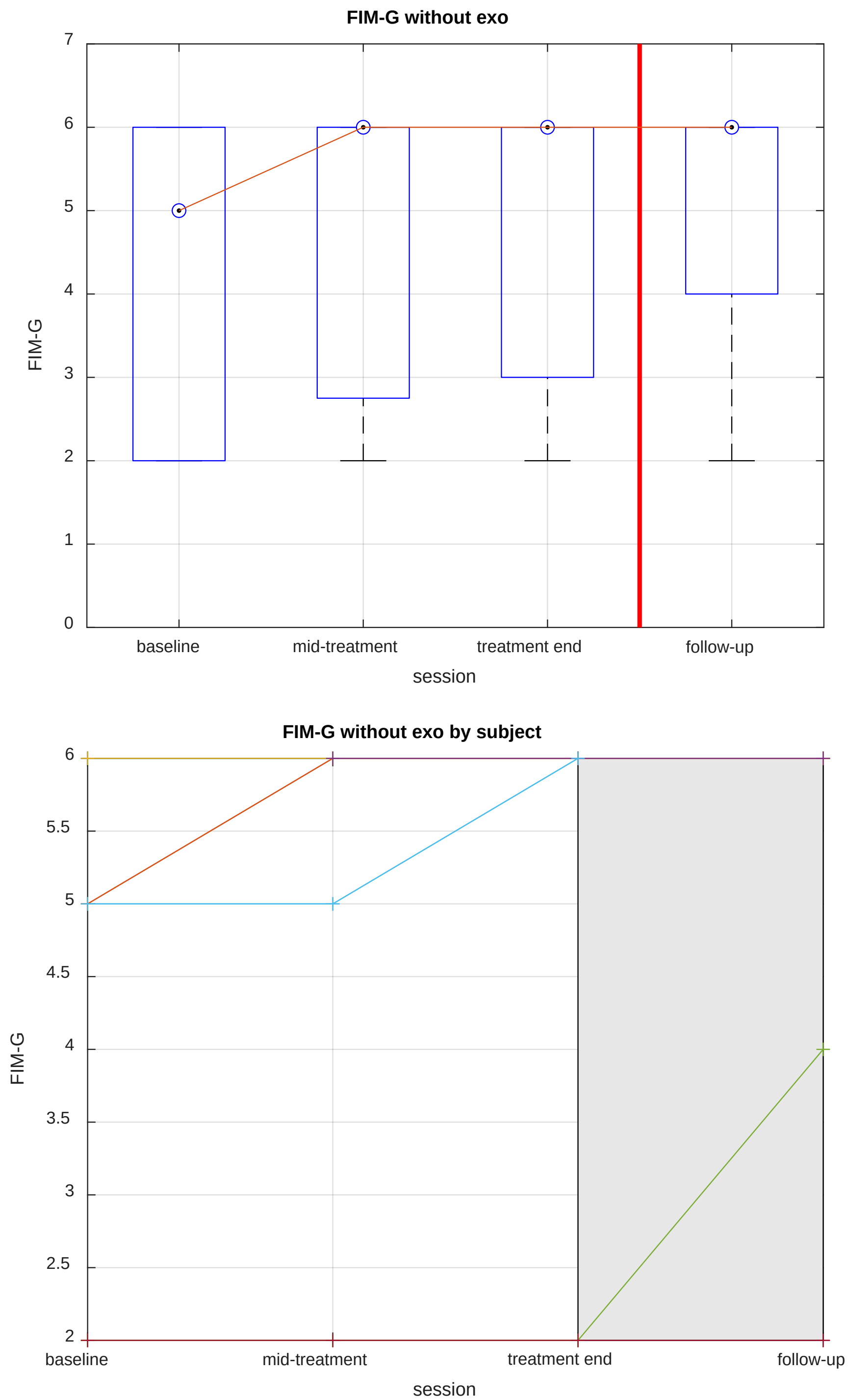
6MWT (ft)
baseline
mid-treatment
treatment end
follow-up
session

Fig. 11



FIM-G without exo
FIM-G
session
baseline
mid-treatment
treatment end
follow-up
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3
4
5
6
7
FIM-G without exo by subject
FIM-G
session
baseline
mid-treatment
treatment end
follow-up
2
2.5
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3.5
4
4.5
5
5.5
6

Fig. 12

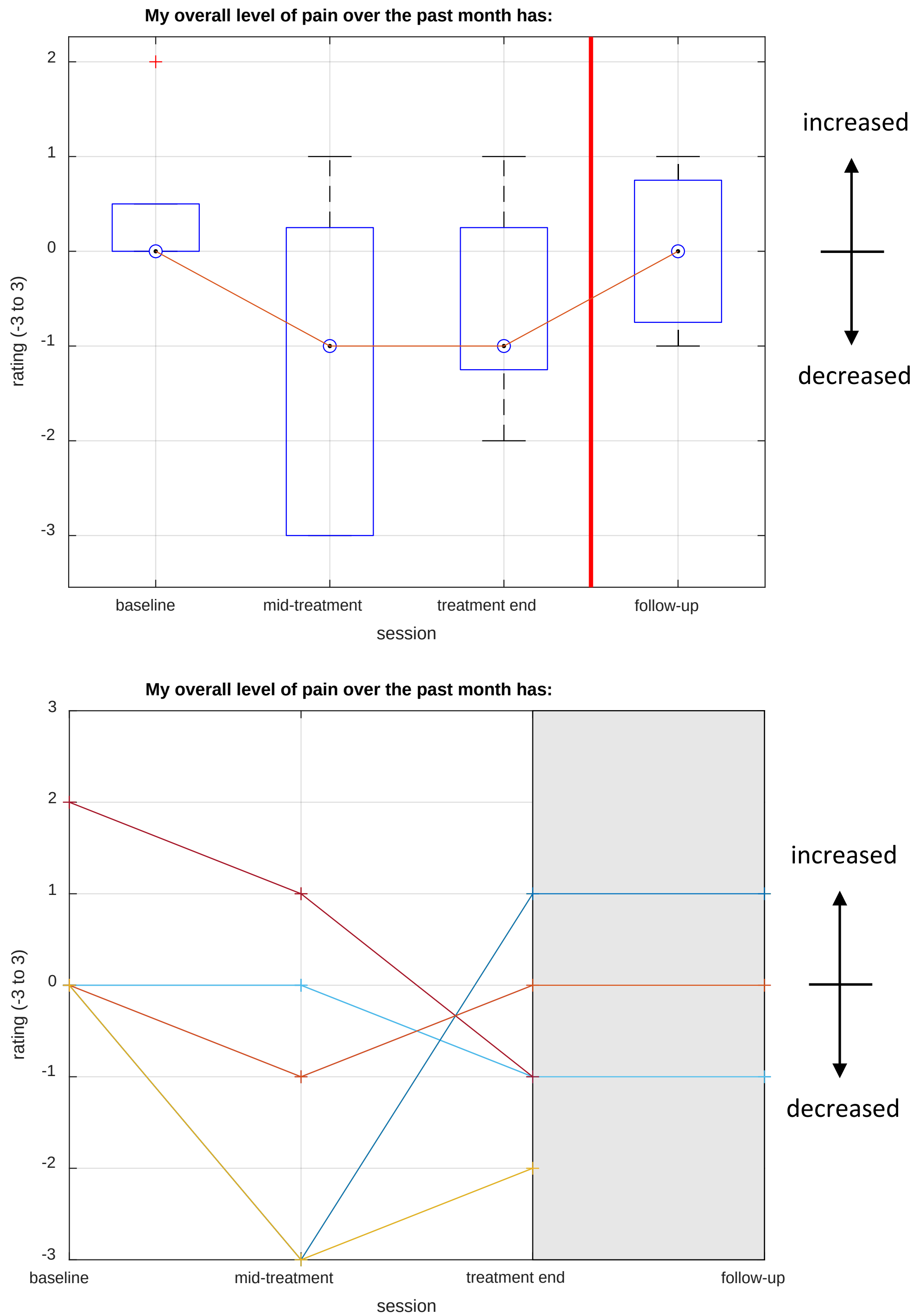

My overall level of pain over the past month has:
2
1
0
-1
-2
-3
rating (-3 to 3)
baseline
mid-treatment
treatment end
follow-up
session
increased
decreased
My overall level of pain over the past month has:
3
2
1
0
-1
-2
-3
rating (-3 to 3)
baseline
mid-treatment
treatment end
follow-up
session
increased
decreased

Fig. 13

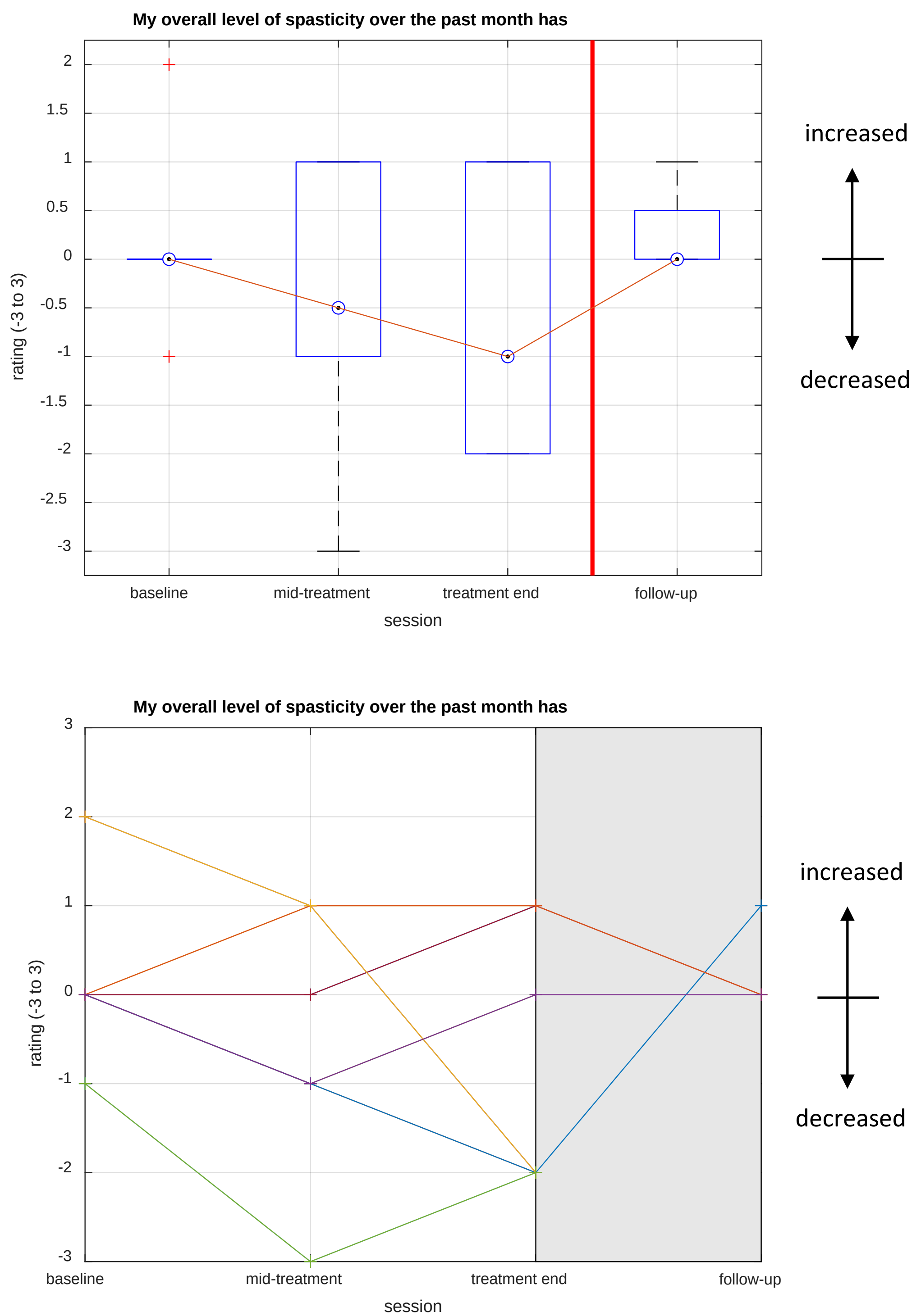
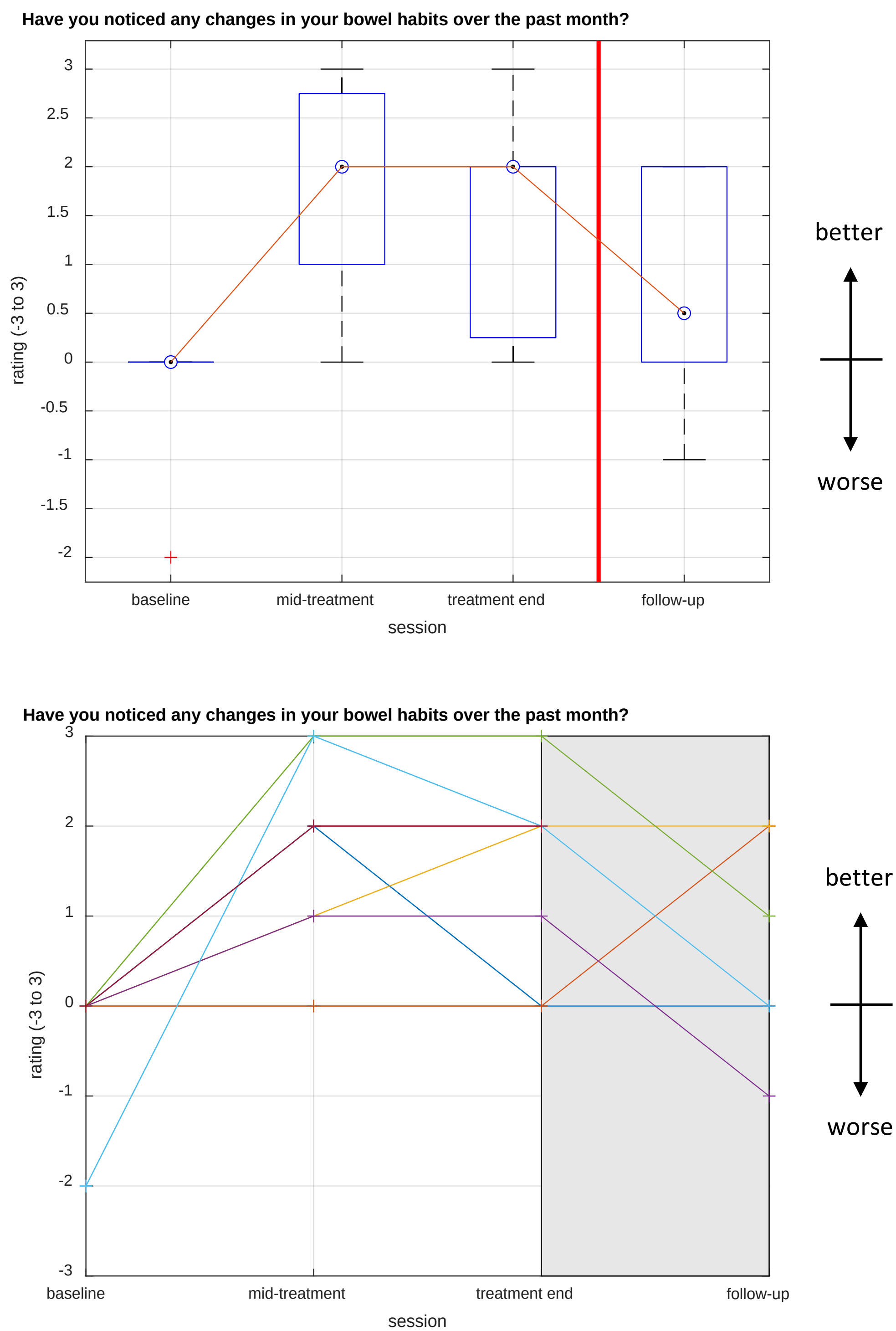
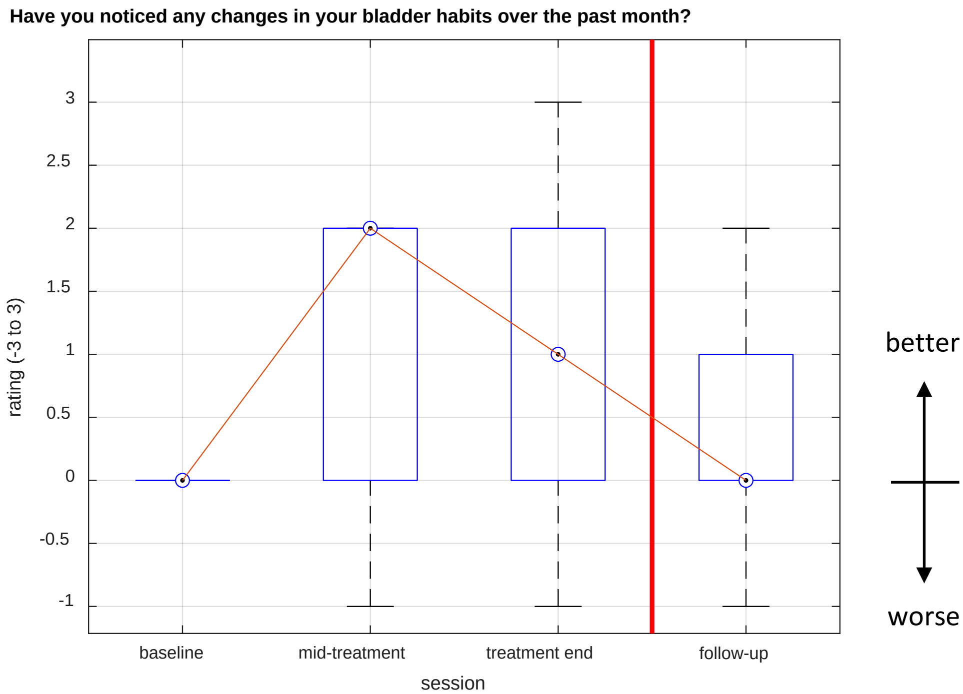

My overall level of spasticity over the past month has
rating (-3 to 3)
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
baseline
mid-treatment
treatment end
follow-up
session
increased
decreased
My overall level of spasticity over the past month has
rating (-3 to 3)
3
2
1
0
-1
-2
-3
baseline
mid-treatment
treatment end
follow-up
session
increased
decreased

Fig. 14.



Have you noticed any changes in your bowel habits over the past month?
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
rating (-3 to 3)
baseline
mid-treatment
treatment end
follow-up
session
better
worse
Have you noticed any changes in your bowel habits over the past month?
3
2
1
0
-1
-2
-3
rating (-3 to 3)
baseline
mid-treatment
treatment end
follow-up
session
better
worse

Fig. 15


Have you noticed any changes in your bladder habits over the past month?
rating (-3 to 3)
3
2.5
2
1.5
1
0.5
0
-0.5
-1
baseline
mid-treatment
treatment end
follow-up
session
better
worse

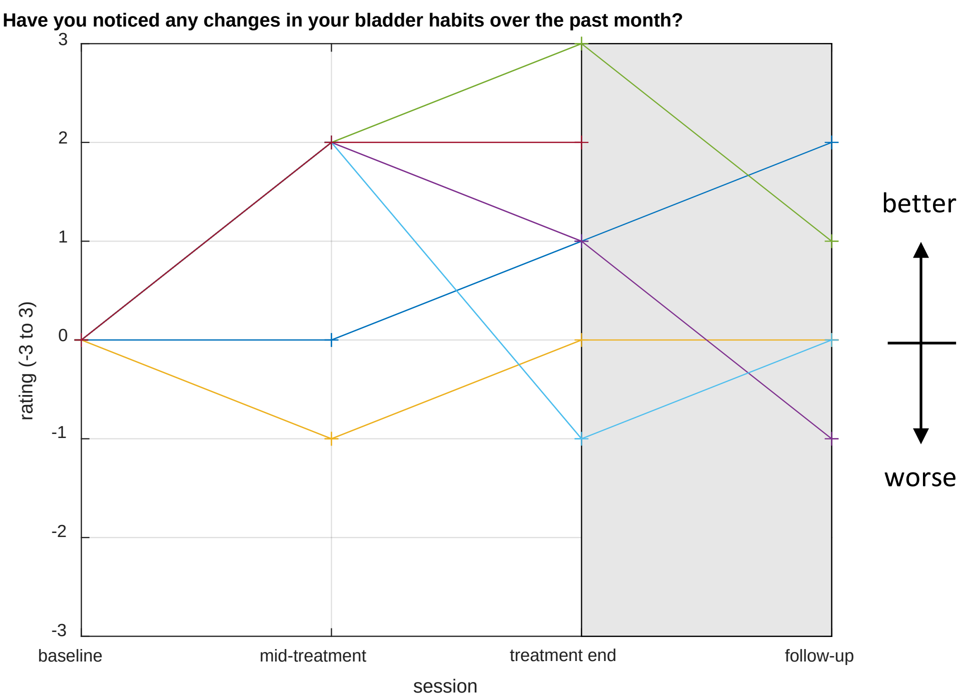

Have you noticed any changes in your bladder habits over the past month?
rating (-3 to 3)
3
2
1
0
-1
-2
-3
baseline
mid-treatment
treatment end
follow-up
session
better
worse

Fig. 16

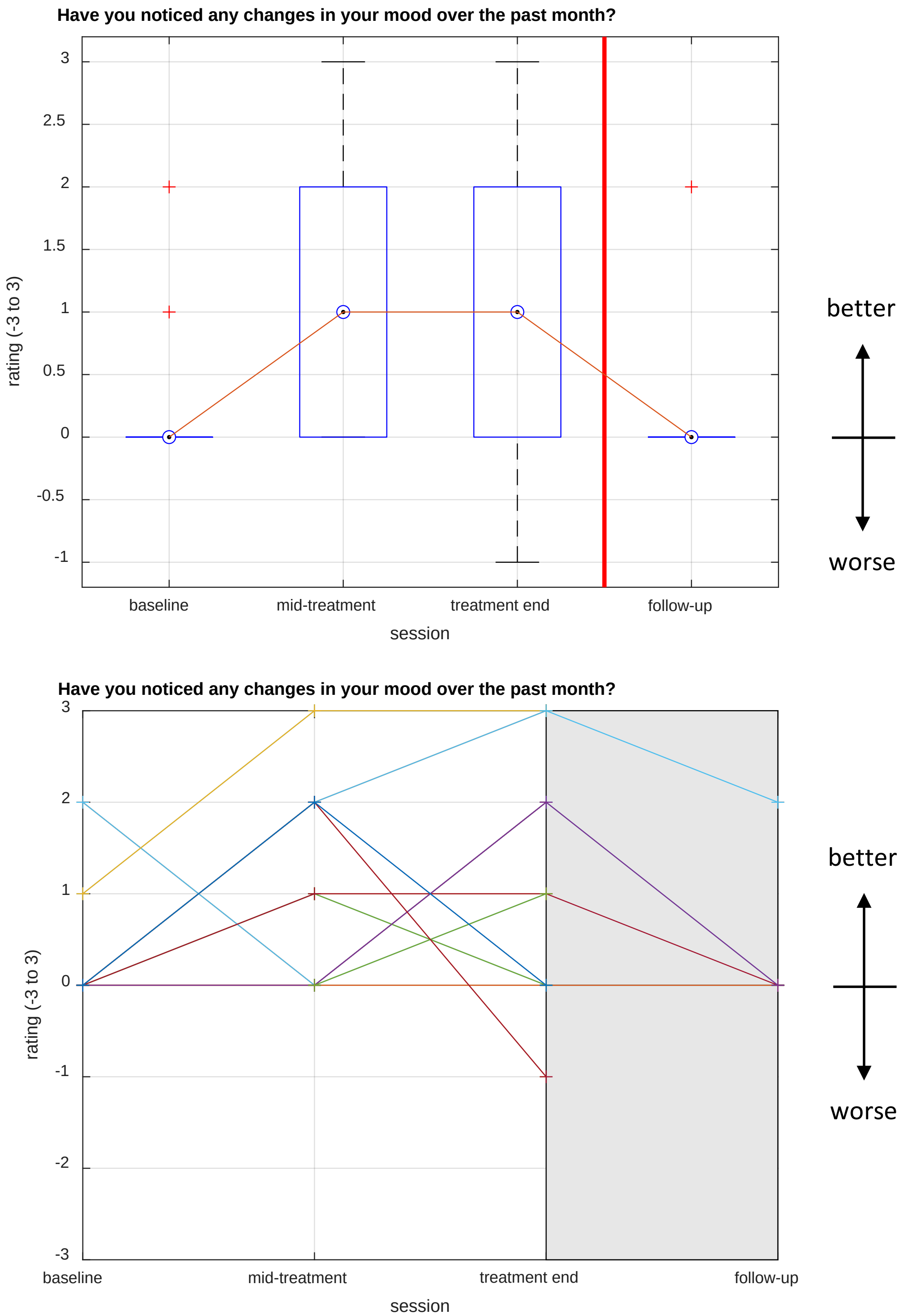

Have you noticed any changes in your mood over the past month?
rating (-3 to 3)
3
2.5
2
1.5
1
0.5
0
-0.5
-1
baseline
mid-treatment
treatment end
follow-up
session
better
worse
Have you noticed any changes in your mood over the past month?
rating (-3 to 3)
3
2
1
0
-1
-2
-3
baseline
mid-treatment
treatment end
follow-up
session
better
worse

Fig. 17

Outcome measure	Measure units	Baseline median	IQR	Treatment-end median	IQR	Percent change in median	p-value
10MWT	s	45.6	30	38	28	-17%	0.20
TUG	s	50.6	25	41	23	-19%	0.13
6MWT	ft	246	227	281	336	14%	0.83
FIM-G	N/A	5	4	6	3	20%	0.42
WISCI-II	N/A	10	7	13	5.5	30%	0.66

Table 1

Health issue	Survey question	Answer options	Scoring range
Pain	My overall level of pain over the past month has:	decreased or increased	-3 (max decrease) to +3 (max increase)
Spasticity	My overall level of spasticity over the past month has:	decreased or increased	-3 (max decrease) to +3 (max increase)
Bowel	Have you noticed any changes in your bowel habits over the past month?	worse or better	-3 (max worse) to +3 (max better)
Bladder	Have you noticed any changes in your bladder habits over the past month?	worse or better	-3 (max worse) to +3 (max better)
Mood	Have you noticed any changes in your mood over the past month?	worse or better	-3 (max worse) to +3 (max better)

Table 2

Health issue	N	Proportion of participants	Baseline median	IQR	Treatment-end median	IQR	Change in median	p-value
Pain	5	24%	0	0.5	-1	1.5	-1	0.12
Spasticity	6	29%	0	0	-1	3	-1	0.48
Bowel	7	33%	0	0	2	1.75	2	0.02
Bladder	7	33%	0	0	1	2	1	0.04
Mood	11	52%	0	0	1	2	1	0.19

Table 3

APPENDIX 2

Study 2 paper draft: “Prospective Effects of Regular Exoskeleton Walking with Supplemental FES on Individuals with SCI”

Prospective Effects of Exoskeleton Walking with Supplemental FES on Individuals with SCI

Ver. 16FEB2021

1. Introduction

About 270,000 individuals in the United States currently live with spinal cord injury, and approximately 12,000 new injuries occur annually [National SCI Statistics Center]. One of the most significant impairments resulting from SCI is loss of mobility. Surveys of persons with SCI indicate that mobility concerns are among the most prevalent [Hanson and Franklin 1976], and that chief among mobility desires is the ability to stand and walk [Brown-Triolo et al. 2002]. In addition to limiting access to places inaccessible by wheelchair, the loss of legged mobility results in substantial secondary adverse health effects, among them increased incidence of pain and muscle spasticity, difficulty associated with bowel and bladder management, and depressive psychological impact [Phillips et al. 1987, Noreau et al. 2000, Ragnarsson 2007]. These secondary health effects can collectively result in a decrease in quality of life and increase in health care costs for individuals with SCI.

Recently, powered lower limb exoskeletons have emerged onto the landscape of rehabilitative interventions for people with SCI (e.g., see recent review [Dijkers et al. 2019]). These devices can provide some degree of upright legged mobility to individuals with substantial mobility impairment due to SCI (e.g., [Tefertiller et al. 2018]). In addition to their potential to provide legged mobility, regular exoskeletal walking may also provide secondary health benefits to non-ambulatory or poorly-ambulatory individuals with SCI, an assertion which is supported by a limited number of recent studies and/or reports on the topic, including those by [Tsai et al. 2020; Alamro et al. 2018; Kressler and Domingo 2019; Maher et al. 2020; Juszczak et al. 2018; Jansen et al. 2018; Chang et al. 2018; Chun et al. 2020; Cirnigliaro et al. 2018]. Specifically, Chun et al. report improvement in bowel function in the majority of enrolled participants (ten non-ambulatory individuals with chronic SCI) [Chun et al. 2020]. In a study of 45 non-ambulatory participants with chronic SCI, each of whom walked in an exoskeleton in 26 sessions over 8 weeks, Juszczak et al. report reduction in spasticity and pain among a subset of participants. In a study of eight participants with chronic SCI, each of whom walked in an exoskeleton for 100 sessions, Cirnigliaro et al. report a significant decrease in total body fat mass among participants. In separate studies of individuals with chronic motor-incomplete SCI, Jansen et al. and Chang et al. each report significant improvement in (unassisted) mobility following exoskeletal walking (with 21 and nine participants, respectively). Other associated potential secondary benefits were described by Alamro et al., who report increased activation of trunk muscle in a study of eight individuals with thoracic-level motor-complete SCI [Alamro et al. 2018]. A study of cardiometabolic responses involving ten participants with chronic SCI suggests the exertion associated with exoskeletal walking may be below that associated with cardiometabolic conditioning [Maher et al. 2020], although a separately-conducted case series suggests that higher metabolic challenge may be achievable for individuals with incomplete SCI walking in a partial-assist mode.

This paper presents the results of a study intended to supplement the collective inquiry of the previously cited studies regarding the potential effects of regular exoskeletal walking on secondary health issues associated with SCI. This study in particular focuses on non-ambulatory and/or poorly-ambulatory participants with chronic SCI, and an exoskeletal intervention that employed supplemental functional electrical stimulation (FES) of multiple muscle groups via surface electrodes. Fourteen participants completed the treatment, which involved exoskeletal walking for 24 approximately one-hour sessions over an eight-week period. The exoskeleton intervention employed up to ten channels of supplemental FES, including stimulation channels corresponding to abdominal trunk muscles; lower back muscles; quadriceps muscle groups; hamstring muscle groups; tibialis anterior muscle stimulation; and gastrocnemius muscle stimulation. Outcome measures were intended to inform the prospective effects of the intervention on: 1) secondary health issues, and 2) unassisted mobility (for participants with motor-incomplete injuries). Regarding the first, the study was intended to inform potential effects on: pain, spasticity, bowel function, bladder function, and mood. Regarding the second, for individuals with motor-incomplete injuries, the study assessed changes in mobility when walking without the exoskeleton over the course of the 8-week treatment period. Primary measurement points were at the study start; after 12 walking sessions (i.e., at 4 weeks); after 24 walking sessions (i.e., at 8 weeks); and then again 8 weeks after the last walking session (i.e., a two-month follow-up). Primary measurement instruments were a self-report survey for secondary healthy effects, and standard mobility measures for the mobility effects.

2. Methods

2.1. Sites

The study occurred at two study sites: the Mayo Clinic (Mayo) in Rochester MN, and the Vanderbilt University Medical Center (Vanderbilt) in Nashville TN. Both sites conducted the same study protocol, as described below. The protocol was approved at both sites by their respective institutional IRBs.

2.2. Participants

A total of 14 participants completed the protocol – 8 at Mayo and 6 at Vanderbilt. Participants were recruited by study staff at each respective study site. The study was listed on ClinicalTrials.gov, identifier NCT03082898. Inclusion criteria for the study were as follows: age 18 years or older; size and limb proportions capable of fitting in the exoskeletal device (e.g., body mass no greater than 114 kg or 250 lb); either non-ambulatory or poorly-ambulatory (discussed further below); sufficient upper extremity strength and coordination to balance using an appropriate stability aid, such as a rolling walker or forearm crutches, during exoskeleton walking; spinal cord injury at neurological injury level (NLI) C5 or lower, with AIS A, B, C or D (as per the International Standard for Neurological Classification of SCI); chronic SCI, defined as at least 6 months post-injury; sufficient bone health for walking with full weight-bearing without undue risk of fracture, as determined by each subject's personal medical doctor, and approved by each site's medical supervisor; passive range of motion (PROM) at shoulders, trunk, upper extremities and lower extremities within functional limits for safe gait and safe use of appropriate assistive device/stability aid; skin intact where interfacing with exoskeleton; Modified Ashworth Score (MAS) of 3 or less in lower extremities; blood pressure and heart rate within established guidelines for locomotor training (i.e., at rest: systolic 150 mmHg or less, diastolic 90 mmHg or less, heart rate 105 bpm or less; during exercise: systolic 180 mmHg or less, diastolic 105 mmHg or less, heart rate 145 bpm or less); and the ability to tolerate an upright standing position for 20 min, passive or active, without being lightheaded or having a headache.

Exclusion criteria included: heterotopic ossification that, in the opinion of the site medical supervisor, would place the subject at undue risk for fracture; inability to follow instructions; use of a colostomy bag; women who are pregnant or attempting to become pregnant during the course of the study; any disease, concomitant injury, or condition that interferes with the performance or interpretation of the protocol-specified assessments.

Note that participation was restricted to chronic injuries to better isolate the prospective effects of exoskeletal walking (i.e., to isolate the study results from potential spontaneous recovery). The classifications of "non-ambulatory" and "poorly" ambulatory were established to examine the potential effect of exoskeletal walking on functional recovery, for individuals who may have the capacity for such recovery. As such, for purposes of this study, "non-ambulatory" is defined as a person who cannot walk, or is classified with a Functional Independence Measure (FIM) Gait score 1, while "poorly ambulatory" is defined as a person with FIM Gait score between 2 and 6 (inclusive), who may be able to walk short distances with or without leg braces or a stability aid, or may be able to walk with assistance of one person, but whose primary means of mobility is a manual or power-operated wheelchair.

2.3. Exoskeletal intervention

The study employed the Indego exoskeleton (Parker Hannifin Corp), shown independent of a user in Fig. 1, and shown as used by a subject in Fig. 2. The exoskeleton incorporates four motors for powered movement of bilateral hip and knee joints in the sagittal plane, in addition to built-in ankle-foot-orthoses (AFOs) at both ankle joints to provide ankle stability and transfer the weight of the exoskeleton to the ground. The mass of the exoskeleton including the battery is approximately 12 kg (26 lb). The general configuration is similar to other commercially-available lower limb exoskeleton devices for SCI (e.g., ReWalk and Ekso), and thus is representative of the most common class of lower limb exoskeletal devices available for clinical use.

The version of the exoskeleton used for this study was an experimental device that included ten channels of supplemental FES, where the stimulation timing and amplitude were controlled automatically to produce muscle contractions that were synchronized with the robot aided motion of the exoskeleton. The FES jacks were located in the hip part of the exoskeleton, with five jacks on each side, as shown in Fig. 3. The five jacks can be configured using software to stimulate any five of the following muscle groups: quadriceps, hamstrings, gluteal muscles, tibialis anterior, gastrocnemius, trunk flexors (lower abdominal muscles), and/or trunk extensors (lower back muscles). Each of these may be stimulated bilaterally, or unilaterally. Simulation of the trunk muscles is applied continuously during standing and walking, while the timing of the leg muscle groups is controlled automatically by the exoskeleton as a function of the gait cycle, as indicated in Fig. 4. The stimulation waveform used by the exoskeleton for this study was a 40 Hz biphasic wave, with a total biphasic pulse width of 500 µs, and where the amplitude of each channel was set at some value between zero and 140 mA by each therapist during the initial training period. For each subject, therapists were instructed to: "Use as many channels as subject is comfortable using." The eight nominal channels were the right and left quadriceps, hamstrings, tibialis anterior, and gastrocnemius muscles. Additional optional channels were right and left gluteal muscles or anterior or posterior trunk muscles, which were to be used "if those are helpful for the subject, and if subject is comfortable using them."

2.4. Study protocol

The timeline of study activity and primary assessments for each participant is shown in Fig. 5. The primary participant activity consisted of 24 "treatment" sessions, which were scheduled at a frequency of three days per week for a nominal treatment period of eight weeks (two months in Fig. 5). Each walking session consisted of approximately 1 hour of walking in the exoskeleton, with an additional 30 min scheduled to accommodate donning/doffing of the exoskeleton, measurement of vital signs, and pre and post walking skin checks. As shown in the figure, the 24 walking sessions were preceded in the study protocol by three fitting and training sessions (lasting approximately 1.5 hours each), which occurred over a one-week period preceding the start of treatment, during which participants were fit with the exoskeleton and trained to stand, sit, and walk in it. In addition to the 24 treatment sessions and three training sessions, the protocol included four assessment sessions (see Fig. 5 bottom), which occurred at the start of the study (baseline); after the first 12 treatment sessions (mid-treatment); after all 24 treatment sessions (treatment end); and finally two months following the end of treatment (follow-up). The assessments and corresponding outcome measures are described in the following section.

2.5. Outcome measures

The study included four primary measurement points: baseline, mid-treatment, treatment end, and follow-up. As indicated in Fig. 5, these measurement points occurred for each participant approximately at the study start; after one month of walking; after two months of walking; and finally, two-months after the end of treatment. The prospective effects of exoskeletal walking were assessed primarily by examining differences between outcome measures at baseline and treatment end. The mid-treatment measurement was employed as an indication of continuity between the baseline and treatment end measurements, while the follow-up measurement point was employed to provide an indication of persistence in a given effect.

For poorly-ambulatory participants, effects relating to the potential improvement of physiological (i.e., non-exoskeletal) walking function were assessed by a combination of walking assessments conducted without the exoskeleton, including: the Ten Meter Walk Test (10MWT); the Timed Up and Go (TUG) test; and the Six Minute Walk Test (6MWT).

In addition to these measures, the level of mobility while using the exoskeleton was assessed at various time points throughout the 24-session walking period. Specifically, 10MWTs were administered in walking sessions 7, 12, 19, and 24; TUG tests were administered in sessions 11 and 23; and 6MWTs were administered in sessions 12 and 24.

3. Results

Study results for various metrics are shown graphically in Figs. 6 through 12, and additionally enumerated in Table 1. Each figure includes plots of both aggregate (top plot) and individual (bottom plot) data. The aggregate data plots show the median (using circled dots) and interquartile ranges (IQRs, extent of boxes), where the whiskers associated with each extend to +/- 1.5 IQRs beyond the 25^{th} and 75^{th} percentiles, such that 99.3% of the data would be contained within the whiskers if the data were normally distributed. Data points that fall outside the whiskers are marked as outliers (red crosses). The individualized plots on the bottom of each figure presents the corresponding data for each individual participant included in each aggregate plot.

3.1. Quantity and nature of exoskeletal walking during treatment

Figure 6 shows the number of steps taken during each of the 24 walking sessions for all 14 participants. Over the 24 walking sessions, patients took a median of 1608 steps per day, or a median total of 38,580 steps over the entire study. The maximum number of steps taken over the study was 62,216, while the minimum number was 21,317. Six of the sessions, shown in the gray bands, were used to conduct clinical assessments of exoskeleton walking (e.g., ten-meter-walk test, time-up-and-go TUG test, etc.), which reduced somewhat the number of steps (particularly in sessions 11 and 12, and sessions 23 and 24.

The six sessions shown within the gray bands were used to assess exoskeleton mobility. In particular, ten-meter-walk tests (10MWTs) in the exoskeleton were conducted during sessions 7, 12, 19, and 24; timed-up-and-go (TUG) tests in the exoskeleton were conducted during sessions 11 and 23; and six-minute-walk tests (6MWTs) were conducted during sessions 12 and 24. The medians and IQRs from these tests are shown in Figs. 4 through 6. At the conclusion of the walking sessions, the median 10MWT was 29.6 s (IQR of 6.6 s), which corresponds to a median walking speed of approximately 0.34 m/s; the median TUG was 68.1 s (IQR of 24.7 s); and the median 6MWT was 369 ft (IQR of 80 ft).

3.2. Effect on unassisted walking function

Four of the 14 participants were poorly-ambulatory (PA), as per the definition listed previously. For these participants, at each of the four assessment time points, each PA participant completed three 10MWTs, two TUG tests, and one 6MWT. The median data corresponding to all measurements for each of the PA participants at each time point is shown in Figs. 8 through 12. The medians and interquartile ranges (IQRs) corresponding to each measure at baseline (BL) and at treatment end (TE) are given in Table 1. The data were determined for each measure to be non-normally distributed, as per a Kolmogorov–Smirnov (KS) test, and as such is represented by median and IQR rather than mean and standard deviation. Differences in medians (between BL and TE) were tested using a Wilcoxon rank-sum test, and corresponding p values are given in Table 1 for each.

4. Discussion

4.1. Facilitation of functional recovery

Table 1 summarizes the mobility measures, all taken without the exoskeleton, for the n=4 poorly-ambulatory participants. In aggregate, between the baseline and treatment-end time points, participants improved mobility in all five mobility measures. The changes included a 7% median improvement in the 10MWT, corresponding to an increase in walking speed from 0.28 m/s at baseline to 0.30 m/s at treatment-end; a 4% reduction in TUG test time; and 12% improvement in 6MWT. The p values associated with these changes were 0.18, 0.96, and 0.48, respectively. As such, the improvement in 10MWT can be considered statistically valid among the four participants, while the changes in TUG and 6MWT cannot. The improvements in 10MWT, although potential statistically significant, are relatively small with respect to a nominal clinical goal of 0.1 m/s improvement, as suggested by [Purser et al. 2005, Hardy et al. 2007].

4.2. Subjective comments

In the questionnaire, participants were allowed to optionally comment on their experience using the exoskeleton. Of the 14 participants, 9 provided comments regarding “your experience with the exoskeleton.” These comments included: “I really like walking on the exoskeleton, it makes me feel like I've a good exercise;” “Excellent in preventing spasticity and reducing muscular atrophy;” “I loved it. It felt great to be able to stretch in it after sitting in the chair all day. I've gained more feeling in bowel movement activity while walking in the exoskeleton;” “It's great weight bearing, exercise the brain to walk, and helps keep spasticity to a minimum;” “I feel use of the exo has helped improve my balance & core strength. It has helped in re-learning weight shifts & walking patterns even though I think more time/sessions is needed to master this. The FES is a great addition to the exo & adds a lot of benefits;” “I feel the exoskeleton w/stim is invaluable to assist in walking. I have had improvement in weak leg. Able to move more natural. Feel need to have extension of study if improvement occurs. Only issue was downtime when machine broke. Love the staff here. they are very good at making the experience positive;” “It's been a great improvement for my circulation; increase function. Boosts level of change in my body. Best rehab tool I've had since my injury;” “love this. I noticed a big change between the 1st study and this one. I felt my walking was more fluid & the researchers needed to assist less. I'm more tuned into my body when I'm involved in the study. I'm healthier overall mentally and physically when I walk;” “It was a great experience. Going into this, I knew I wasn't going to be able to take the device home. I wanted to participate helping in the future someone or perhaps myself might be able to have insurance cover them using data from my study to help prove medical benefits. It also helped my spasticity for the next 12 to 16 hours after each session."

5. Conclusions

The authors report here on the results of a study intended to assess potential benefits of exoskeletal walking with supplemental FES for individuals with SCI. The study included a total of 14 participants, all of whom had chronic SCI, 10 of whom were non-ambulatory, and 4 of whom were poorly ambulatory. The study intervention consisted of 24 approximate 1-hour sessions of exoskeletal walking conducted over an approximate two-month period, with major assessment time points at start, mid-treatment (i.e., after one month), treatment end (i.e., after two months), and finally in a follow-up two months after treatment end. By the conclusion of the study, participants were able to walk in the exoskeleton with a median walk speed of 0.35 m/s. Poorly-ambulatory participants improved walking speed without the exoskeleton from a median of 0.28 m/s to a speed of 0.30 m/s. It's not clear if this improvement is clinically significant. Nonetheless, based on subjective comments, participants expressed strong appreciation for the therapeutic benefits of using the exoskeleton with supplemental FES.

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Paper figures

Fig 1. Indego exoskeleton used in the study.

Fig. 2. SCI subject walking with exoskeleton with supplement FES, with assistance from physical therapist.

Fig. 3. Indego hip unit, showing the five right-side jacks associated with built-in FES.

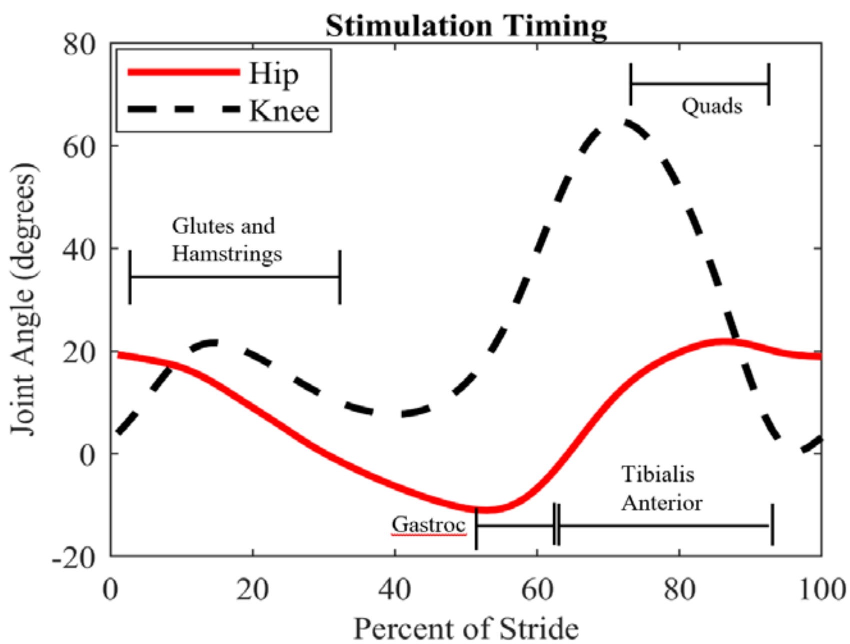


Fig. 4. Timing of stimulation with respect to gait cycle for different muscle groups.

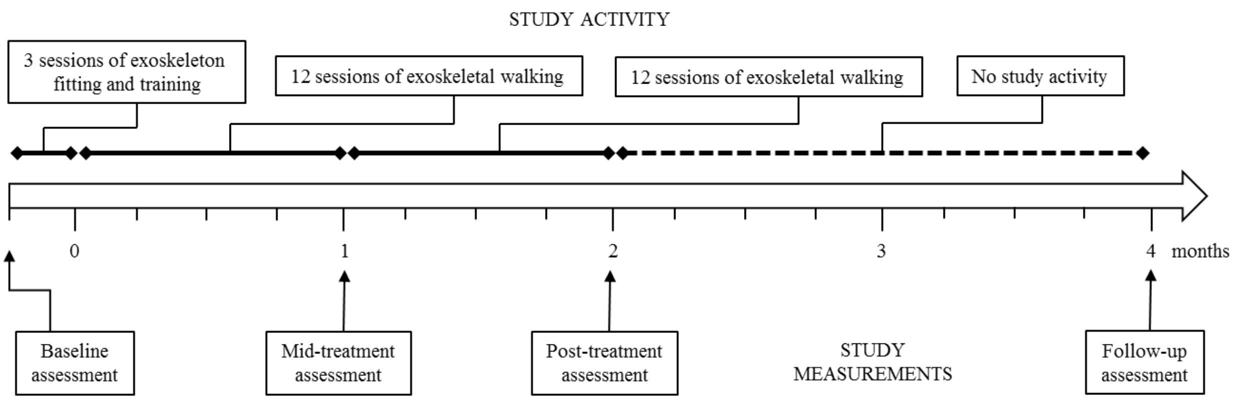


Fig. 5. Timeline of study activity and measurements for each participant.

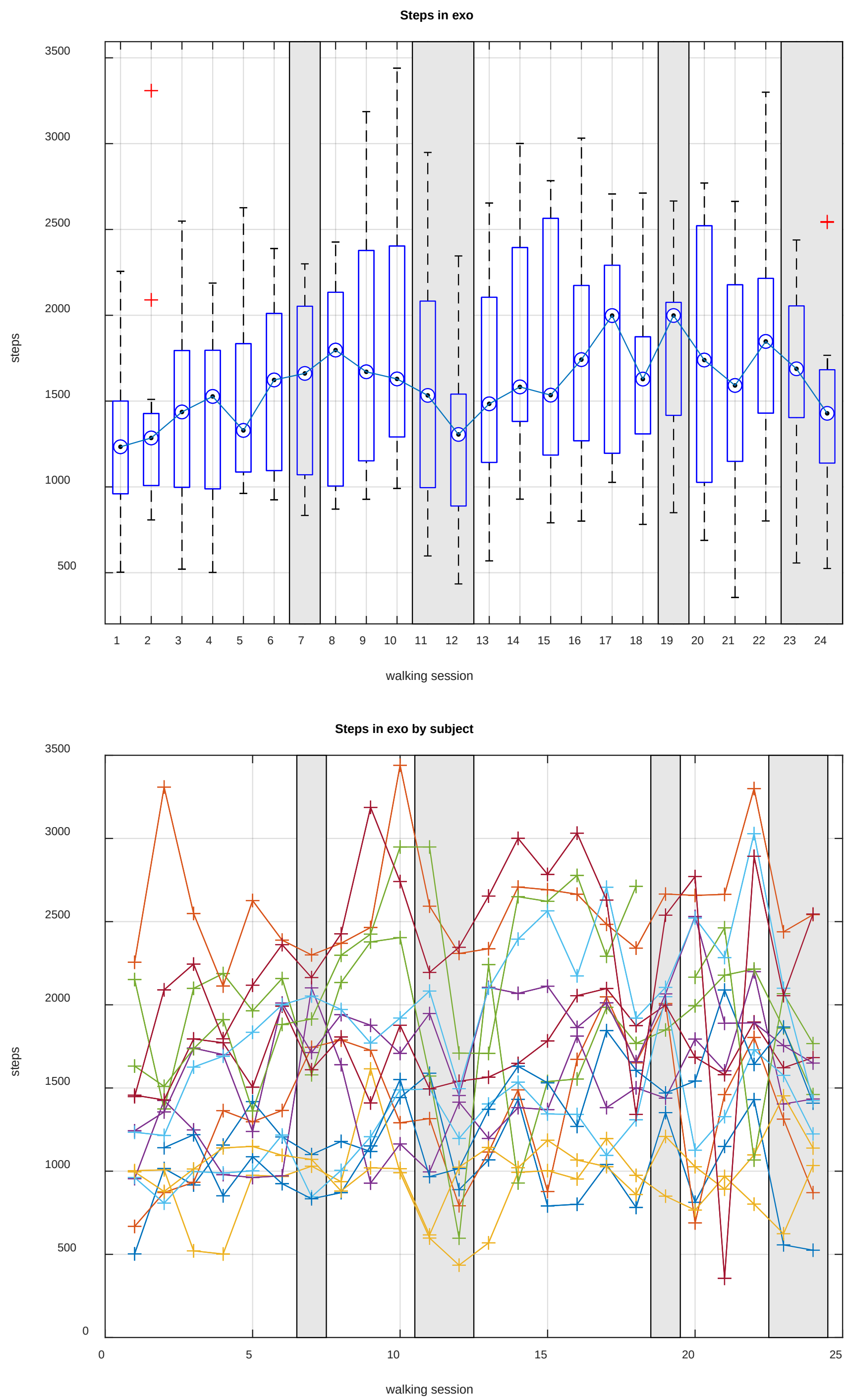
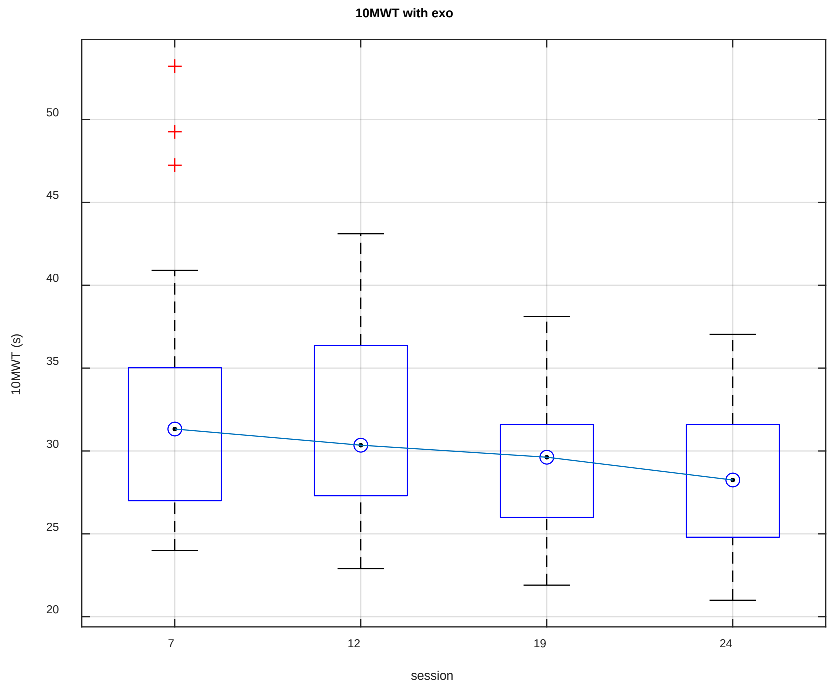


Fig. 6. Median number of steps in exoskeleton during the 24 walking sessions. The gray bands indicate sessions during which some assessments were performed.



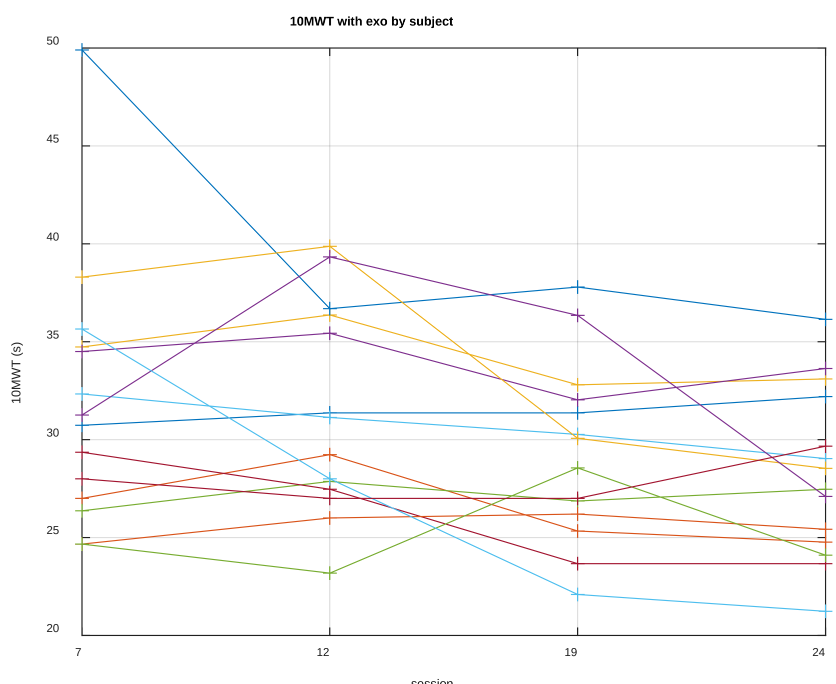


Fig. 7. Ten meter walk tests during the course of the study.

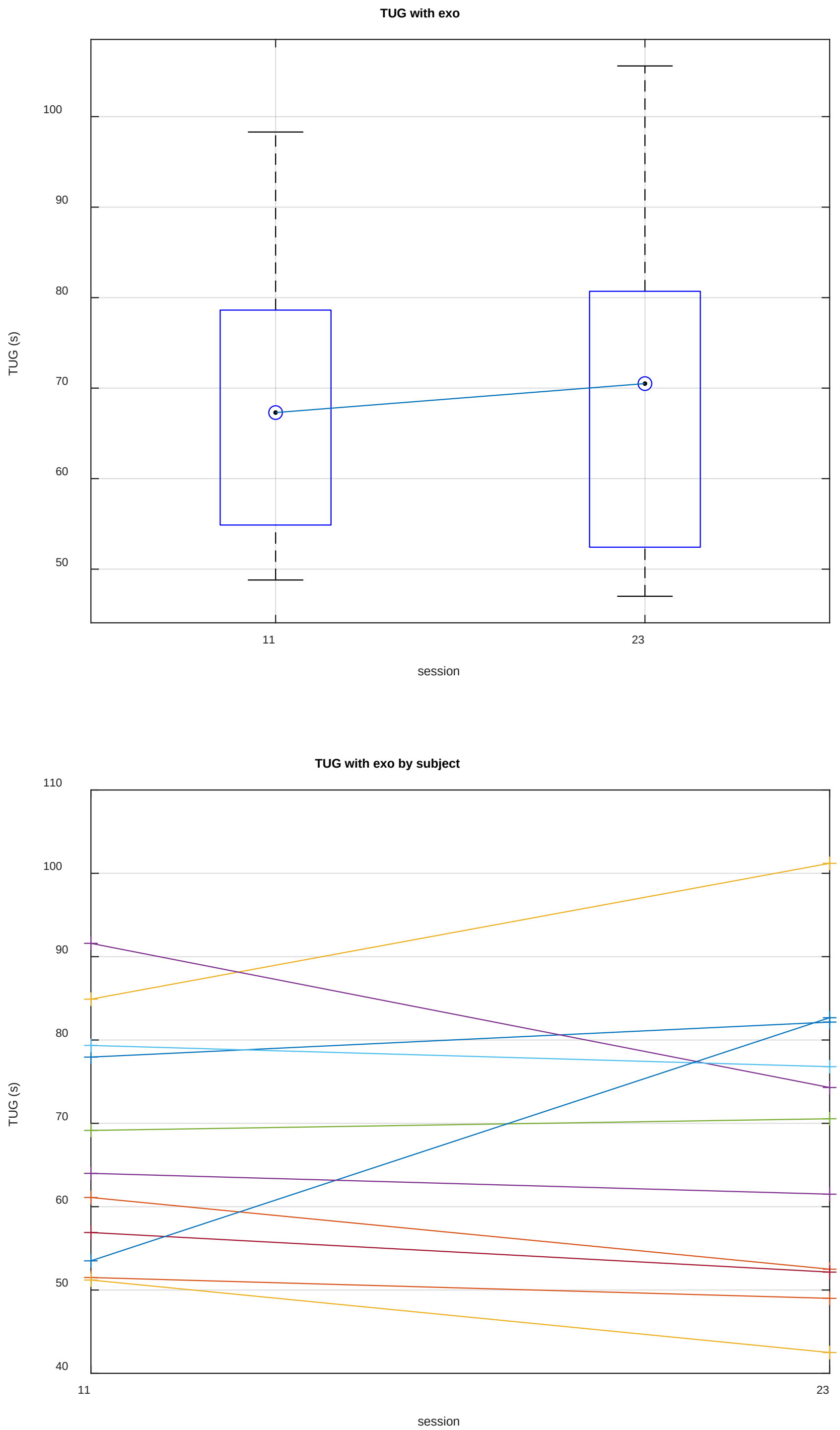


Fig. 8: 11 subjects

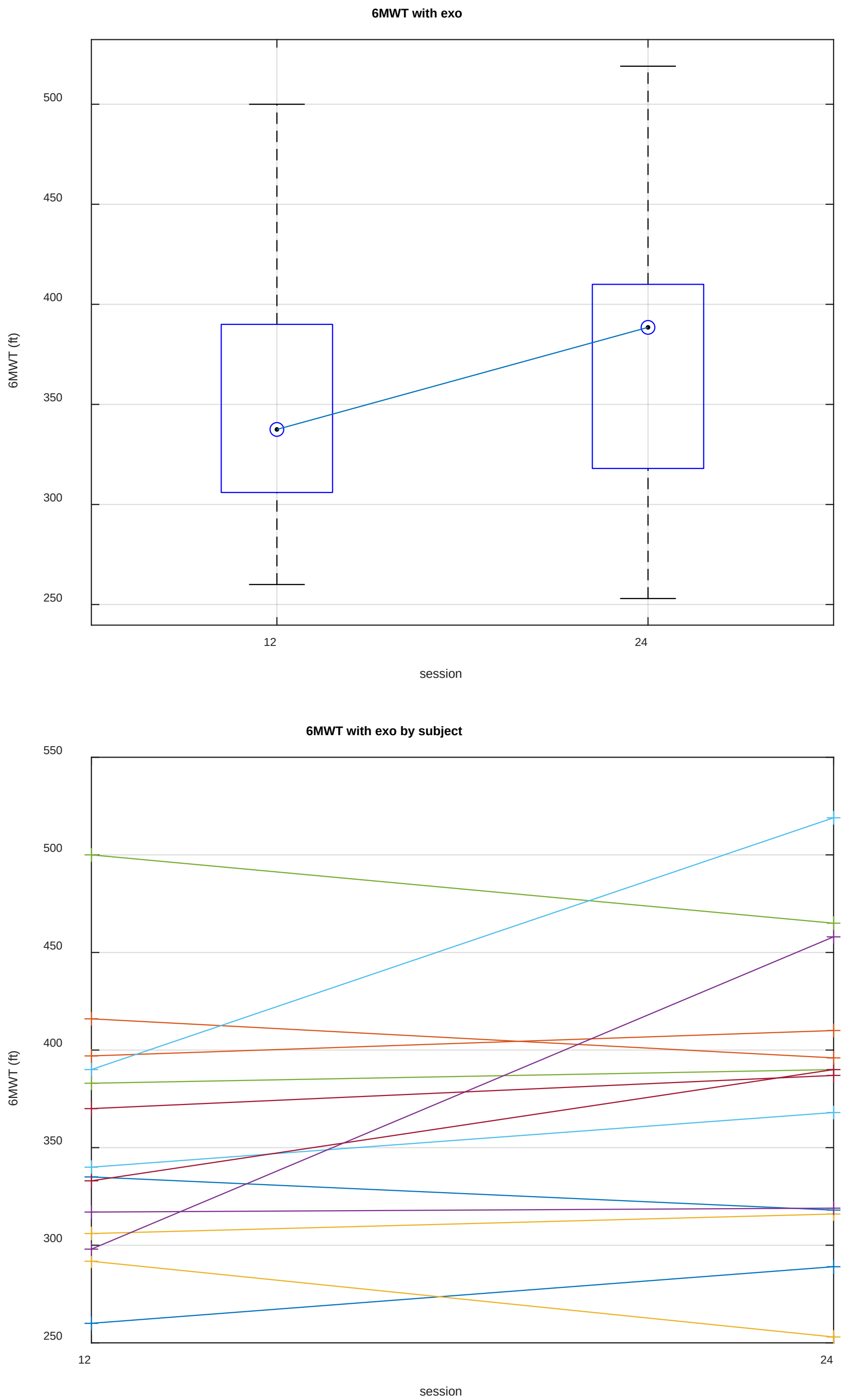

6MWT with exo
6MWT (ft)
500
450
400
350
300
250
12
24
session
6MWT with exo by subject
550
500
450
400
350
300
250
6MWT (ft)
12
24
session

Fig. 9

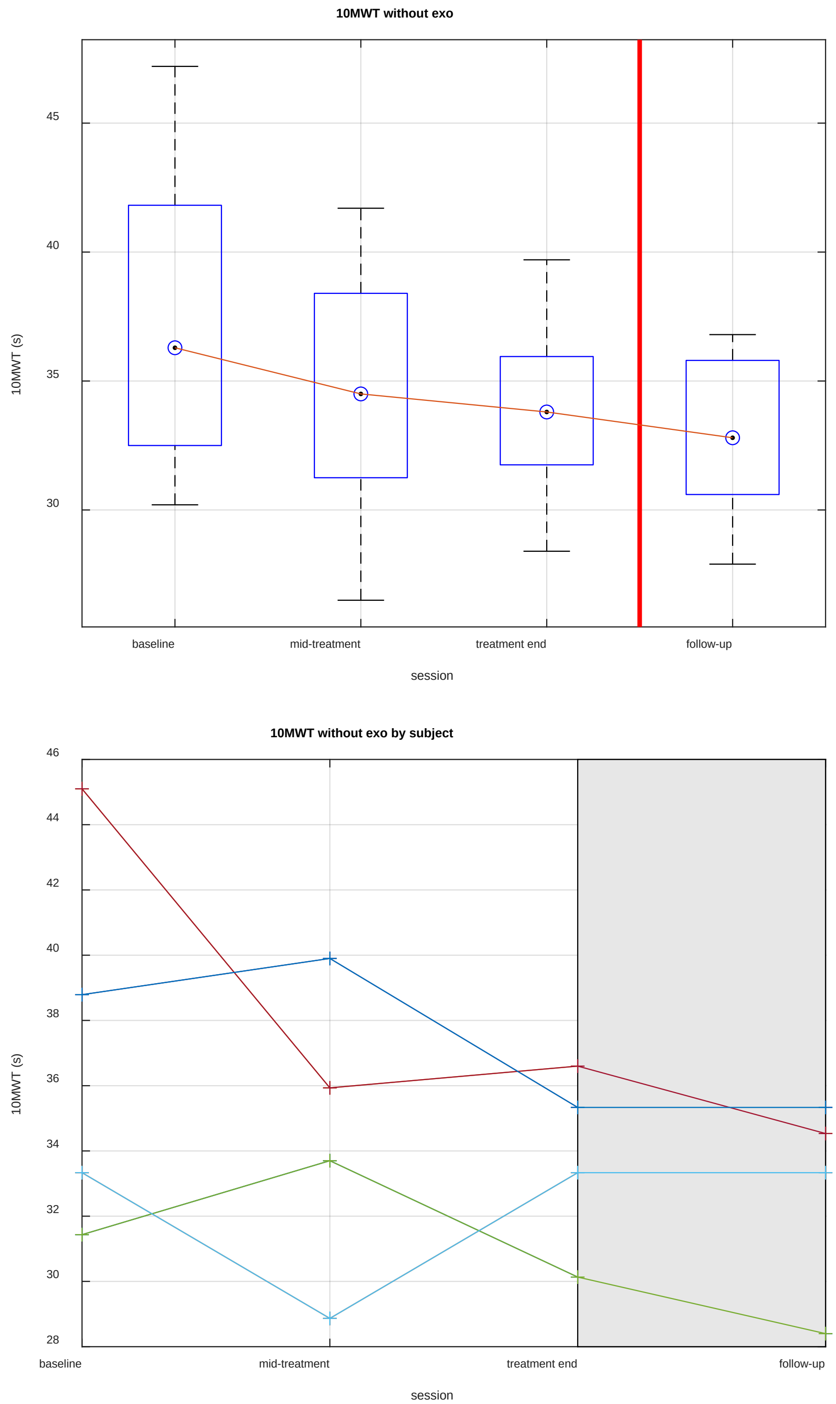
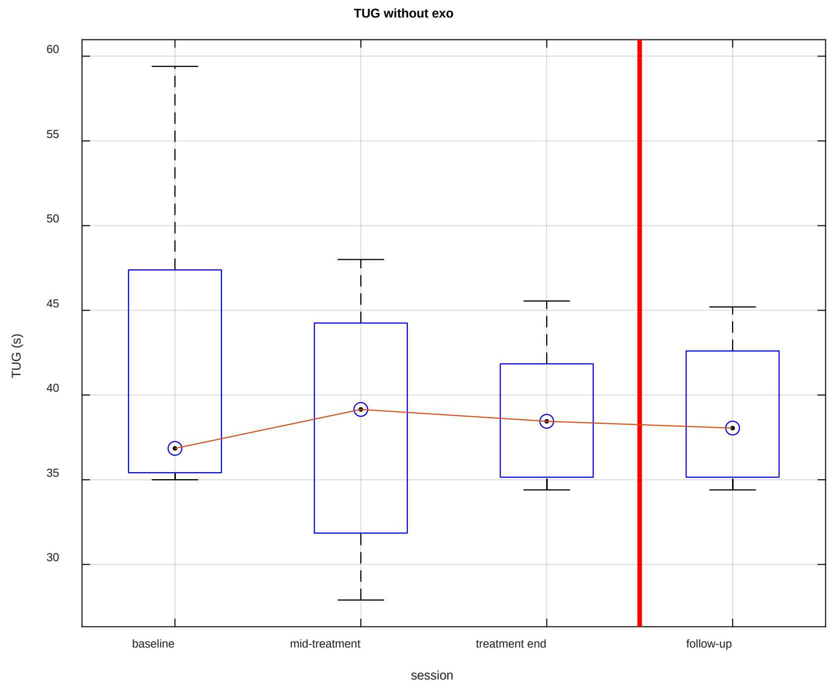

10MWT without exo
10MWT (s)
45
40
35
30
baseline
mid-treatment
treatment end
follow-up
session
10MWT without exo by subject
10MWT (s)
46
44
42
40
38
36
34
32
30
28
baseline
mid-treatment
treatment end
follow-up
session

Fig. 10


TUG without exo
60
55
50
45
40
35
30
TUG (s)
baseline
mid-treatment
treatment end
follow-up
session

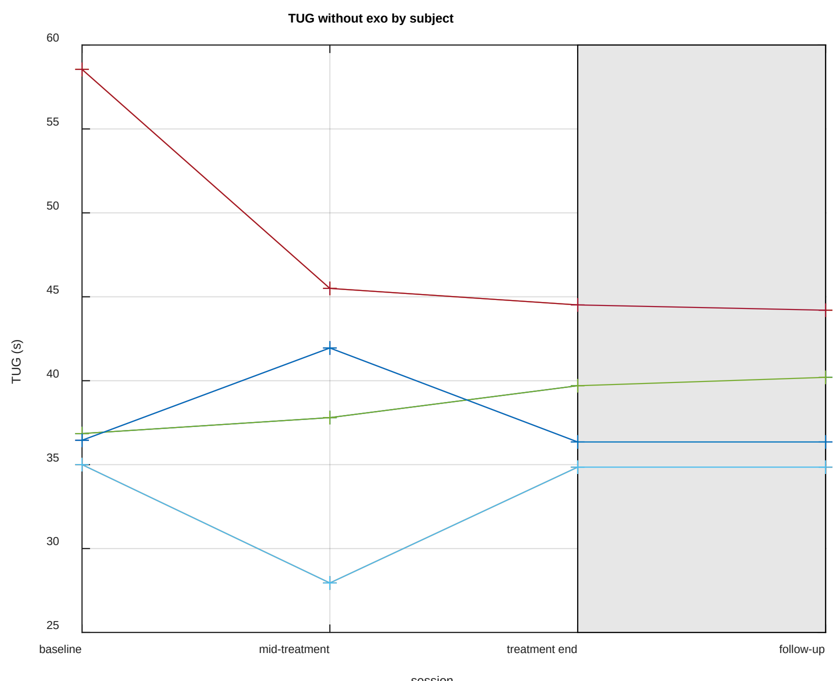

TUG without exo by subject
60
55
50
45
40
35
30
25
TUG (s)
baseline
mid-treatment
treatment end
follow-up
session

Fig. 11

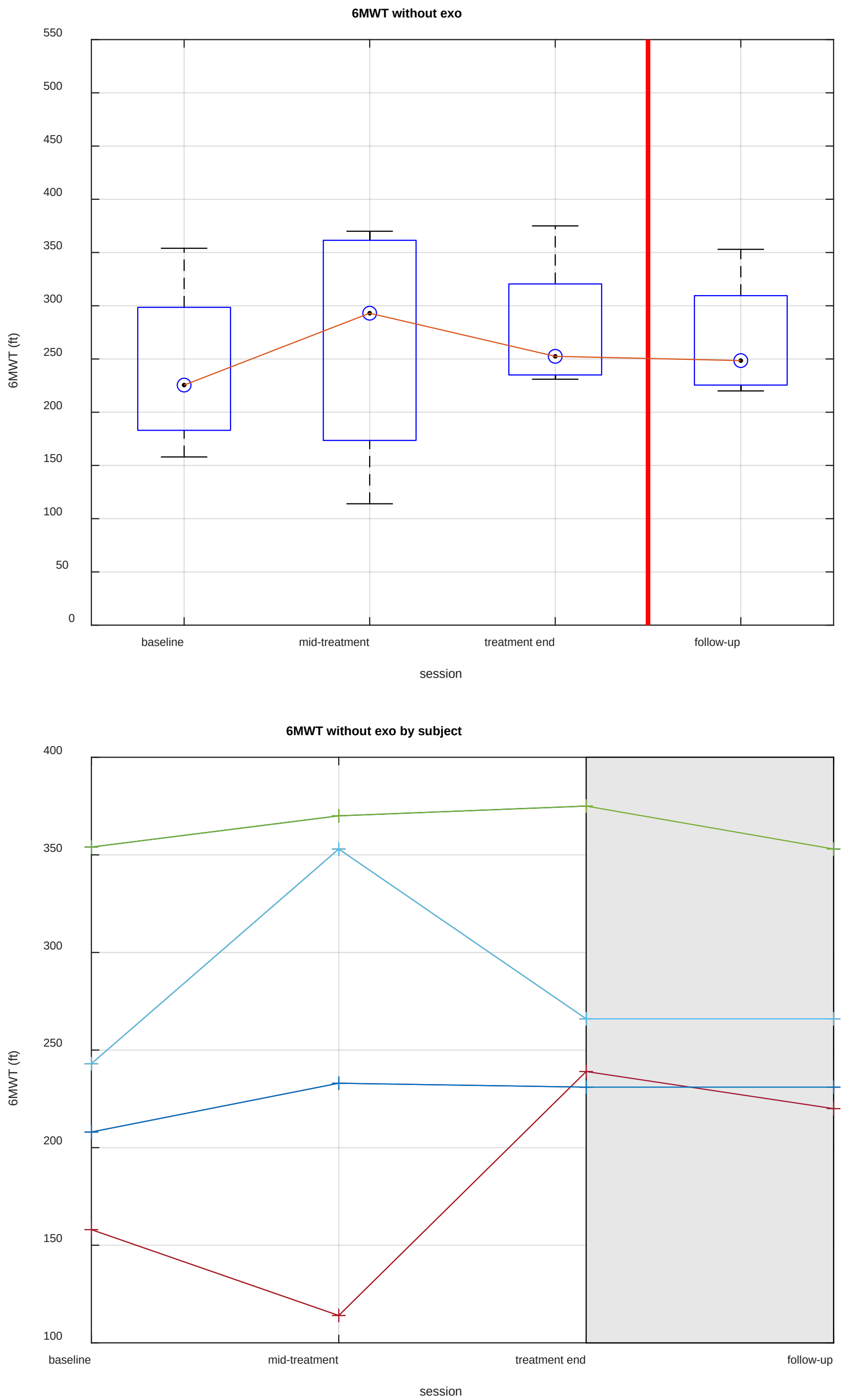

6MWT without exo
550
500
450
400
350
300
250
200
150
100
50
0
6MWT (ft)
baseline
mid-treatment
treatment end
follow-up
session
6MWT without exo by subject
400
350
300
250
200
150
100
6MWT (ft)
baseline
mid-treatment
treatment end
follow-up
session

Fig. 12

Outcome measure	Measure units	Baseline median	IQR	Treatment-end median	IQR	Percent change in median	p-value
10MWT	s	36.3	9.3	33.8	4.2	-7%	0.18
TUG	s	36.9	12.0	38.5	6.7	4%	0.96
6MWT	ft	225	116	253	86	12%	0.48

Table 1