Protocol: A Randomized, Crossover Clinical Trial of Exoskeletal-assisted Walking to Improve Mobility, Bowel Function and Cardio-Metabolic Profiles in Persons with SCI

Background

Rationale: Paralysis from traumatic spinal cord injury (SCI) results in an abrupt reduction in the level of daily physical activity. Those with more severe SCI lose the ability to stand and walk, becoming dependent on a wheelchair for mobility. As a result of this sudden and near permanent immobilization, body composition[1–3], cardiovascular function[4,5], autonomic integrity[6,7], and bowel function[8–10] are but a few of the body systems that are adversely affected. Paralysis from SCI also affects quality of life due to reduced ability to participate in the work force and reduced mobility for community integration [11–15].

Powered exoskeletal systems provide a new mobility option and appear to have potential therapeutic value for persons with chronic SCI. Phase I trials performed in subjects with non-ambulatory SCI resulted in Food and Drug Administration (FDA) approval in 2011 for institutional use of the powered exoskeleton, ReWalk™ (Argo Medical Technologies, Inc., Marlborough, MA)[16,17] and in 2012 for the Ekso™ (Ekso Bionics, Inc., Richmond, CA). Investigators at the James J. Peters VA Medical Center (JJPVAMC), Bronx, NY, began a Phase II clinical trial in September 2011 (Clinicaltrials.gov Identifier: NC0145470) to study the effects of exoskeletal-assisted walking using the ReWalk. Investigators at the Kessler Foundation Research Center (KFRC), Kessler Institute for Rehabilitation, West Orange, NJ began studying the effects of exoskeletal walking in the Ekso in 2012. The investigators at the University of Maryland Rehabilitation and Orthopaedic Institute (UMROI), Baltimore, MD acquired the ReWalk system in 2013 and have begun studying the effects of this device on their participants. Based on the experience of the investigative teams at each of these three centers, the following is a description of how these two systems are best used to accomplish exoskeletal-assisted walking in the SCI population and the physiological challenges placed upon the user to walk in these devices.

Description of how these exoskeletal systems are used (in support of rational for physiological changes): The ReWalk™ and the Ekso™ powered exoskeletal systems are similar in that the external frame supports the paralyzed individual at the level of the feet, ankles, legs, pelvis, and lower trunk. The operator is required to use Loftstrand crutches or a walker for balance and stability while standing, stepping and walking. Over ground ambulation is accomplished with appropriate weight shifts by the user, as well as computer signals and powered motors at the hip and knee joints. In both systems, to ambulate over ground, the operator must actively place his/her body appropriately in space in preparation for each step. The process of walking is an action of leaning forward, losing and regaining balance. The successful execution of this pattern in both the ReWalk, and to a lesser extent in the Ekso, places four important demands on the neuromuscular and sensory systems of the user. First, the user must learn to execute controlled movements of the trunk in order to provide the forward, backward, and lateral weight shifting needed to allow the system to initiate stepping and to maintain balance while upright. These controlled movements are accomplished through activation of back extensor musculature (to attain an upright position and control forward flexion) and abdominal musculature (to provide trunk stability). Second, the user must control the crutches, which requires activation of upper extremity and chest musculature to move the crutches and to provide stability to the shoulder complex as balance is stabilized through the upper extremities. Third, the user must be aware of his/her body position in space, which is accomplished via proprioception, vestibular awareness, auditory recognition of the position of the legs from the sound of the motors and visual observation of body position. Fourth, the user must coordinate his/her movements, shifting weight and crutch placement at the appropriate time and with the appropriate force to maintain balance while walking. The two systems differ in that the ReWalk™ requires more active participation from the user's muscles of the trunk, arms, shoulder, back, neck, and head in order to control the movements of the exoskeleton for walking and stopping, thus, making it more suitable for persons with lower SCI such as those with T3 and below who are more likely to have better trunk stability. The Ekso™ system is more robotic and requires less trunk and upper body input from the user to weight shift in order to initiate walking, making it more suitable for persons with a higher cord SCI such as those with T2 and above. These neuromuscular and sensory exoskeletal-assisted walking stimuli appear to be key attributes towards activating

trunk and upper body muscles that remain innervated above the level of injury and in those whose leg muscles below the level of injury have partial innervation as in those with zones of partial preservation.

Preliminary Studies: A Phase II, single group, pre and post intervention trial was conducted at the James J Peters VA Medical Center (JJPVAMC), Bronx, NY, to test the effect of exoskeletal-assisted walking on mobility and various secondary medical complications, as well as to continue to monitor for potential safety concerns (Clinical Trial #NCT01454570)[18]. This preliminary study was funded by the VA Rehabilitation Research & Development Service and the JJPVAMC. Exoskeletal-assisted walking in the ReWalk[19] for 4 to 6 hours per week (3x/week) was performed in ten participants with chronic (1½-14 years post injury) paraplegia (**Table 1**). All participants were non ambulatory and wheelchair dependent for home and community mobility having ASIA (American Spinal Injury Association) impairment scale AIS A or B. Three participants had lower extremity zones of partial preservation (**Table 1**). Walking tests [10 meter (10m WT) for time in seconds, 6 minute (6min WT) for distance in m and timed-up-and-go (TUG) in seconds (s)] were performed for most sessions (at least weekly) throughout the study. All participants improved their walking test scores by Session 36 (**Figure 1**). Data are reported as the mean ± SD of the group for each of their best achieved walking tests by Session 12 and Session 36 (**Table 2**). By 12 sessions, the group achieved an average exoskeletal-assisted 10m walk time of 62 ±17 s (6 of 10 were <60 s) with mean ± SD 10m velocity of 0.18 ±0.05 m/s (range: 0.11to 0.29 m/s), a 6min walk distance of 55 ±34 m (5 of 10 were >50 m) with a 6min velocity of 0.15 ±0.09 m/s (range: 0.04 to 0.38 m/s), and a TUG time of 145 ±58 s (4 of 8 were <120 s) (**Table 2 and Figure 2**). For the group, all participants improved in the three walking tests assessed by Session 36: 10m WT was 35 ±13 s (0.33 ±0.12 m/s; range: 0.16 to 0.56) with six of ten participants who achieved ≤60 seconds (≥0.17 m/s); the 6min WT was 98 ±41 m (0.27 ±0.11 m/s; range: 0.09 to 0.48) with five of ten having ≥50 m (≥0.14 m/s); and the TUG time was 90 ±44 s (range: 54 to 204 s), with four of ten participants performing <120 seconds. The change from 12 to 36 sessions for the 10m and 6min walking tests reflected an 89±60% (range: 17 to 239) and 105 ±87% (range: 25 to 303) increase, respectively. At 36 Sessions, 8 of 10 The fastest attained 6min velocity by 36 sessions of all participants was #8 who had the greatest zone of partial preservation (albeit a non ambulator) with 0.48 m/s, about 1.1 mph. In four subjects (1 cervical and 3 high thoracic level of SCI) studied at Kessler Institute for Rehabilitation/Kessler Foundation Research Center (KFRC) using the Ekso[20]; average walking velocity was 0.17±0.08 m/s with a range of 0.10 to 0.29 m/s.

Table 1. Demographic and SCI characteristics of the study population

SID	Age (y)	Ht (in)	Wt (lb)	BMI (kg/m^2)	DOI (y)	Gender	Ethnicity	Level of Injury	AIS (A/B)	LEMS
1	34	68	147	22.3	9	male	Caucasian	T4	B	0
2	49	66	150	24.2	4	male	Caucasian	T10	A	0
3	44	72	175	23.7	4	male	Asian	T4	A	4
4	58	63	144	25.5	1	female	Caucasian	T8	A	0
5	61	69	160	23.6	14	male	Caucasian	T11	A	3
6	24	73	165	21.8	5	male	Caucasian	T5	A	0
7	40	72	190	25.8	2	male	Caucasian	T1	B	0
8	50	72	220	29.8	6	male	Hispanic	T9	A	0
9	56	69	185	27.3	4	male	Caucasian	T7	A	30
10	37	67	140	21.9	7	male	Afric. Amer.	T2	A	0

SID-study identification number; y=years; in=inches; lb=pounds; BMI=body mass index; kg/m^2=kilograms per meter squared; DOI=duration of injury; Afric. Amer.=African American; AIS=American Spinal Cord Injury Association Impairment Scale; LEMS=lower extremity motor score; and T=thoracic level lesion.

Table 2. Walking Test Assessment Results (Mean±SD of Best Efforts by Session in 10 Participants)					
Sessions	**10 m WT**		**6 min WT**		**TUG**
	(sec)	(m/s)	(m)	(m/s)	(sec)
5 to 12	62 ±17	0.18 ±0.05	55 ±34	0.15 ±0.09	145 ±58
28 to 36	35 ±13	0.33 ±0.12	98 ±41	0.27 ±0.11	90 ±44
SD=standard deviation; m=meters; WT=walk test; min=minutes; TUG=timed up and go; sec=seconds; and m/s=meters per second.					

Figure 1. Results of Walking Tests at 12 and 36 Sessions by Participant

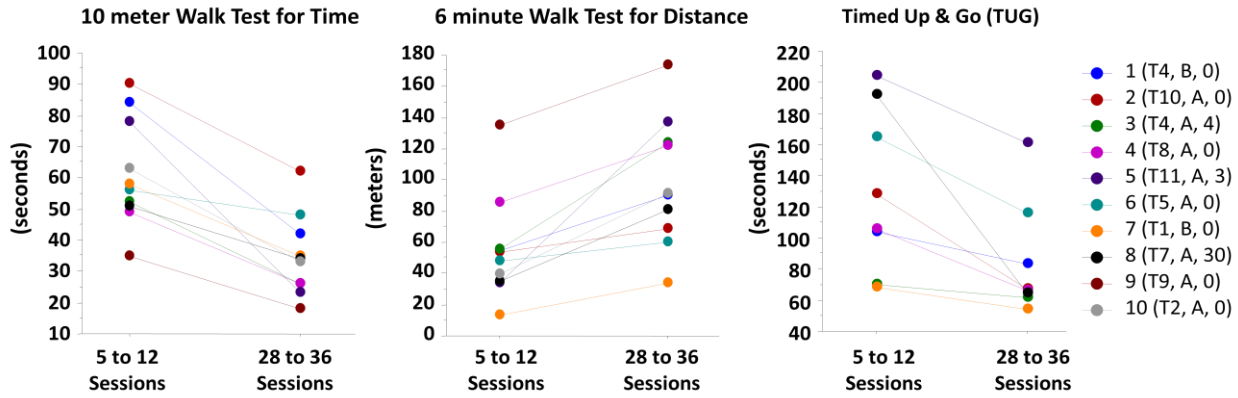
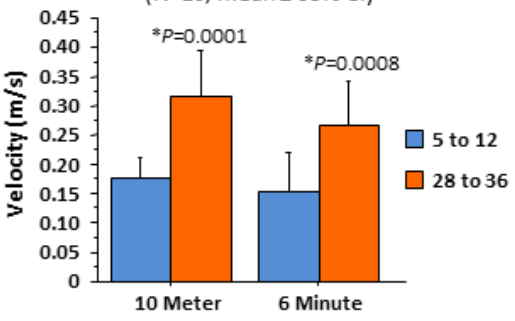


Figure legend displays the each participant's level of thoracic (T) spinal cord injury, AIS score and lower extremity motor score.

Figure 2. Walk Tests Velocity Results

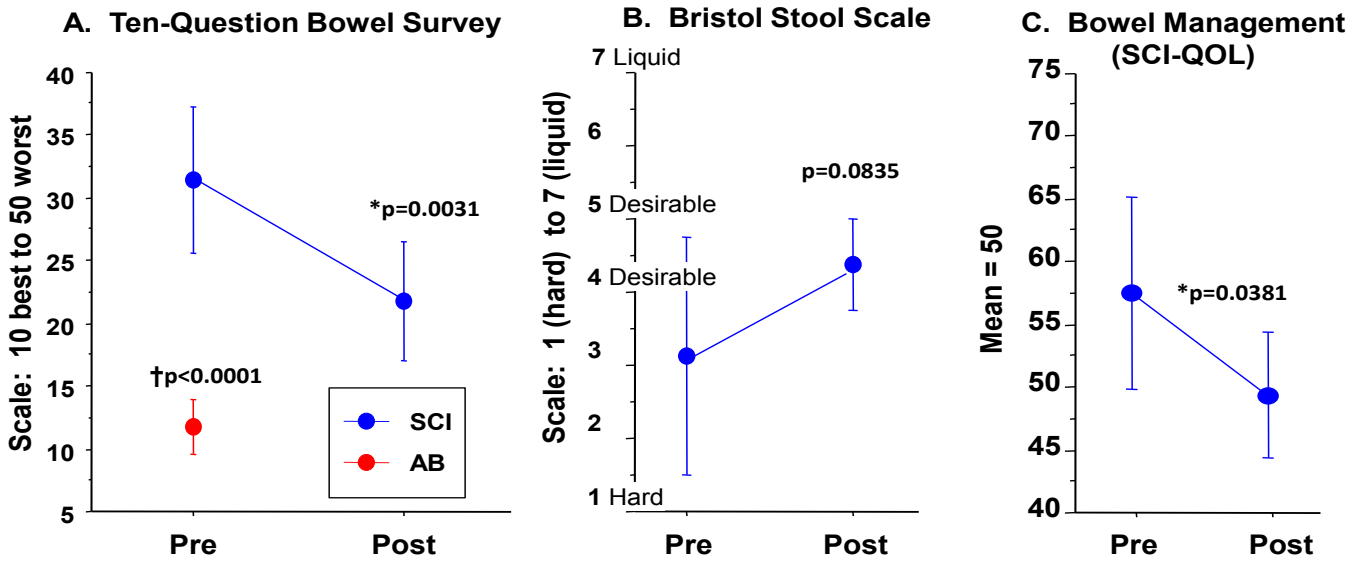


m/s = meters per second; legend: 5 to 12 and 28 to 36 is the number of sessions.

The effect of exoskeletal-assisted walking was investigated on bowel function by using three assessments: a Ten Question Bowel Function Survey (10Q BFS), the Bristol Stool Scale (BSS), and the short-form item bank for Bowel Management from the SCI QOL[21,22] (all questionnaires and survey assessments may be found in the "Surveys" section). The 10Q BFS captures information about the amount of time spent per day and the frequency per week for bowel evacuations, the amount of oral laxatives and stool softener use, frequency of digital stimulation, and frequency of unwanted bowel evacuation episodes. The BSS is an indicator of how hard the stool is and the Bowel Management short form of the SCI QOL assesses the amount of burden. All participants reported improvement for all three measures of bowel function (**Figure 3**). By session 20, significant improvements in bowel function were reported in 6 participants: reduced total time per bowel evacuation (BE) 78±34 to 33±7 minutes, $p<0.05$, power=0.98; Bristol Stool Scale (BSS) 2.6±1.1 to 4.2±0.4, $p<0.05$, power=0.98, indicating a hard to softer stool consistency; and improved weekly frequency of BE: 2±0.5 to 4±0.5, $p<0.05$, power=0.99. Improvement in bowel function continued for all of the training sessions but by one-month after cessation of the walking program the improved bowel function was no longer present[23].

Analysis of the 10Q BFS, BSS, and Bowel Management SCI-QOL was performed in 8 participants before and after 36 sessions (**Figure 3**).

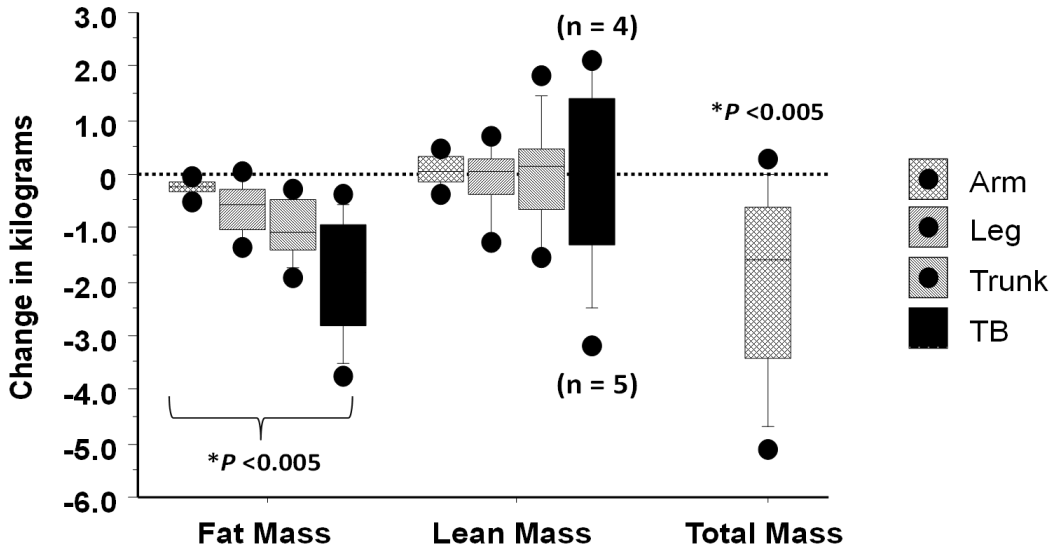
Figure 3. Bowel Function results from the preliminary data, N=8.



Pre=before exoskeletal-assisted walking training; Post=after 20 sessions; SCI=spinal cord injured participants; in Panel A, AB=able-bodied controls matched for age±5 years, gender, and ethnicity.

Dual energy x-ray absorptiometry (DXA) was performed pre- and post-training (36 sessions) in nine of ten participants (one was lost to follow up due to an abrupt change in his school schedule). On average, the group lost total body mass (**Figure 4**). In five participants most of this weight loss was attributed to fat and lean mass loss, but in four participants, the total mass loss was predominantly from fat tissue mass (**Figure 4**). The nine participants demonstrated significant loss of regional and total body fat tissue mass [mean ±SD (95% confidence limits)]: arms: -236 ±159 g (-114 to -358 g), P=0.0021; legs: -641 ±493 g, (-262 to -1020 g), P=0.0045; trunk: -1030 ±566 g, (-595 to -1466 g), P=0.0006; and total body: -1914 ±1150 g, (-595 to -2798), P=0.0011. Note, the body fat mass losses are strongly supported because the confidence limits were outside of 0 and the power for the total and regional body fat losses was at 100%. Regional and total body lean tissue mass improved in four of nine participants, albeit not statistically significant when analyzed for the total group.

Figure 4. Regional and Total Body Fat and Lean mass and Total Mass changes Pre and Post 36 sessions of Exoskeletal-Assisted walking (N=9).



TB=total body; All nine participants lost fat mass. Four gained lean and five lost lean along with fat mass, which is consistent with the total weight loss. Three of the four who gained lean had zones of partial preservation.

To date, with over 1000 hours of exoskeletal-assisted walking, no study-related serious adverse events (SAEs) occurred during this Phase II clinical trial. In the initial weeks of the clinical trial a few minor skin abrasions were noted that fully resolved with improved fitting and padding[24].

Relevance of the study and explain the applicability of the proposed findings:

Mobility: While the USA is one of the best countries in the world for accessibility for the disabled, wheelchair-dependent persons with SCI are at many distinct disadvantages, one of which is the daily loss of the ability to be at eye level with others who are standing. Not all buildings have accessible ramps, and stairs continue present an obstacle for entrance.

Medical complications of SCI: Persons with SCI are plagued with poor bowel function which includes chronic constipation, fecal impaction, involuntary and untimely bowel evacuation accidents, and significant time consumption for bowel care[8–10,25–28]. Difficulty with bowel evacuation is often listed as one of the top three concerns to people with SCI[11]. Bowel function care for constipation and bowel incontinence for persons with SCI has been essentially unchanged for the past few decades[10]. This care involves a regimented routine and the use of oral laxatives, stool softeners, suppositories, digital-rectal stimulation, and/or dietary fiber augmentation[29]. In the able-bodied population, gastric emptying has been demonstrated to be increased with physical activity[30]. The preliminary data, after exoskeletal-assisted walking, was highly supportive of improved bowel function in the participants studied to date. Body composition is dramatically altered following SCI[3,31–34]. Fat mass is gained and lean is lost at an alarming rate during the first year after SCI[1], and these changes continue throughout the course of the lives of those with SCI to a greater extent than in the able-bodied population[3,35]. High density lipoprotein cholesterol (HDL-c) is reduced[36–40]. Testosterone levels have been reported to be reduced in men with SCI studied[41–43]. In a few animal and human studies, testosterone has been shown to improve with exercise or be associated with higher values in those that exercise than in sedentary control subjects[44–47]. One study by You, T., et al. demonstrated that aerobic exercise training could improve severe obesity-related hypogonadism in male rats[48]. In a study performed in military personnel during basic training, it was demonstrated that training improved strength, aerobic capacity, and testosterone[47]. In older men, it has been shown that regular intensive exercise is associated with higher growth hormone and testosterone levels and that exercise may have a role in counteracting the normal decline in growth hormone with aging.[44] As such, it may be reasonable to expect improvements in testosterone levels as a result of the

exoskeletal-assisted walking training. In a recent article, performed in able-bodied men, it was demonstrated that a strong relationship existed between reduction in estradiol and increased fat mass[49]. Preliminary data supports a significant change in body fat in all participants studied to date. Four of nine participants demonstrated an improvement in leg and total body lean mass. These four were those participants who also experienced an improved thoracic sensory level and/or had a zone of partial preservation. It is reasonable to expect that the increased activity results in an improved body composition. As such, the combination of the increased activity and loss of fat may would be expected to result in an improved HDL-c level and improved insulin sensitivity. If this proposed study demonstrates that increased activity level results in subsequent improvement in body composition, insulin sensitivity, and HDL-c, then the risk for heart disease would be anticipated to be reduced. Additionally, we believe that this study will demonstrate in a larger sample size that exoskeletal-assisted walking significantly, and relatively promptly improves bowel function.

Objectives/Specific Aims/Hypotheses

This clinical trial is designed to demonstrate that the walking skills achieved in the preliminary study at the JJPVAMC can be achieved in a larger sample of participants and at three study sites. It is also designed to determine if the body composition and bowel function benefits that were observed with as few as four to six hours per week of walking over three months can be demonstrated in a larger sample. The Phase II trial conducted at the JJPVAMC demonstrated that ten participants were able to use the device to successfully walk for four to six hours per week for three months. It is unknown if a larger sample of persons with SCI can be taught to walk in these devices with a similar proficiency and competence as demonstrated in our pilot study. As such, the **primary objectives** of this proposal are to achieve successful walking skills in the exoskeletal-assisted walking devices for an extended period of time and at specific velocities and distances over the course of 36 sessions in three months in people with chronic SCI who are wheelchair dependent for community mobility. The **secondary objectives** are to determine if this amount of walking is effective in improving bowel function and body composition in the same patient population. The **exploratory objectives** are to address additional questions concerning the retention or non-retention of the positive changes, the effects of the increased physical activity from exoskeletal-assisted walking (WALK) on vagal tone, orthostatic tolerance, lipid profile, total testosterone, estradiol levels, immune system factors, and quality of life (QOL). Other tertiary goals are to explore the relationships among these variables. For example, if there is a change in HDL-c, total testosterone and estradiol levels, what is the relationship of this change with fat mass loss and/or is the magnitude of this change related to the achieved mobility and walking skills? The Primary and Secondary specific aims are supported with the pilot data above and in the power calculations in the Statistical section. The exploratory aims are of interest and may be used to inform the investigators as to the feasibility and design of future work.

Specific Aims

Primary Aims:

1. By session 12 (first month of WALK training), the participants will be able to perform the following exoskeletal-assisted walking tests with or without minimal assistance:
    a. 10m WT
        i. 90% in ≤60 seconds (≥0.17 m/s)
        ii. 10% in ≤40 seconds (≥0.25 m/s)
    b. 6min WT
        i. 80% at a distance of ≥50 m (≥0.14 m/s)
        ii. 20% at a distance ≥80 m (≥0.22 m/s);
    c. TUG
        i. 80% in ≤120 seconds
        ii. 20% in ≤90 seconds

2. By session 36 (three months of WALK training), participants will have improved their ability to walk faster and longer distances and will be able to perform exoskeletal-assisted walking tests with or without minimal assistance as follows:
    a. 10m WT - 70% in ≤40 seconds (≥0.25 m/s)
    b. 6min WT - 70% at a distance ≥80 m (≥0.22 m/s)
    c. TUG - 60% in ≤90 seconds.

Secondary Aims are to affect the following by three months of exoskeletal-assisted walking (WALK):

1. To improve bowel function as measured by established survey instruments; and
2. To reduce total body fat mass and percent as measured by DXA.

Exploratory Aims:

1. To improve autonomic/cardiovascular function (vagal tone) measured by high frequency component of the 24-hour holter monitor;
2. In persons with T6 and above, to improve orthostatic hypotension (OH) tolerance measured by a standard OH challenge test from supine to seated;
3. To improve HDL-c, Homeostatic Model of Assessment – Insulin Resistance (HOMA-IR), serum total testosterone and estradiol levels measured by serum and plasma assay kits; and
4. To improve quality of life (QOL) measured by item banks from the SCI-QOL and Patient Reported Outcomes Measurement Information System (PROMIS).

Hypotheses

Primary Hypothesis (are tested pre and post the WALK arm only):

1. By session 36, 70% of the participants compared with 10% at session 12 will be able to perform the 10m WT ≤40 seconds (≥0.25 m/s);
2. By session 36, 70% of the participants compared with 10% at session 12 will be able to perform the 6min WT distance ≥80 m (≥0.22 m/s); and
3. By session 36, 60% of the participants compared with 20% at session 12 will be able to perform the TUG in ≤90 seconds.

Secondary Hypotheses (are tested between the WALK arm and the UA arm, within-subject)

4. Bowel function will improve by 25% using the Ten-Question bowel survey. (Note, the components of this survey represent a 50% reduction in bowel evacuation (BE) time, a 25% increase in BE weekly frequency per week, a 50% reduction in BE medication use, and/or a 25% improvement in stool consistency from harder to softer.)
5. Total body fat mass is hypothesized to be reduced on average by 9±7 percent (an average of 1.9±1.2 kg decrease from baseline).

Exploratory Hypotheses:

1. In Group 1 (WALK first), the bowel improvement changes will return to baseline values by one month of the UA arm.
2. In Group 1 (WALK first), the body fat mass and percent changes will return to baseline values by 3 months of the UA arm.
3. Associated with increased activity, there will be improved autonomic/cardiovascular function (vagal tone) as measured by the high frequency component of the holter monitor recordings and the tolerance to orthostatic challenge.
4. Associated with increased activity and fat mass loss, there will be statistically significant improvement in HDL-c, HOMA-IR, serum total testosterone and estradiol levels
5. Quality of life (using select SCI-QOL item banks) will be reported to be improve after in the WALK arm, but not for the UA arm

Safety concerns with the use of the exoskeletal devices will continue to be evaluated. Any serious (SAEs) or adverse events (AEs) will be recorded and reported the appropriate oversight bodies.

Study Design

Research design: A Phase III randomized clinical trial (RCT) will be performed using a crossover design and employing an exoskeletal-assisted walking intervention. The experimental arm will be compared to a usual activities (UA) arm, as the control, in 132 persons with chronic SCI (>6 month post injury) who are wheelchair-dependent for outdoor mobility in the community. Eligible participants will be randomized (within site) to one of two groups for 12 weeks (three months): Group 1 (n=32) will receive exoskeletal-assisted walking (WALK) first for 12 weeks then crossover UA for a second 12 weeks; Group 2 (n=32) will receive UA first for 12 weeks then cross-over to the WALK arm for 12 weeks of training. The WALK arm will consist of supervised exoskeletal-assisted walking training, three sessions per week (4-6 h/week) for 36 sessions for their second 12-week period. The UA arm will consist of identification of usual activities for each participant, encouragement to continue with these activities and attention by study team members throughout the 12-week UA arm. These activities will be recorded in a weekly log. A fixed answer format will be used to capture this information.

Rationale for intervention to be studied: This research design has several advantages. Group 1 will serve as the intervention follow-up to assess retention or non-retention of change due to the intervention on the outcome variables. Group 2 will serve as a lead-in to assess stability of the outcome variables prior to the intervention. Additionally, because of tremendous variability in the SCI population and difficulty with case-control matching, the cross-over design will help to control for variability between participants because each participant will serve as their own control. Veterans and nonveterans with SCI generally do not receive further structured rehabilitation once they have completed the acute and sub-acute phases of their rehabilitation. As such, the usual lifestyle activities have been chosen as the control for this study. Dr. Spungen has discussed the optimal control for an exoskeletal-assisted walking program. She has consulted with the Chiefs of several SCI Services in both the VA and non-VA rehabilitation hospitals. A case-controlled, matched RCT study would be strongest with two interventions: exoskeletal-assisted walking compared with any other form of physical activity such as robotically assisted body weight supported treadmill training (Lokomat), body weight supported treadmill training, arm ergometry etc. However, there are two considerations that make this type of study not feasible. One is that it would be extremely difficult to case-control match for independent variables within site, and the second is that most participants would likely not agree to participate if there was a 50% chance they would not get the exoskeletal-assisted walking arm. In order to control for an attention effect, participants in the UA arm will keep weekly activity logs and be contacted by phone calls from the study team to receive attention and encouragement to continue participation in the UA of their choice. In order to control for attention aspects of this type of study, participants will also make in person twice monthly visits to their sites during the UA arm. During these visits, study team staff will review their UA logs and administers the 10Q BFS and BSS.

Because the achievement of improved secondary medical outcomes is likely dependent on the ability to walk in the exoskeletons, the primary outcome will be achievement of mobility skills in the exoskeletal devices. It has not been demonstrated in a large sample that people with SCI can use the device as described by the pilot data. Secondary outcomes will be change in fat mass and bowel function. Exploratory outcomes will be change in cardiovascular and autonomic measures and quality of life surveys [using the newly validated SCI quality of life (SCI-QOL) tool for bowel, bladder and five emotional domains][21,50].

Description of walking in the ReWalk: The ReWalk exoskeletal system requires the user to actively shift their body appropriately over their legs in order to maintain balance on the stance leg allowing the swing leg to clear the floor. This is accomplished with coordinated movements involving the upper extremity muscles in the trunk, arms, shoulder, back, neck, and head for the body to maintain balance dynamically as the system assists the legs to move in a normal walking pattern. Balance is maintained with the use of Loftstrand crutches. At all times

during exoskeleton walking, participants must use both crutches. A mode selector, which is worn on the wrist, is used to select "walk mode" once the person is stable during standing. Following walk mode selection, the user shifts onto the left leg and slightly forward so that the right leg is offloaded. The tilting/leaning action triggers the device to swing the right leg forward and the user weight shifts so that their trunk is over the right leg as they step onto the right foot. This will then initiate the left leg to swing forward; the use weight shifts onto it and continuous walking is achieved if this coordinated weight shifting and stepping onto each leg is continued. The unit will stop walking in two ways. If the user does not shift their weight onto the front foot, then the ReWalk will time out after two seconds and return to the standing position. The second way is if the person does not shift their weight appropriately to have the swing leg clear the floor. This will cause the leg to have some additional external force that the ReWalk will sense and cause the system to return to standing mode. The stepping and walking gait pattern of the ReWalk is very similar to normal walking[51]. The gait pattern settings in the ReWalk can be preset in order to increase or decrease the step length, speed of the step and/or the amount of foot clearance the person will have during walking, permitting a velocity of 0.10 to 0.80 m/s.

In order to successfully accomplish walking with the ReWalk, considerable coordination between the upper extremity muscles in the trunk, arms, shoulder, back, neck, and head is needed in conjunction with dynamic standing balance. A specific pattern of trunk positioning, crutch placement and weight shifting is needed. To prepare for walking, the user must attain a stable standing position with the crutches placed slightly in front of him/her. To begin walking, the user must shift their weight onto the left foot to unweight the right foot. The right foot steps forward first, and this is initiated when the user slightly leans forward, by bringing the crutches forward, away from the stepping leg to allow it to swing forward and clear the floor. As the stepping leg moves forward and extends toward the ground, the user shifts weight forward, stepping onto that leg and then sequentially brings the crutches forward for the next step. Immediately after the weight is shifted, the user must straighten his/her posture with their body perpendicular to the ground before leaning forward to initiate the next step. This is similar to a normal walking pattern. As the leg contralateral to the initial step leg swings forward, the participant must shift the crutches away from that leg to allow it to step forward. This process is repeated for continued walking.

Description of walking in the Ekso: The users are progressed through a series of steps to participate in over ground ambulation. The first method, called FirstStep. This is when the trainer triggers the step by using a controller while verbally cueing the participant that the device is taking a step. The second method, called ActiveStep is when the user to initiates the stepping action by pressing a button on a pair of instrumented crutches for each step. The last method, called ProStep, is when the user shifts their weight lateral and forward onto the front foot, until sensors indicate when an appropriate shift has been performed. The stepping pattern can be adjusted to change the step time and step length. The trajectory of the foot allows for foot clearance similar to a marching pattern. The device has the ability for provide some abduction and plantar/dorsi flexion positioning. This device has the ability to alter the stepping, which would allow the user to take faster or slower steps with a longer or shorter stride length, thus permitting a walking velocity of 0.10 to 0.45 m/s. Stopping is achieved by holding a stationary position and by not activating sensors. The Ekso allows for varying robot-assist levels that can be decrease or increased bilaterally. The robot assistance can operate will full or variable assist, dependent on the level of function of the individual. At all times during exoskeleton walking, participants must use both crutches

Rationale for both devices: The ReWalk and Ekso devices have functional similarities, both requiring the use of crutches for balance. The maximum velocity of the ReWalk is 0.80 m/s and of the Ekso, 0.45 m/s[19,20]. The rationale for using both systems comes from previous clinical experience of the investigators at the JJPVAMC and KFRC. The Ekso, because it provides more robot-assistance (i.e., the leg is lifted in a marching style gait to assure foot clearance, is better able to accommodate those participants with a low cervical (C) or high thoracic (T) level who have less trunk stability and are not able to weight shift to clear the stepping leg. The ReWalk offers a more natural walking pattern, more extensive walking and requires more user input than the Ekso; thus,

this device is better suited for those with lower thoracic SCI (T3 and below) who can perform weight shifting and clear the foot for stepping. By including both the Ekso (for T2 and above in those who have some spared hand function to hold the crutches or can have them securely attached) and the ReWalk (for T3 and below), the effect of exoskeletal-assisted walking can be investigated across all levels of cervical, thoracic and lumbar SCI.

Study variables to be measured: Baseline screening evaluations for eligibility will include a history and physical examination with a complete International Standards for Neurological Classification of SCI (ISNCSCI) examination [the ISNCSCI includes a full American Spinal Cord Injury Impairment Scale (AIS)], range of motion, Ashworth spasticity examination at selected lower extremity joints, standard orthostatic tolerance test, and bone mineral density (BMD). The primary outcome assessments will consist of the 10m, 6min and TUG walking tests. The walking tests will be performed and recorded for each session of the WALK arm. The secondary outcomes include body composition and bowel function. A full battery of outcome assessments will be performed at baseline and after completion of the intervention of WALK arm (after 36 sessions) and the UA (after 12 weeks) periods. Interim assessments for the SCI QOL will be performed at midpoint, after 18 sessions. Bowel function will be measured bi-weekly throughout both arms of the study (**Table 3**).

Table 3. Schedule of Testing for each Intervention Arm

Group 1	Pre 1		**Exoskeletal-Assisted Walking Intervention (WALK)**												Post 1		**Usual Activities (UA)**												Post 2	
Month	-1		1				2				3				4		5				6				7				8	
Week	-1		1	2	3	4	5	6	7	8	9	10	11	12	13		14	15	16	17	18	18	20	21	22	23	24	25	26	
WALK Sessions[1]			3	3	3	3	3	3	3	3	3	3	3	3	Cross-over															
WALK Skills[2]			x	x	x	x	x	x	x	x	x	x	x	x																
Log record																	1	1	1	1	1	1	1	1	1	1	1	1		
DXA Scan	x														x														x	
ISNCSCI Exam	x														x														x	
Holter monitor		x														x														x
OH BP test		x														x														x
Blood Draw	x														x														x	
SCI-QOL		x														x														x
Bowel Function	x	x		x		x		x		x		x		x	x			x		x		x		x		x		x	x	

Group 2	Pre 2		**Usual Activities (UA)**												Post 3		**Exoskeletal-Assisted Walking Intervention (WALK)**												Post 4	
Month	-1		1				2				3				4		5				6				7				8	
Week	-1		1	2	3	4	5	6	7	8	9	10	11	12	13		14	15	16	17	18	18	20	21	22	23	24	25	26	
WALK Sessions[1]															Cross-over		3	3	3	3	3	3	3	3	3	3	3	3		
WALK Skills[2]																	x	x	x	x	x	x	x	x	x	x	x	x		
Log record			1	1	1	1	1	1	1	1	1	1	1	1																
DXA Scan	x														x														x	
ISNCSCI Exam	x														x														x	
Holter monitor		x														x														x
OH BP test		x														x														x
Blood Draw	x														x														x	
SCI-QOL		x						x								x						x								x
Bowel Function	x	x		x		x		x		x		x		x	x			x		x		x		x		x		x	x	

[1]WALK Sessions include heart rate (HR), blood pressure (BP) and Rating of Perceived Exertion (RPE) recordings before, during and after walking and/or more often as clinically indicated.

[2]WALK Skills include 10m WT, 6min WT, TUG, and assorted mobility skills for turning, stopping, reaching, and navigating doors.

DXA=dual energy x-ray absorptiometry scan; ISNCSCI=International Standards for Neurological Classification of Spinal Cord Injury (SCI); OH BP=postural orthostatic hypotension blood pressure tolerance test; and SCI-QOL=spinal cord injury quality of life surveys.

Description of Assessments

Mobility Skills: Exoskeletal-assisted walking tests for the 10m WT, 6min WT, and TUG will be performed at least one time per week during the WALK arm intervention. It was observed during the Phase II trial that weekly assessment of the walking tests provided structured feedback to the participants regarding their progress in mastering the use of the powered exoskeleton and was useful in motivating the participants. Additional mobility skills (turning, wall rest, stopping, and navigating doors) will be assessed throughout the WALK arm; but not to be considered as part of the primary outcomes. The walking tests will be performed as per the standardized descriptions[52,53] with modifications for the exoskeletons. The PI and lead biomedical engineer from the JJPVAMC (Mr. Pierre Asselin) have significant experience and expertise in performing these walking and mobility tests and will travel to the other two sites to train the staff for standardization purposes across the sites during the designated start-up time of the study.

Body Composition: A dual energy x-ray absorptiometry (DXA) scan for regional and total body fat, lean and bone tissue masses will be performed three times: at baseline, at crossover, and after the second arm of the study for both the WALK and UA arm interventions. Standardized DXA scans will be performed as previously described at all three study sites[2,3,54].

ISNCSCI: A neurological evaluation for sensory and motor function, level of injury and lower extremity motor scores will be performed according to the ISNSCI standards[55]. This exam will be performed three times: at baseline, at crossover, and after the second leg of the study for both the WALK and UA arm interventions.

Bowel function surveys: The 10Q Bowel Function Survey (BFS) and the Bristol Stool Scale will be administered before both interventions and then bi-weekly (two times/month) for a total of 16 times during the two arms of the study. This information will be used to determine key components to a participant's weekly bowel regime[23]. The Bowel Management item bank short form from the SCI-QOL will be performed three times: at baseline, at crossover, and after the second arm for both the WALK and UA arm interventions. The PI will instruct the three sites on the standardized method for administering these assessments.

SCI-QOL: The Spinal Cord Injury Quality of Life measurement tool is the first validated SCI-specific QOL measurement tool for the field[22,50,56]. The specific short form item banks to be use are: Ability to Participate, Independence, Positive Affect, and Resilience. These will be performed three times: at baseline, at crossover, and after the second arm for both the WALK and UA arm interventions. The PI will instruct the three sites on the standardized method for administering these assessments.

Blood draw: Over the whole study, a total of three phlebotomy samples (Approximately 13 ml/draw; 3 teaspoons) will be drawn from the participants after an overnight fast. Blood samples will be separated for the lipid profile (assays performed by Quest diagnostics), and the kit assays for fasting plasma insulin and glucose (FPI, FPG), total testosterone (TotT), and estradiol (E2/E3). All kit assays will be performed at the SCDRC at the JJPVAMC; the three samples from each participant will be in the same assay kit to avoid inter-assay variability. The SCDRC core laboratory has been performing kit assays for over 20 years and has published dozens of papers from the results of these assays. The draws will consist of the following: fasting plasma insulin (FPI, 2 ml, green top tube), fasting plasma glucose (FPG, 1 ml, grey top tube), total testosterone (TotT,1 ml, red top tube), and estradiol (E2/E3, 1 ml, red top tube). An additional blood draw (Approximately 8 ml) will be drawn for the lipid profile and immune system factors. Three ml will be required for the lipid profile and sent to Quest Diagnostics and 5 ml for the immune system factors sent to Dr. Ona Bloom, at The Feinstein Institute for Medical Research, Manhasset, NY. The Quest Diagnostics and immune system transfer tubes will labeled only with your participant ID number and study time point. Quest diagnostics will pick up samples as regularly scheduled at each of the sites. A representative from Dr. Bloom's lab will come to pick up the samples directly upon each draw. The total amount of blood to be drawn for each data point collection is approximately 13 ml.

The blood draw will occur 3 times over the course of the whole study before intervention, at crossover WALK or UA) and after intervention (WALK or UA).

Lipid Profile: Total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), triglyceride (TG) and high density lipoprotein cholesterol (HDL-c) values will be measure by Quest Diagnostics Laboratory and samples will be collected at baseline, crossover and at the end of the second arm of the study.
Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) The standard equation for the HOMA-IR will be used to calculate insulin resistance [HOMA-IR = FPG (mg/dl) x FPI(μU/mL) / 405] as first described by Matthews et.al[57]. The HOMA-IR has been demonstrated to be a good indicator of insulin resistance in inactive populations, including the SCI population and to be sensitive to weight loss changes[58–60].

Total Testosterone (TT): Serum total testosterone will be determined by a radioimmunoassay (RIA; MP Biomedicals, Costa Mesa, CA) kit with an intra-assay CV of 10.0, 9.6, and 13% at 1.4, 4.6, and 8.0 nmol/L[41,61,62].

Estradiol (E2/E3): Serum estradiol values will be determined by a commercial kit assay using RIA (MP Biomedicals, Costa Mesa, CA) with an intra-assay CV of 15.7, 5.5, and 3.5% at 25.4, 152, and 657 pg/mL[63].

Immune System Factors: Markers of systemic inflammation are elevated and immune system function is altered in persons with chronic SCI, as demonstrated by articles published by Dr. Ona Bloom, Co-Investigator, Associate Investigator, The Feinstein Institute for Medical Research; WOC employee JJPVAMC. In an exploratory analysis, inflammatory mediators will be measured by Dr. Bloom in sera using commercially available single- and multi-plex suspension immunoassays, and then measured on the Bio-Rad Luminex Magpix platform with Bio-plex Manager software or other standard ELISA platform, as indicated by the manufacturer. Immune mediators to be measured include: C reactive protein (CRP), HMGb1, IL-1β, IL-1Ra, IL-6, IL-8, IL-10, IL-15, MIF, MIP1-α/CCL3, TNF-α leptin, and adipokine, using standard methods and manufacturer's protocols. Due to its clinical utility and widespread use as a biomarker of systemic inflammation in studies related to exercise and risks for coronary heart disease, the primary outcome assessment of systemic inflammation will be levels of CRP. All other biological mediators measured described above will be considered as secondary biological outcome measures.

Cardiovascular Autonomic Tone: A 24-hour Holter Monitor will be used to collect heart rate and blood pressure data for analysis of heart rate and blood pressure variability as non-invasive assessments of cardiac vagal tone and peripheral sympathetic vasomotor tone. The 24-hour Holter monitor provides accurate beat-to-beat measurement of heart rate and blood pressure and calculates variations in the inter-beat-interval of R-waves and systolic peaks to estimate cardiovascular autonomic regulation. The high resolution and sample rate enables quality amplification of cardiac and arterial pulse waveforms for more accurate estimates. The Holter monitor will be placed around the chest for heart rate assessment and a blood pressure cuff will be placed around the upper arm to monitor blood pressure which will self-inflate approximately every 20 minutes over the 24 hours of monitoring.

Postural orthostatic hypotension blood pressure tolerance test (OH BP): The non-invasive autonomic test of postural changes is described as the heart rate response to standing[64,65] has been modified to be performed in persons with SCI due to skeletal muscle paralysis and limitations in assuming the standing position. Therefore, the HR response to postural change will be assessed during re-positioning from the supine to the seated position, as previously described[66]. Participants will be in the supine position on a bed or elevated gym mat and beat-to-beat HR will be recorded for 60 seconds, followed by passive re-positioning to the seated position on a bed or elevated gym mat with the hip and knee at a 90° angle and the lower leg hanging off the side. Passive repositioning will be accomplished by one staff member lifting the participant's torso by the shoulders, while supporting the head and neck, and a second staff member shifting the subject perpendicular to the bed and

allowing the participant's legs to hang off the side. Participants will be instructed not to assist in the passive movement during this transition, and will be supported by staff.

Methods for recruiting subjects: Three sites will participate in this study: 1) JJPVAMC will be the Lead Site and has four ReWalk units; 2) UMROI will be a sub award site and has two ReWalk units with the potential to acquire two additional units through collateral funding and 3) KFRC will be a sub site of the JJPVAMC through the satellite Center of the Spinal Cord Damage Research Center which is located at Kessler Institute of Rehabilitation. KFRC has one Ekso unit. The JJPVAMC and KFRC study sites each have close to 3 years of experience conducting studies using the exoskeletal systems for persons with SCI. UMROI has recently acquired two ReWalk units and has experience conducting a DOD CDMRP Clinical Trial in persons with SCI. UMROI has begun to study the ReWalk in their patients. Potential participants will be recruited from the research databases at each institution and from the clinical outpatient services. At the UMROI site, the principal investigator also is the Director of the SCI support team clinic at the Baltimore VA Medical Center, so he will be able to recruit from both a civilian and a veteran population. Currently, both the JJPVAMC and KFRC have a waiting list of participants who have contacted either Center to become involved an exoskeletal-assisted walking program. All three study sites have a positive and significant history of recruiting and conducting ethically appropriate clinical trials in persons with SCI.

Expected withdrawal rates: In 13 participants enrolled to date at the JJPVAMC, three withdrew (one due to job relocation, one due to an unrelated medical illness, and one due to difficulty with travel). It is expected that these and/or similar reasons will affect the compliance and attendance of this study to some degree. As such a total of 132 participants will be enrolled as follows: JJPVAMC (n=28, T3 and below), KFRC (n=16, T2 and above) and UMROI (n=20, T3 and below). An enrollment schedule by site is provided (**Table 4**).

Table 4. Original Enrollment Schedule by Site

Study Sites and Groups		Y1				Y2				Y3				Y4				Sub Total
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
JJPVAMC (T3 and below, ReWalk)	Group 1			2			4			4			4					14
	Group 2			2			4			4			4					14
	subtotals			4			8			8			8					28
JJPVAMC at KFRC (C5 to T2, Ekso)	Group 1			2			2			2			2					8
	Group 2			2			2			2			2					8
	subtotals			4			4			4			4					16
UMROI (T3 and below, ReWalk)	Group 1			2			3			3			2					10
	Group 2			2			3			3			2					10
	subtotals			4			6			6			4					20
Total Participants by Year				12			18			18			16					**64**

Group assignment process: Participants will be block randomized within site.

Statistical Plan and Data Analysis:

The best value achieved for each walking test during sessions 5 to 12 (T1) and from 13 to 36 (T2) will be recorded separately to be used for comparative analysis. These best T1 and T2 scores will be used to determine

percent of occurrence with the hypothesized goals. Achievement of the hypothesized goals in the WALK intervention group for the primary outcomes (10mWT, 6minWT and TUG at the 12- and 36-session time points) will be reported as categorical data and presented as a percent of occurrence with the 95% upper and lower confidence intervals (CI). Continuous variables for the Secondary outcomes of the body composition and bowel function variables will be presented as mean ±SD. For the continuous variables, a difference score or percent change from pre to post will be calculated for the WALK and UA arms of the study. Comparisons between WALK (Pre-Post) vs. UA (Pre-Post) difference scores will be performed using paired t-tests. Pre to post comparisons for variables that are not normally distributed will be performed by non-parametric tests such as the Wilcox signed rank test or the paired sign test.

Walking outcomes (10mWT, 6minWT, and TUG): Achievement of the hypothesized goals in the WALK intervention group will be reported as categorical data and presented as percent occurrence with 95% confidence intervals (CI). For each of these outcomes, the best value achieved during the T1 period (sessions 5-12) and the T2 period (sessions 13-36) will be recorded separately and compared to the hypothesized goals, as listed below:

Primary Hypothesis (are tested pre and post the WALK arm only):

1. By session 36, 70% of the participants compared with 10% at session 12 will be able to perform the 10m WT ≤40 seconds (≥0.25 m/s);
2. By session 36, 70% of the participants compared with 10% at session 12 will be able to perform the 6min WT distance ≥80 m (≥0.22 m/s); and
3. By session 36, 60% of the participants compared with 20% at session 12 will be able to perform the TUG in ≤90 seconds.

Power Calculation: A one-sample method was chosen to test the observed proportion against the expected proportion determined from the preliminary data of the percent of those who achieved these goals. Using the most stringent criteria above of 20% (session 12) versus 60% (session 36) who achieve the TUG goal, there is 100% power (alpha=5%, double sided Z-power=5.6) with 13 of 63 (20%) versus 38 of 64 (60%) achieving the goal. If the attrition rate is as high as 25%, then the power is still 100%, (alpha=5%, double sided Z-power=4.53), with 10 of 48 (20%) at session 12 versus 29 of 48 (60%) of the participants achieving the goal at session 36.

Secondary Hypotheses

1. Bowel function will improve as demonstrated by 25% improvement on the Ten-question bowel survey.
2. Total body fat mass is hypothesized to be reduced by 2.0±1.2 kg

Power Calculation: The preliminary data demonstrated a total score change of 31.5±7.1 to 22.5±5.3, N=8 and a total body fat mass change from 24.14±8.45 to 22.22±8.19, N=9, alpha=0.05, using a pairwise method, the power for both was 100%. Allowing for 25% dropout, the power is still 100% for 48 participants at an alpha=0.05.

Please note, that both the primary and secondary hypotheses are well powered due to the huge effect observed in the preliminary data. However, performing this study in fewer participants will not permit us to ask many of the exploratory questions. There is no empirical data to support an appropriate power calculation for the exploratory hypotheses.

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