Development and deployment of an at-home strength and conditioning program to support a phase I trial in persons with chronic spinal cord injury

Running Title: At-home strength and conditioning program

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Abstract

Study Design: Non-randomized clinical trial (NCT02354625)

Objectives: As part of a Phase I clinical trial to assess the safety of autologous human Schwann cells (ahSC) in persons with chronic spinal cord injury (SCI), participants engaged in a multimodal conditioning program pre- and post-ahSC transplantation. The program included a home-based strength and endurance training program to prevent lack of fitness and post-transplantation detraining from confounding potential ahSC therapeutic effects. This manuscript describes development, deployment, outcomes, and challenges of the home-based training program.

Setting: University-based laboratory

Methods: Development phase: Two men with paraplegia completed an 8-week laboratory based 'test' of the home-based program. Deployment phase: The first four (2 males, 2 females) participant cohort of the ahSC trial completed the program at home for 12 weeks pre- and 20-weeks post-ahSC transplant.

Results: Development phase: Both participants improved their peak aerobic capacity (VO_{2peak}) (≥17%), peak power output (PO_{peak}) (≥8%) and time to exhaustion (TTE) (≥7%). Deployment phase: Pre-transplant training minimally increased fitness in the two male participants (≥6% PO_{peak} and ≥9% TTE). The two women had no PO_{peak} changes and slight TTE changes (+2.6 and -1.2%, respectively.) All four participants detrained during the post-transplant recovery period. After post-transplant re-training, all four participants increased TTE (4-24%), three increased VO_{2peak} (≥11%), and two increased PO_{peak} (≥7%).

Conclusions: Home-based strength and condition programs can be effective and successfully included in therapeutic SCI trials. However, development of these programs requires substantial content knowledge and experience.

Introduction

The Miami Project to Cure Paralysis conducted a Phase I clinical trial (NCT02354625) to assess the safety of autologous human Schwann cells (ahSC) as a therapeutic agent for functional recovery among persons with chronic spinal cord injury (SCI). As part of this trial, participants completed a multimodal whole-body conditioning program pre- and post- ahSC transplantation. This included locomotor training and functional electrical stimulation (FES) performed in the laboratory and strength and endurance training performed at home. The goals of the strength and endurance program were to 1) condition individuals prior to undergoing surgery and 2) prevent a lack of fitness and/or post-transplantation detraining from confounding potential therapeutic effects of ahSC transplantation. The strength and endurance program was specifically developed for home-based use by the participants.

The impetus for implementing a home-based program was our experience in a feasibility study of the multimodal program [1]. That study included body-weight-supported treadmill training for locomotion (3x weekly), FES for activation of sublesional muscles (3x weekly), and upper body circuit resistance training (CRT) for strength and endurance conditioning (2x weekly) [1]. Participants were required to come to the research facility 5 days a week for 19 weeks, which negatively affected compliance. Therefore, for the phase I ahSC trial, to reduce participant burden, mitigate barriers, and increase compliance, we developed a home-based strength and conditioning program [2].

The home-based program used resistance bands (Bodylastics International, Boca Raton, FL) and dumbbells and was modeled after a laboratory-based CRT protocol [3-5]. Among individuals with tetraplegia and paraplegia, 40-45 minutes of lab-based CRT performed three times weekly

for 12 weeks improved peak aerobic capacity (VO_{2peak}) and muscular strength by 31% and 21%, respectively [3-5]. Home-based exercise interventions in individuals with SCI have increased VO_{2peak} by 13-39% [6-9]. Importantly, home-based program participants achieved nearly 100% adherence during a 6-12-week commitment [6-8]. Participants indicated that home-based programs were "convenient"[6] and addressed barriers such as lack of access, transportation, and time [7], which are often cited as reasons for not participating in clinical trials [2].

Therefore, the purpose of this manuscript is to describe the development of a home-based strength and conditioning program; the results of a laboratory-based, proof-of-concept, 8-week training program (Development phase) using the home-based program; the outcomes of the home-based program (Deployment phase) for the first four phase I ahSC transplantation trial participants; and challenges encountered.

Methods

We first describe methods used in both the Development and Deployment phases followed by descriptions of methods unique to each phase. Individuals voluntarily provided written informed consent and completed the University of Miami Institutional Review Board-approved research protocol. Inclusion/exclusion criteria for each study phase are listed in Table 1.

[Table 1]

Development and Deployment phases shared methods

Peak Aerobic Capacity Assessment: Participants performed a VO_{2peak} assessment using an electronically braked arm-cycle ergometer (Angio, Lode BV, Gronigen, Netherlands) as

previously reported [10]. Participants were asked to refrain from strenuous activity/alcohol or caffeine for 12-h prior to testing. Prior to the first test, a staff member interviewed the participants to determine the individualized wattage starting workload and increments to target a VO_{2peak} in no more than 12-minutes. The interview included questions regarding the participant's current fitness program and general activity level. The starting workload and stage increments were kept consistent throughout the assessment periods. Every one-minute workload was increased until volitional exhaustion manifested as either a non-verbal communication of the desire to stop or the inability to maintain cadence at 60 ± 5 rpm. Heart rate (HR) and oxygen consumption were recorded continuously from baseline through recovery. HR was measured by standard 12-lead electrocardiography and expiratory gases were collected and analyzed with an open-circuit metabolic cart (Vmax Encore 29, Care Fusion, San Diego, CA). Peak oxygen consumption ($VO_{2peak)}$, peak power output (PO_{peak}) and time to exhaustion (TTE) were selected for analysis.

Peak Muscular Strength Assessment

Upper extremity strength testing was performed on a Helms equalizer 1000 multi-station exerciser (Helm Distributing, Polson, MT) using the following six exercises from the laboratory-based CRT: 1) overhead press, 2) horizontal row, 3) chest fly, 4) biceps curl, 5) latissimus pull-down, and 6) triceps press-down (Table 2). We used an iterative, systematic approach whereby participants performed one to three sets of three to five repetitions. Weights for the first set were chosen based on the participant's injury level, sex, and body weight. Weights for sets two and three were based on participants' self-rated effort level of the previous set. One-repetition

maximum (1-RM) was calculated using the Mayhew regression equation [11] which is validated in persons with SCI [12]:

$$1\text{-RM} = WT/ (0.533 + 0.419E - 0.055*REPS)$$

Where '1-RM' is the estimated one-repetition maximum, 'WT' is the resistance used in the last set where more than three, but fewer than eight repetitions are completed, and 'REPS' is the repetitions completed in the final set.

[Table 2]

Exercise sequencing and conversion

We deemed the frequent switches between aerobic and strength exercises and between different strength exercises of the laboratory-based CRT program non-feasible for home-based implementation. We modeled the home-based program exercise sequence after the 'Tetraplegia' CRT [4] concurrent model, which consisted of 10 minutes of aerobic exercise at 60% of heart rate reserve, followed by all sets of each exercise, and then by 10 minutes of aerobic exercise also at 60% of heart rate reserve. For all CRT exercises, we first attempted to recreate the exercise using the resistance band system because it was low-cost, portable, and provided the widest resistance range. We converted the shoulder press and bicep curl to dumbbell exercises. The shoulder press resistance band exercise resulted in a dangerous increase in rearward instability and the biceps curl resistance band exercise could not be completed with good form in a full range of motion.

Prescription Customization Session

The prescription customization session objective was, for each exercise, to identify a resistance by repetition combination that achieved 1) a target per set work volume, 2) proper form

117 throughout each repetition, 3) participant stability in their wheelchair, and 4) wheelchair
118 stability. Per set target work volume was computed as 10 repetitions x load, with load set at 55%
119 of the predicted 1-RM[13]. This target work volume was the initial volume of the laboratory
120 based CRT[3]. Figure 1 outlines the iterative process used to identify the band resistance and
121 repetition combination that achieved all goals.

122 **[Figure 1.]**

123

124 *Home-based concurrent aerobic and resistance training program*

125 Each 50-minute aerobic and strength training session was performed 3 times weekly on
126 nonconsecutive days. Participants began with a 2-minute low intensity warm up on a Saratoga
127 stationary arm cycle (Rand-Scot, Inc, Fort Collins, CO), followed by 10 minutes of vigorous-
128 intensity. They then performed three sets of 10-20 repetitions (based on the customization
129 session) with no more than 20 seconds between each set for each of the six exercises. Time
130 between sets mirrored the time allowed in the laboratory-based protocol, which was limited to
131 the time required for the participants to wheel to the next exercise station (generally ~15-
132 seconds). Participants finished the session with 10 minutes of vigorous-intensity on the
133 stationary cycle [4]. Each 10-minute arm cycle block was self-regulated by the talk test. In order
134 to elicit a vigorous-intensity level, participants were instructed to maintain an intensity that made
135 speaking uncomfortable [14]. Every four weeks, participants completed a 1-RM strength
136 assessment at the laboratory, which was used to increment the target per set work volume and
137 was accompanied by a prescription customization session. Participants in both the development
138 and deployment phases were instructed to maintain their normal activity levels.

139

Development phase methods (proof-of-concept training study)

To determine if the home-based program could elicit fitness changes and to determine if participants could execute the home-based program without staff assistance or guidance, two men with chronic thoracic SCI (Table 3.) completed an 8-week proof-of-concept study using the home-based program in a laboratory setting to assess the effect of the program on VO_{2peak}, PO_{peak} and TTE. Participants completed the program 3 times weekly on nonconsecutive days at the Miami Project to Cure Paralysis.

In weeks one through four, investigators provided physical assistance with setting up each exercise, and verbal guidance regarding form. Participants began the transition to autonomous training in week five and were fully autonomous by the end of week six. During the transition period, staff provided guidance only when participants struggled to remember the next steps in the program or were using improper form. To adjust for conditioning effects, participants' strength was re-assessed, target workloads were re-computed, and a second prescription customization session was completed after four weeks. After 8 weeks, participants completed a VO_{2peak} assessment. Figure 2A outlines the assessment and intervention timeline for the Development phase proof-of-concept study.

[Figure 2A-B]

Deployment Phase methods

Four individuals with chronic thoracic SCI (2 men and 2 women) (Table 3) completed the home-based program as a part of their phase I ahSC trial participation. The home-based training program was administered for a 12-week pre-transplant conditioning phase with assessments at baseline ($PreTx_{BL}$) and one week prior to the transplant (PreTx). Upon medical clearance,

participants resumed training within one-month post-transplant, and continued until six months post-transplant with assessments at month two ($PostTx_{M2}$) and month six ($PostTx_{M6}$). Figure 2B outlines the timeline of assessments and interventions for the Deployment phase.

At $PreTx_{BL}$ and every four weeks thereafter, participants completed the muscular strength assessment and an exercise prescription re-customization session. Participants executed the program in their homes or hotel rooms 3 times weekly on nonconsecutive days. The exercise band system, dumbbells, and a Saratoga arm crank were provided to each participant. Participants were supplied with a pictorial exercise guide for reference. Training logs were completed after each session to confirm compliance. Prior to the first at home session, a member of the study team visited the study participant's home to ensure proper equipment set-up.

Outcome Measures

Due to small sample size, we present data for each participant at each assessment for both development and deployment phases. The highest 20-s average was selected as VO_{2peak} (ml/min). The highest resistance maintained for at least 20 seconds was selected as PO_{peak} (W). TTE (minutes:seconds) was recorded as the length of the test. Respiratory exchange ratio (RER), heart rate (HR) and rate of perceived exertion (RPE) were recorded at peak to confirm that a true peak was achieved. Results are reported as absolute and percent change.

Results

Development Phase

Both participants increased peak power output (20.0 and 8.7%), peak oxygen consumption (22.9 and 17.9%), and time to exhaustion (31.5 and 7.1%) (Table 4). Both participants completed 21 of 24 planned exercise sessions (87.5%), citing illness and scheduling conflicts as reasons for missing training sessions.

[TABLE 4]

Deployment Phase

Pre-transplant Training Phase: $PreTx_{BL}$ to PreTx

Both men increased PO_{peak} (5.9 and 8.3%) and TTE (9.5 and 13.3%) after the 12 weeks of pre-transplantation conditioning. The two women had no PO_{peak} changes and slight TTE changes (+2.6 and -1.2%). Interestingly, these minimal effects were accompanied by large divergent VO_{2peak} changes (+13.7% and -19.8%; Table 4; Figure 3A). Compliance was 92-100% (33-36 completed sessions) for this period.

[FIGURE 3A-C]

Transplant Recovery Phase: PreTx to $PostTx_{M2}$

AhSC transplant surgery was performed immediately following PreTx assessments. The 6-week time period following PreTx to $PostTx_{M2}$ included three to five weeks of post-surgery recovery followed by resumed training, dependent upon medical clearance. At $PostTx_{M2}$, two of four participants (1M, 1F) experienced a decrease in all outcome measures compared to PreTx, with all four participants experiencing a decrease (4.8-28.7%) in TTE (Table 4; Figure 3B).

Post-transplant Training Phase: $PostTx_{M2}$ to $PostTx_{M6}$

All four participants increased TTE between months 2 ($PostTx_{M2}$) and 6 ($PostTx_{M6}$) (4.8-24.6%), three increased VO_{2peak} by ≥10%, and two increased PO_{peak} (Table 4, Figure 3C). Compliance was 90-100% (54-60 sessions) in the 20-week period between $PostTx_{M2}$ and $PostTx_{M6}$,

Adverse events

No adverse events were reported in the development phase. Two participants reported aggravation of pre-existing joint (shoulder and wrist) pain in the deployment phase. For one of these participants, study staff decreased the starting wattage for the peak aerobic capacity test by 20 W at $PostTx_{M2}$ and $PostTx_{M6}$ (Table 4).

Discussion

A home-based strength and conditioning program is effective and feasible. Our program improved fitness pre- and post-ahSC transplant in four individuals with chronic thoracic SCI, but program effectiveness varied highly. A more robust and universal effect may be achieved by increasing the volume and precision of the aerobic component. Staff burden was reduced, compliance was high, and per-participant study expenditures were moderate. However, there were significant challenges that must be addressed by any group wishing to mimic this approach.

General effectiveness

Our results suggest a training effect from pre-transplant training ($PreTx_{BL}$ to PreTx), detraining following transplant surgery (PreTx to $PostTx_{M2}$) and finally, a retraining effect after post-transplant training ($PostTx_{M2}$ to $PostTx_{M6}$). The largest and most universal improvements occurred during the post-transplant training period (Fig. 3C.) and were sufficient to ameliorate

post-transplant detraining. We attribute the larger effects observed in the post vs pre-transplant periods to the longer training duration (20 vs.12 weeks). Changes during both training periods were comparable to those reported in individuals of similar ages and injury levels in previous studies that have used the laboratory-based CRT [3, 5]. However, the effectiveness of both periods was highly variable across outcome variables and participants. Such variance is not unexpected, and can be attributed to many factors, such as, but not limited to variability in response to an exercise intervention, day-to-day variability in peak performance during testing; training above/below the prescribed intensity; and insufficient training intensity.

Variance in effectiveness & proposed solutions

There is strong evidence for considerable natural variation in individual responses (including non-response) to exercise training programs, even when all research participants are subjected to the same volume and relative intensity of physical activity[15]. Mean response of a group to an exercise intervention can mask individual differences in direction and magnitude [15]. As a hypothetical example, a training study might report a 25% mean gain above baseline values in VO_{2max}, however, the range of improvement actually varied from no gain to a doubling of baseline values[16]. It is generally accepted that some individuals are unable to mount a strong physiological response to an exercise training intervention [17]. The heterogeneity in the physiological responses to our exercise program may be explained in part by the natural variance in physiological response to a training stimulus. (Figure 3). However, it may also be explained by natural test-retest fluctuation and/or error in measurement. Establishing true and meaningful individual differences in training programs responses would have required including a comparator sample and assessing aerobic capacity multiple times at each assessment point.

These features were not possible is this study. As phase I clinical trial, per FDA regulations a comparator group was not allowed in the ahSC trial. Practical constraints on the cumulative time burden of testing at each assessment point was a barrier to administering multiple aerobic tests at each assessment. A week was required to complete all primary (full ISNCSCI motor and sensory assessments, MRI, pain and sensory assessments, basic blood chemistry) and secondary (functional, fitness, electrophysiological, autonomic, quality of life and spasticity assessments) outcomes.

Nonetheless, a physiologic non-response to exercise in one metric is not indicative of a ubiquitous non-response. In the deployment phase, despite PO_{peak} and TTE improvements, some individuals saw no increase or a slight decrease in VO_{2peak} (Figure 3). The emphasis of strength over the aerobic component in our home-based program likely favored gains in power over aerobic capacity. The aerobic component (60 min/week) falls well below the generally recommended 150 minutes of moderate-intensity aerobic exercise per week [18, 19], however, it does comply with recently published scientific guidelines for improving cardiorespiratory fitness in adults with SCI [20]. However, aerobic exercise intensity may be more important than duration. Several studies have reported superior improvements in cardiorespiratory fitness in individuals with SCI performing vigorous-intensity exercise [21]. Our participants may have executed the aerobic component at an intensity below the prescribed vigorous-intensity. While the prescribed duration and intensity of the aerobic component was sufficient for some participants to improve or maintain their aerobic capacity, it was likely inadequate for individuals who entered the study with a high aerobic capacity, resulting in a ceiling effect or even detraining.

We did not consider participants' current physical activity level when developing the program. This led to a detraining effect for one deployment phase participant who, prior to relocating for clinical trial participation, was hand-cycling up to 10 hours each week. This highly trained individual was accustomed to a significantly greater training volume than our program offered, was unable to maintain his pre-trial weekly hand cycling program, and thus did not maintain his initial fitness level. Detraining can occur if the program training volume is less than the participant's current dosing. Thus, future implementations in any domain, including FES or gait training, should be flexible enough to achieve conditioning gains in under-conditioned persons and maintain the conditioning of persons who enter the trial at a supra-optimal status. In addition, each individual's response to the training stimulus should be reassessed frequently in order to intensify training for non-responders.

Compliance, participant-staff burden, program materials cost

High program compliance was consistent with interventions of similar content and duration [6-8]. However, compliance was an explicitly stated expectation for trial participation. Individuals who presented themselves as candidates were removed from consideration if there was any doubt about their willingness and ability to comply with the multi-modal pre and post-transplant training. Additionally, all participants were required to be of "average" or greater fitness classification [22] to undergo transplantation. Study participants were informed of their current fitness classification following baseline testing and were likely motivated to complete the training in order to maintain or achieve the minimum fitness required to undergo transplantation surgery. In this particular cohort, both male participants fell in the "excellent" fitness category at

baseline and maintained that throughout the trial. One female participant was above median and one below at baseline. The female who was below median at baseline (and thus not initially eligible to undergo transplantation) improved to above median after pre-transplant conditioning and was approved for surgery.

Participant and staff burden were decreased as a result of the home-based program. Participants did not express that they felt overburdened, in fact, 3 of 4 participants requested permission to perform more physical activity.

The average cost per participant (paid for by the trial) was $2,160-2,258 (United States Dollars). This includes the arm cycle ($1920), resistance bands and door anchor ($198), and dumbbells ($42-140).

Home-based program development and deployment challenges

We encountered multiple sets of challenges during home-based program development and deployment. The first set included maintaining participant stability in the chair and stability of the wheelchair itself. We used 55% of 1-RM values calculated during the 1-RM assessment as a starting point to set resistive loads on the band training system. This resistance resulted in a complete loss of balance when the maneuver was performed bilaterally due to lack of trunk motor control. Therefore we switched to performing the exercises unilaterally which also resulted in a complete loss of balance. To solve this problem we switched to a volume based paradigm, which allowed us to reduce the resistance to a level that enabled the participant to maintain stability by using their ipsilateral arm to grab their chair. However, even when

participant stability was maintained, the wheelchair often slid across the low friction tile floor towards the anchor point of the bands. This problem was solved for all participants by requiring the resistance band system be installed in a room with a carpeted floor. If this is not possible, individuals can place a small mat on a low friction floor or, if they are able to, place wood 2x4s in front of the rear wheels.

The second set was ensuring participants could independently perform all exercises at home with the prescribed resistance and correct form. Band resistance is dependent on the degree of stretch, which in turn is dependent on how far the individual is from the band's anchor point, and thus must be consistent across training sessions. During the prescription customization session, for each maneuver, the wheelchair's position relative to and distance from the anchor point was documented. When participants returned home, they marked the wheelchair position for each exercise on the floor with a piece of tape, which enabled consistent band resistance across sessions. Customization sessions were also used to correct and coach participants on proper form, and included key tips for each exercise. To further facilitate compliance, participants were provided with a packet after each customization session that described for each exercise where to place tape markers, which bands to use, the anchor points, the required number of sets and reps, photos of the start and end positions and training logs for each session. If requested, a staff member travelled back to the participant's residence after each prescription customization session to check the tape markers and band system set-up. For exercises where the tape markers resulted in a position more than an arm length from the band anchor, a piece of rope was tied to the resistance band's handle. Participants placed the rope in their lap while they assumed the prescribed position and then used the rope to pull the handle towards them. Finally, to prevent

the participant from having to re-configure the bands for each exercise during the session, a unique set of bands were provided for each exercise. The bands for each exercise were attached to the anchor system after each customization session and remained in place until the next prescription customization session.

To our knowledge, these challenges have not been specifically reported by other studies investigating the use of a home-based band resistance training program [8, 23] in individuals with SCI. In a case series [8], the participant spent 90 minute with study staff learning the details and correct form for the exercises and establishing the proper band resistance. Band resistance was established by identifying a challenging load during the last 3 repetitions in a set of 10 [8]. An earlier study used 50% of 1-RM established on the laboratory-based CRT exercises to convert into band resistance equivalents by attaching 20-cm loops of band to a calibrated tensiometer [23]. The authors of previous studies did not specifically address any challenges regarding chair stability or the ability to achieve the desired training volume using these methods.

Methodological weaknesses and limitations

The small sample size limits statistical analysis as well as generalizability of findings, however, this limitation is inherent to all phase I trials. Participation in this clinical trial required that participants relocated to the Miami area for 10 months. This substantial environmental change likely affected general living habits, especially diet and exercise/rehabilitation participation, for which we did not account. Our compliance monitoring was based on self-report and therefore we could not verify that each session was actually performed. Finally, testing bias was possible,

as the investigator performing the prescription customizations was also, at times, conducting VO_{2peak} assessments. Ideally, the individual conducting the VO_{2peak} assessment would be blinded to the prescription customization and to the participants' mid-assessment progress.

Conclusions

Home-based strength and condition programs can be successfully included in therapeutic SCI trials and can be effective to achieve target fitness levels. However, development of these programs requires substantial content knowledge and experience. In addition, for each mode of a multi-modal condition program designed to support an intervention, future studies should strongly consider customizing training loads for highly trained persons in addition to a standardized training load for non-trained participants.

Data Archiving All data generated and analyzed in this study are available from the corresponding author on request.

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Author Contributions All authors were responsible for research conception and design and critical review and revision of the article. JM, RC, and KA were involved converting the CRT exercises to band/dumbbell exercises. JM was additionally involved in data collection, analysis and drafting this manuscript.

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Statement of Ethics We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Conflicts of Interest The authors declare that they have no conflicts of interest.

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Figure Legends

Figure 1. Flow chart describing the iterative process used for each exercise to identify the combination of resistance and repetitions that achieved the target workload.

Figure 2. Timeline of assessment and interventions for the A.) Development Phase and B). Deployment Phase. BL, baseline; Post, post-training; $PreTx_{BL,}$ Pre-treatment Baseline; PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$, Post-transplant Month 6.

Figure 3. Percent change across deployment phase assessments: A.) $PreTx_{BL}$ to PreTx, B.) PreTx to $PostTx_{M2,}$ C.) $PostTx_{M2}$ to $PostTx_{M6}$. $PreTx_{BL,}$ Pre-treatment Baseline; PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$, Post-transplant Month 6; PO, power output; VO_2, oxygen consumption; TTE, time to exhaustion. ☐PO ■VO_2 ▤TTE

Table Legends

Table 1. Inclusion Exclusion Criteria

Table 2. Strengthening exercises used in laboratory and home-based programs. Anatomical movement, main muscles activated, and home-based resistance mode are indicated.

503 **Table 3.** Participant descriptive characteristics. BL, baseline; Post, post-training; kg, kilogram;
504 cm, centimeter; BMI, body mass index; km, kilometer; m, meter; M, male; F, female; yrs, years;
505 AIS, American Spinal Injury Association Impairment Scale; $PreTx_{BL,}$ Pre-treatment Baseline;
506 PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$, Post-transplant Month 6.

507 **Table 4.** Physiological responses to arm ergometry testing (values at test termination). $PreTx_{BL,}$
508 Pre-treatment Baseline; PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$,
509 Post-transplant Month 6; BL, baseline; Post, post-training; M, male; F, female; PO_{peak}, peak
510 power output; VO_{2peak}, peak oxygen consumption; RER, respiratory exchange ratio; HR, heart
511 rate; %max, % of age predicted max HR; RPE, rate of perceived exertion; TTE, time to
512 exhaustion; W, watts; ml/min, milliliters per minute; ml/kg.min, milliliters per kg body weight
513 per minute; min:sec, minutes: seconds. [a] Testing parameters were modified (20 W decrease in
514 starting W) secondary to non-study related shoulder pain.

Figure 1. Flow chart describing the iterative process used for each exercise to identify the combination of resistance and repetitions that achieved the target workload

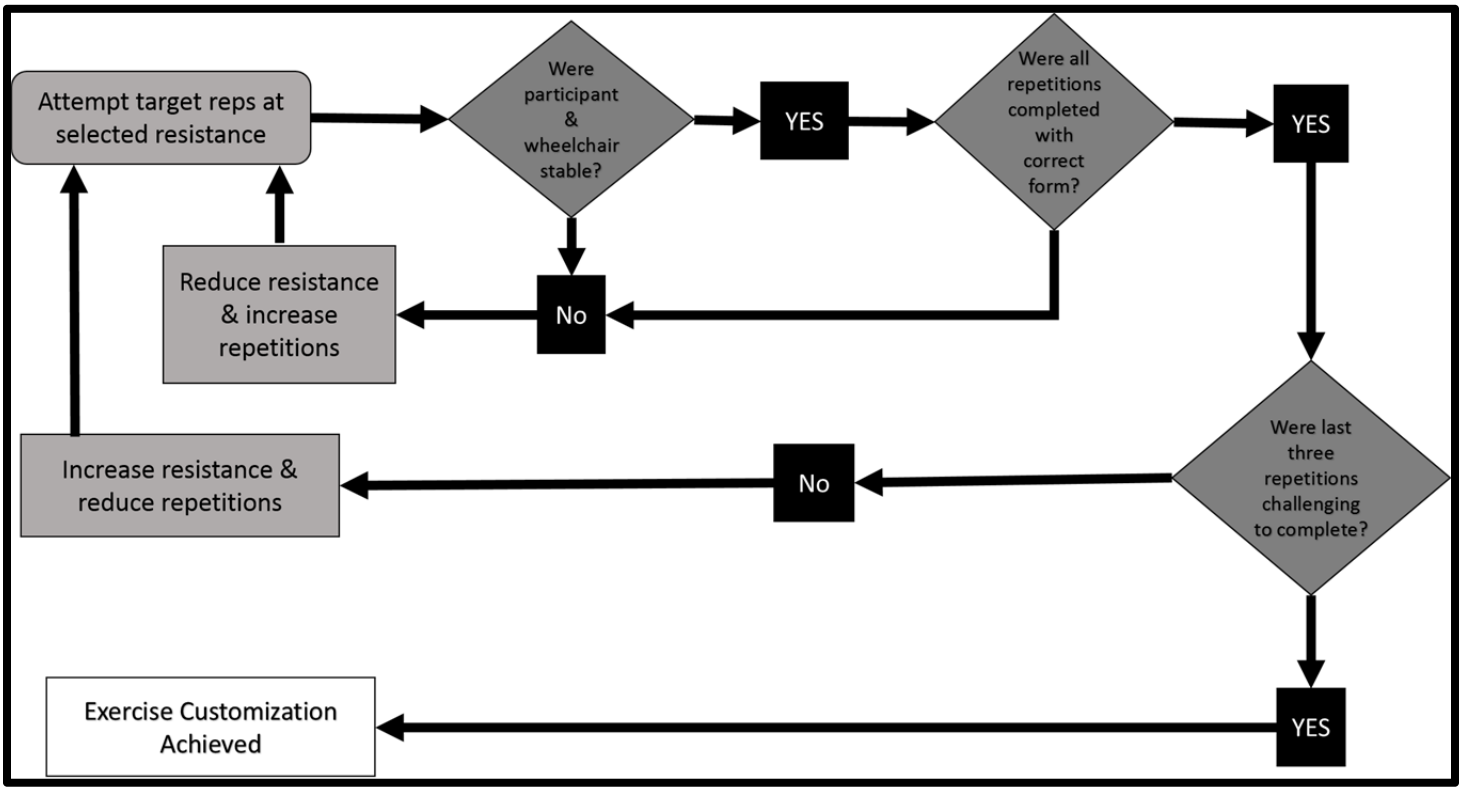

Figure 2. A-B. Timeline of assessment and interventions for the A.) Development Phase and B). Deployment Phase.

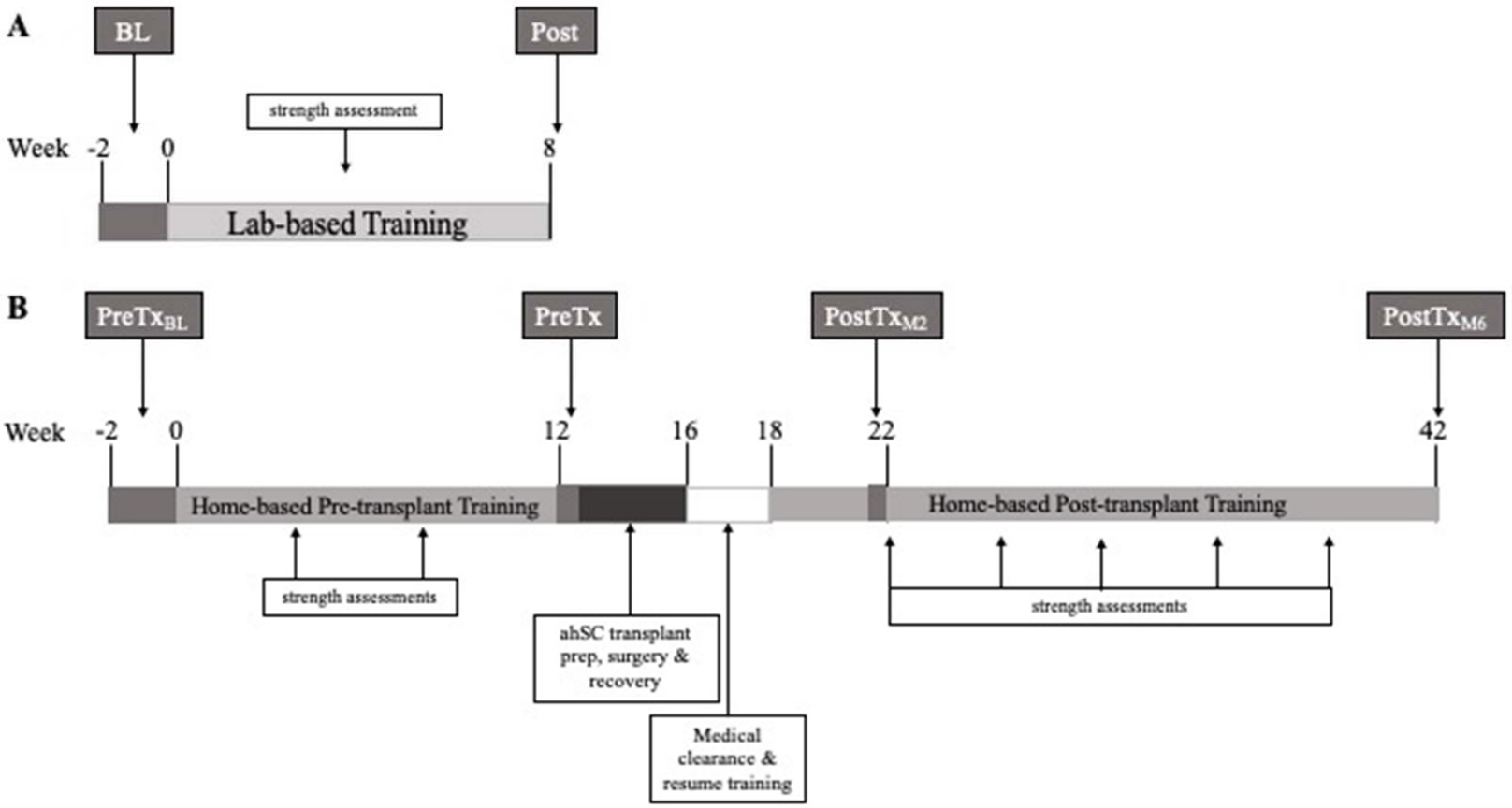

Figure 3. A-C Percent change across deployment phase assessments

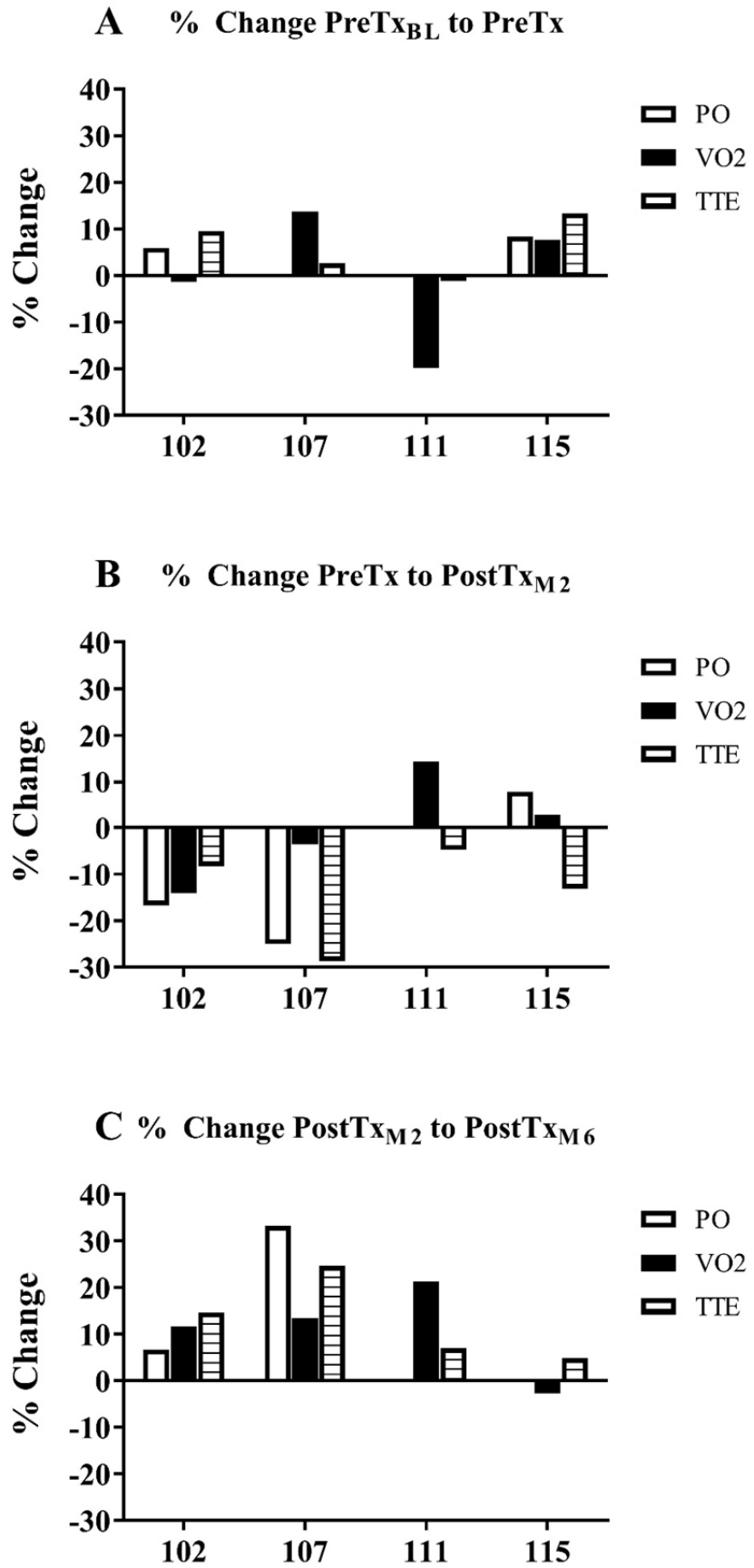

Table 1. Inclusion Exclusion Criteria

Inclusion/Exclusion Criteria	Development Phase	Deployment Phase[a]	Deployment Phase[a] (transplant surgery)
Inclusion Criteria			
Persons with traumatic SCI that occurred a minimum of 12 months prior to enrollment		√	
Persons with SCI/D that occurred a minimum of 6 months prior to enrollment	√		
Between the ages of 18 and 65 at last birthday	√	√	
SCI between spinal levels C5-T12 as defined by the most caudal level of intact motor and sensory function on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)	√	√	
ASIA Impairment Scale (AIS) grade A, B, or C at time of enrollment	√	√	
Lesion length ≤ 3 cm and lesion volume ≤ 2 cc, as approximated by MRI		√	
Exclusion Criteria			
Persons unable to safely undergo an MRI		√	
Persons with penetrating injury of the spinal cord or complete transection of the cord, as identified by MRI		√	
Persons with severe, uncorrected post-injury spinal deformity and/or spinal cord inadequately decompressed		√	

Persons with a cavity structure that would preclude successful transplantation, as identified by MRI		√	
Persons with syringomyelia – defined as patients with progressively enlarging cysts on T2 weighted images with associated neurological decline		√	
Intolerance to functional electrical stimulation of muscles		√	
Exercise induced abnormalities		√	
Range of motion of the upper or lower extremities outside functional limits for targeted fitness and rehabilitation activities	√	√	
Evidence of bone or joint pathology that adversely influences participation in the fitness and rehabilitation activities		√	
Fracture, dislocation, or extremity instruments (implanted or external) that adversely influences participation in the fitness and rehabilitation activities		√	
Unhealed pressure ulcer	√	√	
History of documented seizures, stroke, brain tumor, serious head injury, or any other intracranial problem that could increase the risk of seizures during motor evoked potentials testing		√	
Pregnant women or a positive pregnancy test in those women with reproductive potential prior to enrollment	√	√	

Presence of disease that might interfere with participant safety, compliance, or evaluation of the condition under study		√	
Body Mass Index (BMI) ≥ 35		√	
History of active substance abuse		√	
Persons who are current participants in any interventional trial		√	
Persons with a history of prior intrathecal or intraspinal cell therapy for SCI		√	
Persons allergic to gentamicin		√	
Persons who test positive for HIV or Hepatitis B or C virus		√	
Persons with lab values significantly outside pre-specified upper and lower limits		√	
Persons who can independently ambulate	√	√	
Persons who gain the ability to independently ambulate after completing the 12 week fitness and rehabilitation protocol			√
Failure to achieve a fitness level in or above the 'average' category established for persons with chronic paraplegia or chronic tetraplegia[20]			√
Failure to obtain cultured SC that meet lot release criteria			√
Active medical conditions precluding safe transplantation			√

[a]Inclusion/exclusion criteria for phase I clinical trial (NCT02354625)

Table 2. Strengthening exercises used in laboratory and home-based programs. Anatomical movement, main muscles activated, and home-based resistance mode are indicated.

Exercises	Anatomical Movement	Main Muscles Activated	Resistance mode (Home-based program)
Overhead press	Shoulder abduction with scapular elevation and upward rotation	Anterior & medial deltoids, triceps	Dumbbell
Horizontal row	Shoulder horizontal abduction with scapular adduction	Erector spinae, trapezius, rhomboids, latissimus dorsi, teres major, posterior deltoids	Resistance band
Chest fly	Shoulder horizontal adduction while in external rotation to the midline	Pectoralis major & minor	Resistance band
Biceps curl	Elbow flexion	Brachialis, biceps brachii, brachioradialis	Dumbbell
Latissimus pull-down	Shoulder adduction with scapular downward rotation and depression	Latissimus dorsi, rhomboids, trapezius, teres major & minor, infraspinatus	Resistance band
Triceps press-down	Shoulder flexion, scapular depression and elbow extension	Triceps, deltoids	Resistance band

Table 3. Participant descriptive characteristics

Participant Number	Timepoint	Weight (kg)	Height (cm)	BMI (kg/m^2)	Sex (M/F)	Age (yrs)	Level of Injury/AIS grade	Time since Injury (yrs)
Development Phase								
1	BL	54.5	170	18.8	M	21	T3/A	3
	Post	57.8		20.0				
2	BL	152.4	185	44.5	M	47	T7/A	10
	Post	151.7		44.3				
Deployment Phase								
102	$PreTx_{BL}$	83.0	170	28.7	M	46	T10/A	15
	PreTx	84.0		29.0				
	$PostTx_{M2}$	96.0		29.7				
	$PostTx_{M6}$	87.7		30.3				
107	$PreTx_{BL}$	65.0	168	23.1	F	31	T2/A	1
	PreTx	66.0		23.5				
	$PostTx_{M2}$	66.0		23.5				
	$PostTx_{M6}$	68.9		24.5				
111	$PreTx_{BL}$	67.7	168	24.1	F	52	T10/C	10
	PreTx	63.0		22.4				
	$PostTx_{M2}$	63.0		22.4				
	$PostTx_{M6}$	64.3		22.9				
113	$PreTx_{BL}$	76.4	188	21.6	M	27	T11/B	2
	PreTx	71.5		20.2				
	$PostTx_{M2}$	70.7		20.0				
	$PostTx_{M6}$	71.0		20.1				

BL, baseline; Post, post-training; kg, kilogram; cm, centimeter; BMI, body mass index; km, kilometer; m, meter; M, male; F, female; yrs, years; AIS, American Spinal Injury Association Impairment Scale; $PreTx_{BL,}$ Pre-treatment Baseline; PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$, Post-transplant Month 6.

Table 4. Physiological responses to arm ergometry testing (values at test termination)

Participant		PO_{peak} W	VO_{2peak} ml/min	VO_{2peak} ml/kg/min	RER	HR (%max)	RPE (6-20)	TTE min:sec
Development Phase								
1	BL	50	874	16.0	0.95	182 (91)	20	4:30
	Post	60	852	14.7	1.34	188 (94)	*	5:55
2	BL	115	2017	13.2	1.25	136 (79)	18	8:01
	Post	125	2266	14.9	1.32	127 (73)	*	8:35
Deployment Phase								
102 (M)	$PreTx_{BL}$	170	2905	35.0	1.22	168 (97)	16	8:46
	PreTx	180	2864	34.1	1.27	163 (94)	20	9:36
	$PostTx_{M2}$	150	2460	28.6	1.35	173 (99)	20	6:48[a]
	$PostTx_{M6}$	160	2745	31.3	1.29	175 (100)	19	8:05[a]
107 (F)	$PreTx_{BL}$	40	488	7.5	1.23	134 (71)	12	4:32
	PreTx	40	554	8.4	1.21	143 (76)	20	4:39
	$PostTx_{M2}$	30	535	8.1	1.35	140 (74)	7	3:19
	$PostTx_{M6}$	40	606	8.8	1.33	155 (82)	14	4:08
111 (F)	$PreTx_{BL}$	65	982	14.5	1.36	155 (92)	15	7:05
	PreTx	65	788	12.5	1.45	150 (89)	15	7:00
	$PostTx_{M2}$	65	901	14.3	1.19	141 (84)	15	6:40
	$PostTx_{M6}$	65	1093	17.0	1.24	149 (92)	14	7:08
113 (M)	$PreTx_{BL}$	120	2032	26.6	1.51	201 (104)	16	10:40
	PreTx	130	2188	30.6	1.33	203 (105)	18	12:05
	$PostTx_{M2}$	140	2248	31.8	1.36	191 (99)	17	10:30
	$PostTx_{M6}$	140	2187	30.8	1.41	198 (103)	16	11:00

$PreTx_{BL,}$ Pre-treatment Baseline; PreTx, Pre-transplant; $PostTx_{M2}$, Post-transplant Month 2; $PostTx_{M6}$, Post-transplant Month 6; BL, baseline; Post, post-training; M, male; F, female; PO_{peak}, peak power output; VO_{2peak}, peak oxygen consumption; RER, respiratory exchange ratio; HR, heart rate; %max, % of age predicted max HR; RPE, rate of perceived exertion; TTE, time to exhaustion; W, watts; ml/min, milliliters per minute; ml/kg.min, milliliters per kg body weight per minute; min:sec, minutes: seconds. [a] Testing parameters were modified (20 W decrease in starting W) secondary to non-study related shoulder pain.

*This data needs to be obtained from study hardcopy files stored in the laboratory. Due to the current COVID-19 pandemic, we do not have access to them. We should be able to fill in the blanks for these 2 missing data points by the time the proofs come out.