Neuromodulation using MyndMove therapy compared to intensive upper-limb conventional therapy among individuals with traumatic spinal cord injury: The MyndMove Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039650
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2020
Complete List of Authors:	Anderson, Kim; MetroHealth System, Physical Medicine and Rehabilitation; Case Western Reserve University, Physical Medicine and Rehabilitation Wilson, James; MetroHealth System, Physical Medicine and Rehabilitation; Case Western Reserve University, Physical Medicine and Rehabilitation Korupolu, Radha; University of Texas Health Science Center at Houston, Physical Medicine and Rehabilitation; Institute for Rehabilitation and Research Pierce, Jacqueline; Health Tech Connex, Centre for Neurology Studies Bowen, James; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; University of Toronto, Toronto Health Economics and Technology Assessment (THETA) Collaboration O'Reilly, Daria; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; TELUS Health Kapadia, Naaz; University Health Network, Toronto Rehabilitation Institute; University of Toronto, Department of Physical Therapy Popovic, Milos; University Health Network, The KITE Research Institute; University of Toronto, Institute of Biomaterials and Biomedical Engineering Thabane, Lehana ; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; St. Joseph's Healthcare, Biostatistics Unit Musselman, Kristin; University Health Network, Toronto Rehabilitation Institute; University of Toronto, Physical Therapy
Keywords:	Neuromuscular disease < NEUROLOGY, REHABILITATION MEDICINE, Spine < ORTHOPAEDIC & TRAUMA SURGERY

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Neuromodulation using MyndMove therapy compared to intensive upper-limb conventional therapy among individuals with traumatic spinal cord injury: The MyndMove Trial

Authors:
Kim D. Anderson[1,2]; James R. Wilson[1,2]; Radha Korupolu[3]; Jacqueline Pierce[4]; Jim Bowen[5,8]; Daria O'Reilly[8,9]; Naaz Kapadia[6,10]; Milos R. Popovic[7,11]; Lehana Thabane[8,12]; Kristin Musselman[6,10]*

Affiliations:
[1]MetroHealth Rehabilitation Institute, MetroHealth System, Cleveland, OH, USA
[2]Department of Physical Medicine and Rehabilitation, Case Western Reserve University, Cleveland, OH, USA
[3]Department of Physical Medicine and Rehabilitation, McGovern Medical School, The University of Texas Health Science Center at Houston, TX, USA / The Institute of Rehabilitation & Research (TIRR) Memorial Hermann, Houston, TX, USA
[4]HealthTech Connex Centre for Neurology Studies/ Neuromotion Physiotherapy, Vancouver, BC, Canada
[5]Toronto Health Economics and Technology Assessment (THETA) Collaboration, [6]Toronto Rehabilitation Institute; [7]The KITE Research Institute, University Health Network, Toronto, ON, Canada
[8]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton ON, Canada
[9]Pharmacy Consulting TELUS Health, Toronto, ON, Canada
[10]Department of Physical Therapy, [11]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada
[12]Biostatistics Unit at St. Joseph's Healthcare, Hamilton, Hamilton ON, Canada

*corresponding author: Kristin Musselman, PT, PhD; 520 Sutherland Dr., Room 206-K, Toronto, ON, M4G 3V9, Canada; Kristin.Musselman@uhn.ca ; (416) 597-3422 x6190

Word count: 4000

Abstract

Introduction: This protocol is describing a multi-center, single-blind randomized controlled trial. The objective is to compare the efficacy of MyndMove therapy vs conventional therapy (CT) in improving upper extremity function in individuals with C4-C7 traumatic, incomplete spinal cord injury (SCI). It is being conducted in two US and two Canadian SCI rehabilitation centers.

Methods and analysis: Sixty people aged 18 or older with a C4-C7 incomplete SCI between 4 months to 8 years' post-injury will be randomized to receive 40 sessions of MyndMove neuromodulation therapy or CT within a 14-week period of time. Therapy sessions will be 1 hour in duration with a dose of 3-5 sessions per week. Assessments will occur prior to randomization (T1), after 20 sessions (T2), after 40 sessions (T3), and 10 weeks after the last session (T4). The primary outcome measure is the efficacy of MyndMove therapy vs CT in improving upper extremity function as measured by Spinal Cord Independence Measure III: Self-Care sub score (SCIM-SC). Secondary outcomes will include: 1) Improvements in the SCIM mobility sub score; 2) Upper limb functions measured by Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) and 3) Toronto Rehab Institute Hand Function Test (TRI-HFT); 4) To assess safety as measured by serious and non-serious adverse events recorded for participants in both groups of the study population over the duration of the study; 5) To compare the change in quality of life as measured by the Spinal Cord Injury-Quality of Life (SCI-QOL); and 6) To evaluate the impact on healthcare resource utilization.

Ethics and dissemination: All ethical approvals will be obtained prior to enrolling any participants. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals

Registration: This trial is registered on www.ClinicalTrials.gov, study number NCT03439319.

2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords: neuromodulation; upper extremity; spinal cord injury; conventional therapy

Article summary

Strengths and limitations of this study

- A strength of this study is that it is a properly powered randomized controlled trial designed to detect functionally meaningful change in participants with tetraplegia.

- This therapy requires the use of a device that is not currently part of standard rehabilitation for spinal cord injury and, as a result, the participant and treating therapist are not blinded.

- The assessing therapist is blinded to reduce the risk of bias.

- The statistical analysis team is blinded to the study group.

3

INTRODUCTION

Spinal cord injury (SCI) is a devastating, life altering event that can lead to significant disability, in addition to socioeconomic challenges for the individual, family, and community at large. A survey of people with SCI revealed that the majority of people with tetraplegia (which constitutes more than 50% of individuals with SCI) rated recovery of hand function as their highest priority.[1, 2] Currently, various approaches to improve hand function after SCI are used, for example: exercises, biofeedback, robotic therapy, task specific movement therapy, reconstructive surgeries, and functional electrical stimulation (FES) therapy. To date, FES therapy has been found to be one of the most promising approaches in improving voluntary hand function.[3-18] One school of thought proposes that FES can be used as a short-term therapeutic intervention to help improve voluntary grasping function. A number of FES systems have been used for this application, for example: NESS H200;[4-6] the Bionic Glove and its newer version HandEstim Wireless Hand Stimulator (HEWHS);[8-9] and the Complex Motion system (Popovic et al., 2006; Mangold et al., 2005).[12, 18]

MyndMove therapy is a non-invasive FES neuromodulation therapy designed to restore voluntary reaching and grasping movements in individuals paralyzed by SCI or stroke. It is based on FES principles and therapeutic interventions[19] to provide clinically meaningful gains in both upper extremity function and self-care functional independence.[20] The MyndMove system promotes development and reestablishment of neural pathways within the central nervous system (CNS) and between CNS and the upper extremities by engaging neuroplasticity following neurological injury.[21] Therapists use the device with surface electrodes to deliver proprietary electrical stimulation sequences to induce targeted muscle contractions leading to functional movements.

4

Over multiple sessions, the treatments are thought to reconnect the signal from the brain to the muscles, restoring voluntary use of their arms and hands. MyndMove therapy is approved for sale by Health Canada (License Number 93158) and has been confirmed by the FDA (510(k) Number K170564). MyndMove therapy has also been confirmed by FDA to be a non-significant risk device and exempt from an IDE [reference file Q131135].

A pilot study comparing the effectiveness of FES neuromodulation therapy to conventional therapy (CT) has been conducted in individuals with cervical, incomplete SCI.[22] In that study, a small number of participants with chronic C4-C7 American Spinal Injury Association Impairment Scale (AIS) B-D SCI were randomized to FES neuromodulation therapy or CT and received 39 hours of therapy over 13-16 weeks. The FES neuromodulation therapy group improved 5-fold on the primary outcome measure (Toronto Rehabilitation Institute-Hand Function Test) compared to the CT group. However, because there were only 8 people enrolled and the study was open label, a larger randomized controlled trial (RCT) with blinded assessments was needed to definitively compare the effectiveness of the two interventions.

The proposed multi-center RCT in people with tetraplegia following traumatic SCI thus aims to (i) confirm the FES neuromodulation treatment effect as delivered by the MyndMove device across multiple investigational sites, (ii) characterize the long term benefits and retention of function by including long-term follow up assessments, and (iii) compare the efficacy of MyndMove therapy to an equivalent number of hours of CT. The study will also evaluate the impact of MyndMove therapy on the quality of life for people with traumatic SCI (C4-C7) over the course of 24 weeks.

5

Ultimately the data from these studies will assist in redefining clinical best practices in SCI rehabilitation.

METHODS AND ANALYSIS

Trial design and setting

This study is designed as a multicenter, parallel group, two arm, single-blind, randomized controlled trial to compare the clinical outcomes of MyndMove therapy to CT for individuals with C4-C7 traumatic incomplete SCI with upper extremity paresis. See Figure 1 for the study flow chart. The study will be conducted at four regional rehabilitation medical centers, in Canada and the United States, that specialize in providing neurorehabilitation to people with SCI.

Recruitment and retention

Each of the investigational sites has experience in recruiting individuals with SCI for clinical studies and each investigational site will have a study coordinator assigned to the study who will routinely review charts to identify potential study participants and to increase awareness of the planned clinical study within their community. Recruitment strategies will also include outreach to advocacy and support groups for individuals with SCI. Study coordinators will enhance retention of participants by developing rapport with them during the active portion of the trial, then periodically communicating with participants during the follow-up portion of the trial.

Eligibility criteria

Inclusion criteria:

1. Traumatic incomplete (AIS B-D) C4-C7 SCI

6

2. Paralysis or paresis in both upper extremities

3. At least 4 months (120 days) and less than 96 months (2,920 days) post-traumatic SCI

4. Baseline SCIM-SC ≤ 10

5. From an inpatient (such as skilled nursing facility) or outpatient care setting

6. Able to understand and follow instructions

7. Able to tolerate being in a seated position for a least one hour required to deliver upper limb therapy

8. Willing to attend treatment sessions and all assessment sessions

9. Able to understand and provide informed consent

10. Male and female participants ≥ 18 years of age at the time of enrollment

Exclusion criteria:

1. Previous history of any other neuromuscular disorder or conditions that may affect motor response

2. Upper extremity injury or condition prior to SCI that limits the function of the hand or arm

3. Malignant skin lesion on the affected upper extremity

4. Rash or open wound at any potential electrode site

5. History of seizure disorder not effectively managed by seizure medications

6. An implanted metallic part (e.g. plates, screws or joint replacement) or electrical device (e.g. Implantable Cardiac Defibrillator, Pacemaker, Spinal Stimulation). (Note: If the participant has passive metallic implants, the therapy can be delivered if the implants are located in an area other than where the electrical stimulant is to be delivered.)

7

7. Complete denervation of muscles that are targeted by MyndMove such that MyndMove is unable to elicit tetanic muscle contraction when upper limits of stimulation intensity (of the device) for the targeted muscle are applied

8. Poorly controlled autonomic dysreflexia (as determined by the local site physician)

9. History of psychiatric illness requiring hospitalization within past 24 months

10. Active drug treatment for dementia

11. Life expectancy of less than 12 months due to other illness

12. In the judgment of the medical provider, participant has medical complications that may interfere with the execution of the study

13. Currently enrolled in another upper limb intervention study and/ or has received MyndMove therapy within the past 3 months

14. Enrolled, in the past six months, in a clinical study involving drugs or biologics

15. Currently dependent on a ventilator

16. Botulinum toxin injection into affected upper extremity and the muscle targeted by MyndMove therapy within 6 months prior to the study start. No botulinum toxin injections in the upper extremity during the study treatment and follow up period

17. Females who are pregnant or planning to become pregnant in the duration of the trial

18. Regional disorder of the upper extremities such as fracture, dislocation, or joint contractures to less than 50% of expected range of motion

Sample size

The sample size calculation is based on the test of the research hypothesis that the mean difference in SCIM -SC in the MyndMove intervention group is better than CT control group. The primary

8

measure of effect is the difference in function measured using SCIM-SC at 6, 14, and 24 weeks. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which implies that a mean difference in either direction will be interpreted. The sample was calculated using the *power procedure* in SAS 9.2 (Cary, NC). With the proposed sample size of 30 in each of the two groups (i.e. assuming a 1:1 allocation ratio) (i.e. total sample size of 60), the study will have power of at least 80% to yield a statistically significant result using T-test (assuming an intention-to-treat principle for the analysis) of the difference between mean SCIM-SC scores at 24 weeks adjusting for baseline SCIM-SC scores at alpha = 0.05. It is important to note that using the assumption of a T-test is more conservative in that an analysis of variance (ANCOVA) will lead to better power. This computation assumes that SCIM-SC scores are normally distributed, the mean difference is 3 points and the common within-group standard deviation is 4.05. These estimates are modified estimates from the pilot study[22] which account for the type of intervention planned for in this study. The assumed Minimal Clinically Important Difference is considered to correspond to a substantially meaningful improvement on the SCIM-SC, approximately 3 points,[23-24] and also represents a moderate effect of the intervention.

Allocation and blinding

Study participants will be stratified by rehabilitation site and will be allocated in a 1:1 ratio to the following two treatment arms:

1. MyndMove therapy: Participants will receive a minimum-maximum of 36-40 one-hour sessions per day of MyndMove therapy within a 14-week period of time.

9

2. CT: Participants will receive upper-limb conventional therapy of equivalent frequency, intensity, and duration to MyndMove therapy (i.e. a minimum-maximum of 36-40 one-hour sessions per day of CT within a 14-week period of time)

The randomization schedule will be generated and maintained by a statistician at the Biostatistics Unit. A 1:1 allocation occur as per a computerized randomization schedule stratified by site (to account for variation in rehabilitation programs) using permutated blocks of random sizes and to ensure equal assignment of the MyndMove and the CT at each site. The block sizes will not be disclosed, to ensure concealment. Sufficient randomization sequence allocation, prior to study activation, will be generated to permit the enrollment and drop-out of at least 40% of the total sample size.

Participants who provide signed informed consent, meet all inclusion/exclusion criteria for the study, and complete the baseline visit will be randomly assigned to one of the two treatment arms requested directly from REDCap system. Through REDCap, the randomization allocation will be provided to the study coordinator. The study coordinator will then provide the information about treatment allocation to the participant and treating therapist. The therapist who is the outcome assessor will be blinded to the treatment allocation. All therapists (whether treating or assessing) will be licensed in physical or occupational therapy.

Intervention

Participants randomized to the MyndMove therapy group will receive FES therapy bilaterally at the therapist discretion based on clinical presentation/dominance and participant's goals.

10

Treatment will be provided in one-hour sessions per day for a minimum-maximum of 36-40 sessions delivered no less than 3 times per week and up to 5 times per week within a 14-week period of time. Over the course of the sessions, the participants will progress through various movement sequences aimed at regaining natural, unassisted voluntary movements in the affected limb(s). The proposed volume of therapy is guided by discussions with clinicians experienced with delivery of MyndMove therapy along with previous clinical research studies.[25]

The type and frequency of protocols used will follow a standardized regimen in order to minimize co-intervention variation across sites.[25] Training for MyndMove will be provided prior to the initiation of the study. Guidance regarding protocol selection, sequence, and frequency of repetition will be provided as a part of the training by MyndTec. The selection of protocols used during each treatment session will be captured. During each treatment session, therapists will select from a menu of pre-programmed stimulation protocols to facilitate various movements that include, but are not limited to: a) Palmar Grasp, b) Lateral Pinch Grasp, c) Pinch Grasp, d) Lumbrical Grasp, e) Tripod Grasp, f) Bilateral Palmar Grasp, g) Bilateral Pinch Grasp, h) Side Reach and Grasp, i) Forward Reach and Grasp, and j) Hand to Mouth.

The CT intervention serves as an active control group and will use conventional rehabilitative therapy with control for the schedule, form, and intensity of participant-therapist interactions and therapeutic activities in the MyndMove therapy group. During each treatment session, participants will receive conventional therapy of equivalent duration to the one-hour sessions per day of MyndMove therapy. The type and frequency of interventions used will follow a standardized regimen developed by consensus across the centers for the CT in order to minimize intervention

11

variation across sites. Conventional upper limb rehabilitation therapy, at the local institution, may include any or all of the following: a) facilitation of reaching or prehension movements; b) bilateral task training; c) range of motion and mobilization of joints; d) splinting; e) sensorimotor stimulation (ex. TENS, acupuncture, muscle stimulation, biofeedback); f) electrical stimulation (for strength, not function); and g) reduction of edema, if needed. The use of other FES devices during the course of the study will not be permitted.

All other rehabilitation services will be provided throughout the intervention and follow-up period. This concomitant care, which may influence outcomes, will be captured throughout the study by self-report through the use of a healthcare resource utilization questionnaire, provided to the participant and confirmed by the study staff. During the intervention period, the questionnaire will be completed by the participant to record any rehabilitation services and provide a categorical description of the treatment provided and duration of treatment sessions. This information will be reviewed by study staff and verified with the participant.

For all treatment arms, adherence to therapy will be captured to document any missed research therapy visits. This will allow for the assessment of the effectiveness of the treatment and the practicality of daily administration of the treatment. Current suggested requirements are that a minimum of 36 hours of total therapy will be considered appropriate. A per-protocol analysis will be completed using only data from those participants completing sufficient number of treatments and assessment visits.

Data collection and management

12

The Biostatistics Unit at St. Joseph's Healthcare Hamilton will provide data management and analysis for the study. All data will be deidentified to maintain confidentiality and captured on paper case report forms. Key data will be entered into the electronic database created in REDCap. Data will be directly entered into REDCap at the sites.

An independent Research Monitor will be appointed, with expertise consonant with the nature of risk(s) identified within the research protocol. The duties, authorities, and responsibilities of the independent Research Monitor will include: observation of recruitment and enrollment procedures and the consent process for individuals, overseeing study interventions and interactions, reviewing monitoring plans, and Unanticipated Problems Involving Risk to Subjects or Others reports; and overseeing data matching, data collection, and analysis. Monitoring activities will be performed both on- and off-site according to GCP guidelines. A MyndTec Study Monitor will conduct the site initiation visit, periodic site visits (with the independent Research Monitor), and a close-out visit for each site.

Schedule of data collection

A schedule of assessments and data collection is provided in Table 1.

| Events | Screening Visit | Baseline Visit | Randomization | Treatment Period | | Early Termination Assessment |
				Interim Assessment (After 20th treatment session)	End of Treatment Assessment (After 40th treatment session / 14 weeks Post First Treatment Visit)	End of Study Follow-up Assessment (24 weeks Post First Treatment Visit)
Consent						
Informed Consent Form	X					
Eligibility						

13

Inclusion/Exclusion Criteria	X					
Enrollment		X				
Interventions						
MyndMove® Therapy				▓	▓	
Intensive Conventional Therapy				▓	▓	
Assessments						
Demographics and Social Status		X				
General Health History		X				
History of Injury Event		X				
Neurologic	X	X				
Blood Pressure	X	X*		X*	X*	X*
Functional Assessments						
SCIM	X	X		X	X	X
GRASSP		X		X	X	X
TRI-HFT		X			X	X
Participation and Quality of Life						
AE/SAE				X	X	X
SCI-QOL		X			X	X
Healthcare Resource Utilization Questionnaire		X		X	X	X
End of Therapy Questionnaire					X	

X* = Blood pressure is only required if the measurement is deemed abnormal or up to investigator's discretion. SCIM - Spinal Cord Independence Measure III; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; TRI-HFT - Toronto Rehab Institute Hand Function Test; SCI-QOL - Spinal Cord Injury-Quality of Life; AE - Adverse Event; SAE - Serious Adverse Event

Table 1. A summary of assessments and data collection.

Adverse Events and Serious Adverse Events

All adverse events (AE) will be recorded and used to assess participant safety. AE will be recorded on the appropriate case report forms from the time written informed consent is obtained until completion of the study or until resolution of the reportable event. Information to be collected includes the description of the AE, date and time of onset, severity, duration, causality, outcome, and relationship to the study procedure.

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1) leads to death, 2) is life threatening, or places the

14

participant at immediate risk of death, 3) requires or prolongs inpatient hospitalization, 4) results in a significant, persistent, or permanent change, impairment, damage, or disruption in the participant's body function/structure, physical activities, and/or quality of life, 5) results in congenital anomaly/birth defect, or 6) any other serious or important event that may jeopardize the participant and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

All AEs and Serious Adverse Events (SAE) will be followed until: 1) AE is resolved, 2) AE is declared clinically insignificant, 3) AE has stabilized, 4) participant is lost to follow-up or withdraws consent, 5) participant completes study, including required follow-up visits, or 6) study closure.

MyndTec Inc. shall reimburse all reasonable and necessary expenses incurred for medical care received by study participants, including hospitalization, in the treatment of any injury or illness sustained by a clinical trial participant as a result of receiving treatment with MyndMove therapy in the study.

Outcomes

Primary outcome

The primary outcome for the study is the change in SCIM-SC between baseline and end of treatment (after the 36-40 sessions). This is the basis for the *a priori* sample size and sensitivity estimates. The SCIM is a disability scale that has been specifically developed to evaluate the functional outcomes of people with traumatic and non-traumatic SCI.[26]

15

Secondary outcomes

The GRASSP test[27-29] is a multi-modality test designed to assess the integration of sensorimotor hand and upper limb impairment and function. The TRI-HFT[30] was developed to evaluate improvements in the gross motor function of the unilateral grasp due to FES for reaching and grasping treatment. The SCI-QOL measurement system is a multifaceted system of measuring participants reported outcomes across a wide variety of functioning specifically targeted for individuals with SCI.[31] Participants will complete nine out of twenty-two areas of measure in the SCI-QOL. The nine measures are: basic mobility, fine motor, manual wheelchair, power wheelchair, self-care, independence, pain behavior, pain interference, and satisfaction with social roles & activities. A healthcare resource utilization questionnaire to capture inpatient, outpatient, and community-based rehabilitation and healthcare services during the follow-up period will also be collected. Participants will be asked to complete an end of therapy questionnaire that consists of 3 open-ended questions to understand their acceptance and impression of the therapy they received in the trial.

Participant and disease characteristics (demographics, SCI info)

The following participant characteristics will be captured: AIS grade and neurologic level, concomitant medications, biologic sex, age, race, ethnicity, marital status, number of members in household, years of education, primary occupation, family income range, handedness, International SCI Upper Extremity basic data set, general medical history, cause of SCI, current medical complications related to SCI, surgical history, current medical symptoms, smoking status, and alcohol consumption.

16

Data analysis plan

The analysis and reporting of the results with follow the CONSORT guideline [www.consort-statement.org]. The statistician/data analyst will be blinded to the study group. The process of participant selection and flow throughout the study will be summarized using a flow-diagram. The analysis results of participant demographics and baseline outcome variables (both primary and secondary) will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables. We will adopt an intention-to-treat principle to analyze all outcomes. We will also use multiple-imputation to handle missing outcome data.[32] Research has shown that this is the most optimal strategy for handling missing outcome data in trials under the assumption of missing at random.[33] All statistical tests will be performed using two-sided tests at the 0.05 level of significance. The overall level of significance will not be adjusted for multiple testing for secondary outcomes because these are exploratory. We will use analysis of covariance (ANCOVA) for the analyses of both primary and secondary outcomes, with treatment group as an independent variable and baseline values of each outcome as a covariate. For all models, the results will be expressed as mean difference, corresponding two-sided 95% confidence intervals and associated p-values. P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. We will conduct some sensitivity analyses to assess the robustness of the results: 1) Per-protocol analysis: this analysis will be based only on participants with complete data that completed study procedures as per-protocol; 2) Using last-observation-carried-forward (LOCF) for missing data: this analysis will use the LOCF to impute missing data; 3) Adjusted analysis: this analysis will adjust for some baseline variables that we think may impact the results

17

if not balanced. These include age, baseline function and baseline quality of life. To the extent that these sensitivity analyses yield similar results to the main analysis, inferences about the primary outcome will be strengthened.[34-35] Goodness-of-fit will be assessed by examining the residuals for model assumptions and chi-squared test of goodness-of-fit. Please see Table 2 for a summary of the analysis for each objective, outcome, and corresponding hypothesis. All analyses will be performed using SAS version 9.2 (Cary, NC).

Variable/Outcome	Hypothesis	Outcome Measure (type of outcome)	Methods of Analysis
1) Primary • Upper extremity function	FES Intervention [I] is better than Conventional Therapy Control [C]	Spinal Cord Independence Measure III self-care sub score (SCIM-SC)	ANCOVA
2) Secondary • Limb function	I is better than C	SCIM	ANCOVA
• Upper limb function	I is better than C	Graded Redefined Assessment of Strength, Sensibility and Prehension(GRASSP)	ANCOVA
• Upper limb function	I is better than C	Toronto Rehab Institute Hand Function Test (TRI-HFT)	ANCOVA
• Quality of life	I is better than C	Spinal Cord Injury-Quality of Life (SCI-QOL)	ANCOVA
• Safety	I is better than C	Serious and non-serious adverse events	Descriptive
• Healthcare resource utilization	Reduced healthcare resource utilization with I compared to C	Healthcare Resource Utilization Questionnaire	ANCOVA
3) Sensitivity Analyses: • Per-protocol • Missing data based imputed based on LOCF • Adjusted analysis with key baseline characteristics: Age, baseline function and QoL	Results of analysis of primary analysis will remain robust	SCIM-SC	ANCOVA, with multi-variable analysis for adjusted analysis
IMPORTANT REMARKS: • In all analyses results will be expressed as coefficient, standard errors, corresponding 95% and associated p-values. • Goodness-of-fit will be assessed by examining the residuals for model assumptions and chi-squared test of goodness-of-fit			
ANCOVA - Analysis of Covariance; C – Control; FES - Functional Electrical Stimulation; I – Intervention; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; LOCF - Last Observation Carried Forward; QOL - Quality of Life; SCIM - Spinal Cord Independence Measure III; SCIM-SC - Spinal Cord Independence Measure III self-care sub-scale; SCI-QOL - Spinal Cord Injury-Quality of Life; TRI-HFT - Toronto Rehab Institute Hand Function Test			

Table 2. Summary of the analysis for each objective, outcome, and corresponding hypothesis

18

ETHICS AND DISSEMINATION

The study design is described according to the SPIRIT reporting guidelines.[36] In accordance with CFR 21 Part 56, this study will commence after site's ethics approval is attained as well as approval from the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). Amendments to the protocol will be submitted to each of the site's ethics boards and HRPO. Changes to the protocol will not be implemented until approval has been obtained. Amendments will be numbered in a sequential manner and assigned an amendment date and version.

Data collected as a part of the study will be maintained at Biostatistics Unit on behalf of the investigators.   The initial evaluation of the clinical study results will be provided to the investigators and to MyndTec Inc. MyndTec Inc. will not prevent publication of the results regardless of the outcome of the study. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals.   Participant confidentiality will be maintained in all analyses and presentations.

Patient and public involvement

Patients were not involved in the design of this protocol. Collaborations will be developed with SCI community organizations to co-develop lay descriptions of the results of the trial for the public.

Summary

19

Spinal cord injury to the cervical region is the most common injury level with an increasing number resulting in incomplete tetraplegia. The resulting impaired upper extremity function continues to limit self-care, independence, and quality of life. Additional options and enhancements to conventional therapy are needed. The evidence for electrical stimulation having a neuromodulatory effect on spared pathways is growing, but the trials have been small and not necessarily comparative. When completed, this study will provide evidence of the effectiveness of MyndMove therapy compared to conventional therapy. These data will assist in redefining clinical best practices in SCI rehabilitation and contribute to maximizing functional recovery.

Author contributions

All of the authors made substantial contributions to study design and were involved in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be published.

Competing interests

MyndTec Inc. is the Contracting Organization of this study and through funding provided by the US DOD AMRMC SCIRP, the researchers are reimbursed for doing this study. All Investigators have an interest in completing the study.

Ethics approval

This study has ethics approval from:

MetroHealth System Institutional Review Board (IRB18-0751)

University Health Network Research Ethics Board (REB17-6029)

University of Texas Health Science Center Institutional Review Board (HSC-MS-18-0862)

Advarra Institutional Review Board for HealthTech Connex Centre for Neurology Studies (Pro00030094)

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

All data from this work will be maintained at the Biostatistics Unit at St. Joseph's Healthcare Hamilton. Data sharing and access to the trial dataset will be incorporated into the Clinical Trial Agreements between the MyndTec Inc. and each of the Principal Investigators and Sites according to institutional requirements. Access to the trial dataset by individuals outside the study will be reviewed on a case-by-case basis.

21

REFERENCES

1. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21:1371-83.

2. Noonan VK, Fingas M, Farry A, et al. Incidence and prevalence of spinal cord injury in Canada: a national perspective. *Neuroepidemiology* 2012;38:219-26.

3. Hoshimiya N, Handa Y. A master-slave type multi-channel functional electrical stimulation (FES) system for the control of the paralyzed upper extremities. *Automedica* 1989;11:209-20.

4. Handa Y, Handa T, Ichie M, et al. Functional electrical stimulation (FES) systems for restoration of motor function of paralyzed muscles--versatile systems and a portable system. *Front Med Biol Eng* 1992;4:241-55.

5. Nathan RH, Ohry A. Upper limb functions regained in quadriplegia: a hybrid computerized neuromuscular stimulation system. *Arch Phys Med Rehabil* 1990;71:415-21.

6. IJzerman MJS, Stoffers TS, in 't Groen FACG, et al. The NESS Handmaster orthosis: restoration of hand function in C5 and stroke patients by means of electrical stimulation. *J Rehabil Sci* 1996;9:86-9.

22

7. Snoek GJ, IJzerman MJ, in 't Groen FA, et al. Use of the NESS handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients. *Spinal Cord* 2000;38:244-49.

8. Prochazka A, Gauthier M, Wieler M, et al. The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch Phys Med Rehabil* 1997;78:608-14.

9. Popovic DS A, Pjanovic A, Radosavljevic S, et al. Clinical evaluation of the Bionic Glove. *Arch Phys Med Rehabil* 1999;80:299-304.

10. Popovic MR, Popovic DB, Keller T. Neuroprostheses for grasping. *Neurol Res* 2002;24:443-52.

11. Popovic MR, Thrasher TA, Zivanovic V, et al. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. *Neuromodulation* 2005;8:58-72.

12. Popovic MR, Thrasher TA, Adams ME, et al. Functional electrical therapy: retraining grasping in spinal cord injury. *Spinal Cord* 2006;44:143-51.

13. Rebersek S, Vodovnik L. Proportionally controlled functional electrical stimulation of hand. *Arch Phys Med Rehabil* 1973;54:378-82.

23

14. Peckham PH, Marsolais EB, Mortimer JT. Restoration of key grip and release in the C6 tetraplegic patient through functional electrical stimulation. *J Hand Surg Am* 1980;5:462-69.

15. Peckham PH, Mortimer JT, Marsolais EB. Controlled prehension and release in the C5 quadriplegic elicited by functional electrical stimulation of the paralyzed forearm musculature. *Ann Biomed Eng* 1980;8:369-88.

16. Kilgore KL, Peckham PH, Thrope GB, et al. Synthesis of hand grasp using functional neuromuscular stimulation. *IEEE Trans Biomed Eng* 1989;36:761-70.

17. Wuolle KS, Van Doren CL, Thrope GB, et al. Development of a quantitative hand grasp and release test for patients with tetraplegia using a hand neuroprosthesis. *J Hand Surg Am* 1994;19:209-18.

18. Mangold S, Keller T, Curt A, et al. Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. *Spinal Cord* 2005;43:1-13.

19. Teferra M. Functional electrical stimulation (FES): review. *IJLRET* 2017;3:95-101.

20. Popovic MR, Kapadia N, Zivanovic V, et al. Functional electrical stimulation therapy of voluntary grasping versus only conventional rehabilitation for patients with subacute

24

incomplete tetraplegia: a randomized clinical trial. *Neurorehabil Neural Repair* 2011;25:433-42.

21. Nagai MK, Marquez-Chin C, Popovic MR. Why is functional electrical stimulation therapy capable of restoring motor function following severe injury to the central nervous system? In: Tuszynski MH, ed. Translational Neuroscience. New York, NY: Springer Science and Business Media 2016:479-98.

22. Kapadia N, Zivanovic V, Popovic MR. Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: pilot study. *Top Spinal Cord Inj Rehabil* 2013;19:279-87.

23. Scivoletto G, Tamburella F, Laurenza L, et al. The Spinal Cord Independence Measure: how much change is clinically significant for spinal cord injury subjects. *Disabil Rehabil* 2013;35:1808-13.

24. Scivoletto G, Tamburella F, Laurenza L, et al. Distribution-based estimates of clinically significant changes in the International Standards for Neurological Classification of Spinal Cord Injury motor and sensory scores. *Eur J Phys Rehabil Med* 2013;49:373-84.

25. Hebert DA, Bowens JM, Ho C, et al. Examining a new functional electrical stimulation therapy with people with severe upper extremity hemiparesis and chronic stroke: a feasibility study. *Br J Occup Ther* 2017;80:651-59.

25

26. Catz A, Itzkovich M, Agranov E, et al. SCIM--spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord* 1997;35:850-56.

27. Kalsi-Ryan S, Beaton D, McIlroy W, et al. Quantification of multi-modality sensation of the hand in cervical spinal cord injury. *J Spinal Cord Med*. 2006;29:311.

28. Kalsi-Ryan S, Beaton D, Curt A, et al. The Graded Redefined Assessment of Sensibility Strength and Prehension: reliability and validity. *J Neurotrauma* 2012;29:905-14.

29. Kalsi-Ryan S, Curt A, Verrier M, et al. Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia. *J Neurosurg Spine* 2012;17:65-76.

30. Kapadia N, Zivanovic V, Verrier M, et al. Toronto Rehabilitation Institute-Hand Function Test: assessment of gross motor function in individuals with spinal cord injury. *Top Spinal Cord Inj Rehabil* 2012;18:167-86.

31. Tulsky DS, Kisala PA, Victorson D, et al. Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system. *J Spinal Cord Med* 2015;38:257-69.

32. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons. 1987.

26

33. Zhang Y, Alyass A, Vanniyasingam T, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials. *J Clin Epid* 2017;88:67-80.

34. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol* 2013;13:92.

35. De Souza RJ, Eisen R, Perera S, et al. Best (but oft-forgotten) practices: sensitivity analyses in randomized controlled trials. *Am J Clin Nutr* 2016;103: 5-17.

36. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-07.

27

Acknowledgements

FIGURE LEGENDS

Figure 1. CONSORT diagram of study flow chart.

28

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1. Study Flow Chart

```
┌─────────────────────────────────────┐
│            Recruitment               │
│     (rehabilitation, community)      │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│           Informed Consent           │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│           Screening Visit            │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│          Baseline Assessment         │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│         Randomization 1:1 ratio      │
└─────────────────────────────────────┘
         ↓                    ↓
┌──────────────┐      ┌──────────────┐
│  MyndMove    │      │  Intensive   │
│  Therapy     │      │  Conventional│
│              │      │  Therapy     │
└──────────────┘      └──────────────┘
         ↘                    ↙
                  ↓
┌─────────────────────────────────────┐
│  Interim Assessment (after 20th session) │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│      End of Treatment Assessment     │
│      (after 40th session / 14 weeks) │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│   End of Study Follow-up Assessment  │
│  (24 weeks Post First Treatment Visit)│
└─────────────────────────────────────┘
```
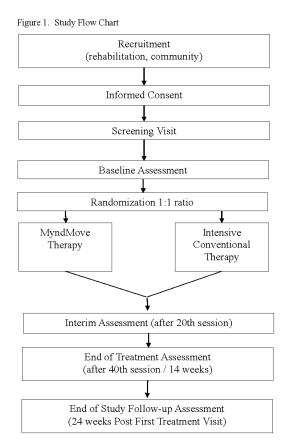
Figure 1. CONSORT diagram of study flow chart.

215x279mm (150 x 150 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	19
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13,20,21

other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10,11

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9,10

Allocation concealment mechanism	[#16b](#)	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	[#16c](#)	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9,10
Blinding (masking)	[#17a](#)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9,10
Blinding (masking): emergency unblinding	[#17b](#)	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

Data collection plan	[#18a](#)	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
Data collection plan: retention	[#18b](#)	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	[#19](#)	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17,18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17

Methods: Monitoring

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14,15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19,21

Protocol amendments	[#25](#)	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	[#26a](#)	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7,10
Consent or assent: ancillary studies	[#26b](#)	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	[#27](#)	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	[#28](#)	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	[#29](#)	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19,21
Ancillary and post trial care	[#30](#)	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy: trial results	[#31a](#)	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	[#31b](#)	Authorship eligibility guidelines and any intended use of professional writers	20,21
Dissemination policy: reproducible research	[#31c](#)	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21

Appendices

| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Protocol for a multi-center, single-blind randomized controlled trial comparing MyndMove neuromodulation therapy to conventional therapy in traumatic spinal cord injury

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protocol for a multi-center, single-blind randomized controlled trial comparing MyndMove neuromodulation therapy to conventional therapy in traumatic spinal cord injury

Authors:
Kim D. Anderson[1,2]; James R. Wilson[1,2]; Radha Korupolu[3]; Jacqueline Pierce[4]; Jim Bowen[5,8]; Daria O'Reilly[8,9]; Naaz Kapadia[6,10]; Milos R. Popovic[7,11]; Lehana Thabane[8,12]; Kristin Musselman[6,10]*

Affiliations:
[1]MetroHealth Rehabilitation Institute, MetroHealth System, Cleveland, OH, USA
[2]Department of Physical Medicine and Rehabilitation, Case Western Reserve University, Cleveland, OH, USA
[3]Department of Physical Medicine and Rehabilitation, McGovern Medical School, The University of Texas Health Science Center at Houston, TX, USA / The Institute of Rehabilitation & Research (TIRR) Memorial Hermann, Houston, TX, USA
[4]HealthTech Connex Centre for Neurology Studies/ Neuromotion Physiotherapy, Vancouver, BC, Canada
[5]Toronto Health Economics and Technology Assessment (THETA) Collaboration, [6]Toronto Rehabilitation Institute; [7]The KITE Research Institute, University Health Network, Toronto, ON, Canada
[8]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton ON, Canada
[9]Pharmacy Consulting TELUS Health, Toronto, ON, Canada
[10]Department of Physical Therapy, [11]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada
[12]Biostatistics Unit at St. Joseph's Healthcare, Hamilton, Hamilton ON, Canada

*corresponding author: Kristin Musselman, PT, PhD; 520 Sutherland Dr., Room 206-K, Toronto, ON, M4G 3V9, Canada; Kristin.Musselman@uhn.ca ; (416) 597-3422 x6190

Word count: 4000

1

Abstract

Introduction: This protocol is describing a multi-center, single-blind randomized controlled trial. The objective is to compare the efficacy of MyndMove therapy vs conventional therapy (CT) in improving upper extremity function in individuals with C4-C7 traumatic, incomplete spinal cord injury (SCI). It is being conducted in two US and two Canadian SCI rehabilitation centers.

Methods and analysis: Sixty people aged 18 or older with a C4-C7 incomplete (AIS B-D) SCI between 4 months to 8 years' post-injury are randomized to receive 40 sessions of MyndMove neuromodulation therapy or CT within a 14-week period of time. Therapy sessions are 1 hour in duration with a dose of 3-5 sessions per week. Assessments occur prior to randomization, after 20 sessions, after 40 sessions, and 10 weeks after the last session. The primary outcome measure is the efficacy of MyndMove therapy vs CT in improving upper extremity function as measured by Spinal Cord Independence Measure III: Self-Care sub score (SCIM-SC) after 40 sessions. Secondary outcomes include: 1) Improvements in the SCIM mobility sub score; 2) Upper limb functions measured by Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) and 3) Toronto Rehab Institute Hand Function Test (TRI-HFT); 4) To assess safety as measured by serious and non-serious adverse events recorded for participants in both groups of the study population over the duration of the study; 5) To compare the change in quality of life as measured by the Spinal Cord Injury-Quality of Life (SCI-QOL); and 6) To evaluate the impact on healthcare resource utilization.

Ethics and dissemination: All ethical approvals were obtained prior to enrolling any participants. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals

Registration: This trial is registered on www.ClinicalTrials.gov, study number NCT03439319.

2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Article summary

Strengths and limitations of this study

- A strength of this study is that it is a properly powered randomized controlled trial designed to detect functionally meaningful change in participants with tetraplegia.

- This therapy requires the use of a device that is not currently part of standard rehabilitation for spinal cord injury and, as a result, the participant and treating therapist are not blinded.

- The assessing therapist is blinded to reduce the risk of bias.

- The statistical analysis team is blinded to the study group.

3

INTRODUCTION

Spinal cord injury (SCI) is a devastating, life altering event that can lead to significant disability, in addition to socioeconomic challenges for the individual, family, and community at large. A survey of people with SCI revealed that the majority of people with tetraplegia (which constitutes more than 50% of individuals with SCI) rated recovery of hand function as their highest priority.[1, 2] Currently, various approaches to improve hand function after SCI are used, for example: exercises, biofeedback, robotic therapy, task specific movement therapy, reconstructive surgeries, and functional electrical stimulation (FES) therapy. To date, FES therapy has been found to be one of the most promising approaches in improving voluntary hand function.[3-18] One school of thought proposes that FES can be used as a short-term therapeutic intervention to help improve voluntary grasping function. A number of FES systems have been used for this application, for example: NESS H200;[4-6] the Bionic Glove and its newer version HandEstim Wireless Hand Stimulator (HEWHS);[8-9] and the Complex Motion system .[12, 18] Emerging evidence in tetraplegia suggests that electrical stimulation and FES therapy improve arm and hand function more than conventional therapy, particularly when provided in combination with various types of conventional therapy. Recently a study demonstrated that the functional benefits of massed practice of conventional therapy were greater when augmented by sensory stimulation.[19] Another study demonstrated that exercise therapy combined with FES produced greater functional improvements compared to exercise therapy combined with traditional electrical stimulation.[20]

MyndMove therapy is a non-invasive FES neuromodulation therapy designed to restore voluntary reaching and grasping movements in individuals paralyzed by SCI or stroke. It is based on FES principles and therapeutic interventions[21] to provide clinically meaningful gains in both upper

extremity function and self-care functional independence.[22] The MyndMove system promotes

development and reestablishment of neural pathways within the central nervous system (CNS) and

between CNS and the upper extremities by engaging neuroplasticity following neurological

injury.[23] Therapists use the device with surface electrodes to deliver proprietary electrical

stimulation sequences to induce targeted muscle contractions leading to functional movements.

Over multiple sessions, the treatments are thought to reconnect the signal from the brain to the

muscles, restoring voluntary use of their arms and hands. MyndMove therapy is approved for sale

by Health Canada (License Number 93158) and has been confirmed by the FDA (510(k) Number

K170564). MyndMove therapy has also been confirmed by FDA to be a non-significant risk

device and exempt from an IDE [reference file Q131135].

A pilot study comparing the effectiveness of FES neuromodulation therapy to conventional

therapy (CT) has been conducted in individuals with cervical, incomplete SCI.[24] In that study,

a small number of participants with chronic C4-C7 American Spinal Injury Association

Impairment Scale (AIS) B-D SCI were randomized to FES neuromodulation therapy or CT and

received 39 hours of therapy over 13-16 weeks. The FES neuromodulation therapy group

improved 5-fold on the primary outcome measure (Toronto Rehabilitation Institute-Hand Function

Test) compared to the CT group. However, because there were only 8 people enrolled and the

study was open label, a larger randomized controlled trial (RCT) with blinded assessments was

needed to definitively compare the effectiveness of the two interventions.

The protocol for this multi-center RCT in people with tetraplegia following traumatic SCI aims to

(i) confirm the FES neuromodulation treatment effect as delivered by the MyndMove device across

5

multiple investigational sites, (ii) characterize the long term benefits and retention of function by including long-term follow up assessments, and (iii) compare the efficacy of MyndMove therapy to an equivalent number of hours of CT. The study will also evaluate the impact of MyndMove therapy on the quality of life for people with traumatic SCI (C4-C7) over the course of 24 weeks. Ultimately the data from these studies will assist in redefining clinical best practices in SCI rehabilitation.

METHODS AND ANALYSIS

Trial design and setting

This study is designed as a multicenter, parallel group, two arm, single-blind, randomized controlled trial to compare the clinical outcomes of MyndMove therapy to CT for individuals with C4-C7 traumatic incomplete SCI with upper extremity paresis. See Figure 1 for the study flow chart. The study is being conducted at four regional rehabilitation medical centers, in Canada and the United States, that specialize in providing neurorehabilitation to people with SCI. The first participant was enrolled in June 2019. It is estimated that the final participant will be enrolled by December 2020, but this may be negatively impacted by COVID-19.

Recruitment and retention

Each of the investigational sites has experience in recruiting individuals with SCI for clinical studies and each investigational site has a study coordinator assigned to the study who routinely reviews charts to identify potential study participants and to increase awareness of the planned clinical study within their community. Recruitment strategies include outreach to advocacy and support groups for individuals with SCI. Study coordinators will enhance retention of participants

6

by developing rapport with them during the active portion of the trial, then periodically communicating with participants during the follow-up portion of the trial.

Eligibility criteria

Inclusion criteria:

1. Traumatic incomplete (AIS B-D) C4-C7 SCI

2. Paralysis or paresis in both upper extremities

3. At least 4 months (120 days) and less than 96 months (2,920 days) post-traumatic SCI

4. Baseline SCIM-SC ≤ 10

5. From an inpatient (such as skilled nursing facility) or outpatient care setting

6. Able to understand and follow instructions

7. Able to tolerate being in a seated position for a least one hour required to deliver upper limb therapy

8. Willing to attend treatment sessions and all assessment sessions

9. Able to understand and provide informed consent

10. Male and female participants ≥ 18 years of age at the time of enrollment

Exclusion criteria:

1. Previous history of any other neuromuscular disorder or conditions that may affect motor response

2. Upper extremity injury or condition prior to SCI that limits the function of the hand or arm

3. Malignant skin lesion on the affected upper extremity

4. Rash or open wound at any potential electrode site

7

5. History of seizure disorder not effectively managed by seizure medications

6. An implanted metallic part (e.g. plates, screws or joint replacement) or electrical device (e.g. Implantable Cardiac Defibrillator, Pacemaker, Spinal Stimulation). (Note: If the participant has passive metallic implants, the therapy can be delivered if the implants are located in an area other than where the electrical stimulant is to be delivered.)

7. Complete denervation of muscles that are targeted by MyndMove such that MyndMove is unable to elicit tetanic muscle contraction when upper limits of stimulation intensity (of the device) for the targeted muscle are applied

8. Poorly controlled autonomic dysreflexia (as determined by the local site physician)

9. History of psychiatric illness requiring hospitalization within past 24 months

10. Active drug treatment for dementia

11. Life expectancy of less than 12 months due to other illness

12. In the judgment of the medical provider, participant has medical complications that may interfere with the execution of the study

13. Currently enrolled in another upper limb intervention study and/ or has received MyndMove therapy within the past 3 months

14. Enrolled, in the past six months, in a clinical study involving drugs or biologics

15. Currently dependent on a ventilator

16. Botulinum toxin injection into affected upper extremity and the muscle targeted by MyndMove therapy within 6 months prior to the study start. No botulinum toxin injections in the upper extremity during the study treatment and follow up period

17. Females who are pregnant or planning to become pregnant in the duration of the trial

8

18. Regional disorder of the upper extremities such as fracture, dislocation, or joint contractures to less than 50% of expected range of motion

Sample size

The sample size calculation is based on the test of the research hypothesis that the mean difference in SCIM -SC in the MyndMove intervention group is better than CT control group. The primary measure of effect is the difference in function measured using SCIM-SC at 14 weeks. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which implies that a mean difference in either direction will be interpreted. The sample was calculated using the *power procedure* in SAS 9.2 (Cary, NC). With the proposed sample size of 30 in each of the two groups (i.e. assuming a 1:1 allocation ratio) (i.e. total sample size of 60), the study will have power of at least 80% to yield a statistically significant result using T-test (assuming an intention-to-treat principle for the analysis) of the difference between mean SCIM-SC scores at 14 weeks adjusting for baseline SCIM-SC scores at alpha = 0.05. It is important to note that using the assumption of a T-test is more conservative in that an analysis of variance (ANCOVA) will lead to better power. This computation assumes that SCIM-SC scores are normally distributed, the mean difference is 3 points and the common within-group standard deviation is 4.05. These estimates are modified estimates from the pilot study[24] which account for the type of intervention planned for in this study. The assumed Minimal Clinically Important Difference is considered to correspond to a substantially meaningful improvement on the SCIM-SC, approximately 3 points,[25-26] and also represents a moderate effect of the intervention.

Allocation and blinding

9

Study participants will be stratified by rehabilitation site and will be allocated in a 1:1 ratio to the following two treatment arms:

1. MyndMove therapy: Participants will receive a minimum-maximum of 36-40 one-hour sessions per day of MyndMove therapy within a 14-week period of time.

2. CT: Participants will receive upper-limb conventional therapy of equivalent frequency, intensity, and duration to MyndMove therapy (i.e. a minimum-maximum of 36-40 one-hour sessions per day of CT within a 14-week period of time)

The randomization schedule will be generated and maintained by a statistician at the Biostatistics Unit. A 1:1 allocation occur as per a computerized randomization schedule stratified by site (to account for variation in rehabilitation programs between Canada and the US) using permutated blocks of random sizes and to ensure equal assignment of the MyndMove and the CT at each site. The block sizes will not be disclosed, to ensure concealment. Sufficient randomization sequence allocation, prior to study activation, will be generated to permit the enrollment and drop-out of at least 40% of the total sample size.

Participants who provide signed informed consent, meet all inclusion/exclusion criteria for the study, and complete the baseline visit will be randomly assigned to one of the two treatment arms requested directly from REDCap system. Through REDCap, the randomization allocation will be provided to the study coordinator. The study coordinator will then provide the information about treatment allocation to the participant and treating therapist. The therapist who is the outcome assessor will be blinded to the treatment allocation. All therapists (whether treating or assessing) will be licensed in physical or occupational therapy.

10

Intervention

Participants randomized to the MyndMove therapy group will receive FES therapy bilaterally at the therapist discretion based on clinical presentation/dominance and participant's goals. Treatment will be provided in one-hour sessions per day for a minimum-maximum of 36-40 sessions delivered no less than 3 times per week and up to 5 times per week within a 14-week period of time. Over the course of the sessions, the participants will progress through various movement sequences aimed at regaining natural, unassisted voluntary movements in the affected limb(s). The proposed volume of therapy is guided by discussions with clinicians experienced with delivery of MyndMove therapy along with previous clinical research studies.[27]

The type and frequency of protocols used will follow a standardized regimen in order to minimize co-intervention variation across sites.[27] Training for MyndMove will be provided prior to the initiation of the study. Guidance regarding protocol selection, sequence, and frequency of repetition will be provided as a part of the training by MyndTec. The selection of protocols used during each treatment session will be captured. During each treatment session, therapists will select from a menu of pre-programmed stimulation protocols to facilitate various task-specific movements (Table 1). Movement practice may be massed or distributed, depending on the tolerance of the participant (i.e. muscle fatigue).

Movement Practiced*	Muscles Stimulated with MyndMove®**
Palmar grasp^	- Flexor digitorum superficialis and profundus - Thenar muscles - Extensor digitorum
Lateral pinch grasp^	- Flexor digitorum superficialis and profundus - Thenar muscles - Extensor digitorum
Pinch grasp^	- Thenar muscles - Extensor digitorum

11

	- First lumbrical
Lumbrical grasp	- Thenar muscles - Extensor digitorum - First, second and third lumbricals
Tripod grasp	- Flexor digitorum superficialis - Thenar muscles - Extensor digitorum - Second dorsal interosseous
Side reach with finger extension	- Biceps - Triceps - Middle deltoid - Extensor digitorum - Extensor carpi radialis longus - Extensor carpi ulnaris
Forward reach and grasp	- Biceps - Triceps - Posterior deltoid - Anterior deltoid - Extensor digitorum - Extensor carpi radialis longus - Extensor carpi ulnaris - Flexor digitorum superficialis and profundus - Thenar muscles
Hand to mouth	- Biceps - Triceps - Anterior deltoid

*The movement is demonstrated for the participant by the therapist. The therapist then instructs the participant to voluntarily attempt the movement for about 10 seconds, after which electrical stimulation is provided with the appropriate MyndMove® protocol.[28] **muscles not listed in order of stimulation. ^Unilateral or bilateral stimulation may be used.
Table 1: Example MyndMove® Protocols

The CT intervention serves as an active control group and will use conventional rehabilitative

therapy with control for the schedule, form, and intensity of participant-therapist interactions and

therapeutic activities in the MyndMove therapy group. During each treatment session, participants

will receive conventional therapy of equivalent duration to the one-hour sessions per day of

MyndMove therapy. The type and frequency of interventions used will follow a standardized

regimen developed by consensus across the centers for the CT in order to minimize intervention

variation across sites. Conventional upper limb rehabilitation therapy, at the local institution, may

include any or all of the following: a) facilitation of reaching or prehension movements; b) bilateral

task-specific movement practice (distributed or massed, dependent on participant tolerance); c)

range of motion and mobilization of joints; d) splinting; e) sensorimotor stimulation (ex. TENS,

12

acupuncture, muscle stimulation, biofeedback); f) electrical stimulation (for strength, not function); and g) reduction of edema, if needed. The use of other FES devices during the course of the study will not be permitted.

All other rehabilitation services will be provided throughout the intervention and follow-up period. This concomitant care, which may influence outcomes, will be captured throughout the study by self-report through the use of a healthcare resource utilization questionnaire, provided to the participant and confirmed by the study staff. During the intervention period, the questionnaire will be completed by the participant to record any rehabilitation services and provide a categorical description of the treatment provided and duration of treatment sessions. This information will be reviewed by study staff and verified with the participant.

For all treatment arms, adherence to therapy will be captured to document any missed research therapy visits. This will allow for the assessment of the effectiveness of the treatment and the practicality of daily administration of the treatment. A per-protocol analysis will be completed using only data from those participants completing at least 30 treatments, which corresponds to 75% of allocated treatments.

Data collection and management

The Biostatistics Unit will provide data management and analysis for the study. All data will be deidentified to maintain confidentiality and captured on paper case report forms. Key data will be entered at each site directly into the electronic database created in REDCap.

13

An independent Research Monitor will be appointed, with expertise consonant with the nature of risk(s) identified within the research protocol. The duties, authorities, and responsibilities of the independent Research Monitor will include: observation of recruitment and enrollment procedures and the consent process for individuals, overseeing study interventions and interactions, reviewing monitoring plans, and Unanticipated Problems Involving Risk to Subjects or Others reports; and overseeing data matching, data collection, and analysis. Monitoring activities will be performed both on- and off-site according to GCP guidelines. A MyndTec Study Monitor will conduct the site initiation visit, periodic site visits (with the independent Research Monitor), and a close-out visit for each site.

Schedule of data collection

A schedule of assessments and data collection is provided in Table 2.

| Events | Screening Visit | Baseline Visit | Randomization | Treatment Period | | Early Termination Assessment |
				Interim Assessment (After 20th treatment session)	End of Treatment Assessment (After 40th treatment session / 14 weeks Post First Treatment Visit)	End of Study Follow-up Assessment (24 weeks Post First Treatment Visit)
Consent						
Informed Consent Form	X					
Eligibility						
Inclusion/Exclusion Criteria	X					
Enrollment			X			
Interventions						
MyndMove® Therapy						
Intensive Conventional Therapy						
Assessments						
Demographics and Social Status		X				
General Health History		X				

14

History of Injury Event		X			
Neurologic	X	X			
Blood Pressure	X	X*	X*	X*	X*
Functional Assessments					
SCIM	X	X	X	X	X
GRASSP		X	X	X	X
TRI-HFT		X		X	X
Participation and Quality of Life					
AE/SAE			X	X	X
SCI-QOL		X		X	X
Healthcare Resource Utilization Questionnaire		X	X	X	X
End of Therapy Questionnaire				X	

X* = Blood pressure is only required if the measurement is deemed abnormal or up to investigator's discretion. SCIM - Spinal Cord Independence Measure III; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; TRI-HFT - Toronto Rehab Institute Hand Function Test; SCI-QOL - Spinal Cord Injury-Quality of Life; AE - Adverse Event; SAE - Serious Adverse Event

Table 2. A summary of assessments and data collection.

Adverse Events and Serious Adverse Events

All adverse events (AE) will be recorded and used to assess participant safety. AE will be recorded on the appropriate case report forms from the time written informed consent is obtained until completion of the study or until resolution of the reportable event. Information to be collected includes the description of the AE, date and time of onset, severity, duration, causality, outcome, and relationship to the study procedure.

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1) leads to death, 2) is life threatening, or places the participant at immediate risk of death, 3) requires or prolongs inpatient hospitalization, 4) results in a significant, persistent, or permanent change, impairment, damage, or disruption in the participant's body function/structure, physical activities, and/or quality of life, 5) results in congenital anomaly/birth defect, or 6) any other serious or important event that may jeopardize the

15

participant and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

All AEs and Serious Adverse Events (SAE) will be followed until: 1) AE is resolved, 2) AE is declared clinically insignificant, 3) AE has stabilized, 4) participant is lost to follow-up or withdraws consent, 5) participant completes study, including required follow-up visits, or 6) study closure.

MyndTec Inc. shall reimburse all reasonable and necessary expenses incurred for medical care received by study participants, including hospitalization, in the treatment of any injury or illness sustained by a clinical trial participant as a result of receiving treatment with MyndMove therapy in the study.

Outcomes

Primary outcome

The primary outcome for the study is the change in SCIM-SC between baseline and end of treatment (14 weeks). This is the basis for the *a priori* sample size and sensitivity estimates. The SCIM is a disability scale that has been specifically developed to evaluate the functional outcomes of people with traumatic and non-traumatic SCI.[29]

Secondary outcomes

Additional secondary analyses of the SCIM self-care and mobility subscales will be performed at the interim, end of treatment, and end of study assessments (see Table 2 schedule of assessments).

16

The GRASSP test[30-32] is a multi-modality test designed to assess the integration of sensorimotor hand and upper limb impairment and function. The baseline scores for each of the GRASSP subscales will be compared to the scores at interim, end of treatment, and end of study assessments. The TRI-HFT[33] was developed to evaluate improvements in the gross motor function of the unilateral grasp due to FES for reaching and grasping treatment. The baseline scores for each of the TRI-HFT subscales will be compared to the scores at the end of treatment and end of study assessments. The SCI-QOL measurement system is a multifaceted system of measuring participants reported outcomes across a wide variety of functioning specifically targeted for individuals with SCI.[34] Participants will complete nine out of twenty-two areas of measure in the SCI-QOL (Table 3). The baseline scores for each of the SCI-QOL subscales will be compared to the scores at the end of treatment and end of study assessments. A healthcare resource utilization questionnaire to capture inpatient, outpatient, and community-based rehabilitation and healthcare services during the follow-up period will also be collected. The total number of minutes utilized from baseline to the end of study assessment will be compared between groups. Participants will be asked to complete an end of therapy questionnaire that consists of 3 open-ended questions to understand their acceptance and impression of the therapy they received in the trial. See Table 3 for the analysis plan for each secondary outcome.

Participant and disease characteristics (demographics, SCI info)

The following participant characteristics will be captured: AIS grade and neurologic level, concomitant medications, biologic sex, age, race, ethnicity, marital status, number of members in household, years of education, primary occupation, family income range, handedness, International SCI Upper Extremity basic data set, general medical history, cause of SCI, current

17

medical complications related to SCI, surgical history, current medical symptoms, smoking status, and alcohol consumption.

Data analysis plan

The analysis and reporting of the results with follow the CONSORT guideline [www.consort-statement.org]. The statistician/data analyst will be blinded to the study group. The process of participant selection and flow throughout the study will be summarized using a flow-diagram. The analysis results of participant demographics and baseline outcome variables (both primary and secondary) will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables. We will adopt an intention-to-treat principle to analyze all outcomes. We will also use multiple-imputation to handle missing outcome data.[35] Research has shown that this is the most optimal strategy for handling missing outcome data in trials under the assumption of missing at random.[36] All statistical tests will be performed using two-sided tests at the 0.05 level of significance. The overall level of significance will not be adjusted for multiple testing for secondary outcomes because these are exploratory. We will use analysis of covariance (ANCOVA) for the analyses of both primary and secondary outcomes, with treatment group as an independent variable and baseline values of each outcome as a covariate. For all models, the results will be expressed as mean difference, corresponding two-sided 95% confidence intervals and associated p-values. P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. We will conduct some sensitivity analyses to assess the robustness of the results: 1) Per-protocol analysis: this analysis will be based only on participants with complete data that completed study procedures as per-protocol; 2) Using last-observation-carried-forward

18

(LOCF) for missing data: this analysis will use the LOCF to impute missing data; 3) Adjusted

analysis: this analysis will adjust for some baseline variables that we think may impact the results

if not balanced. These include age, time post-injury, baseline function, baseline quality of life,

and, potentially, site. To the extent that these sensitivity analyses yield similar results to the main

analysis, inferences about the primary outcome will be strengthened.[37-38] Goodness-of-fit will

be assessed by examining the residuals for model assumptions and chi-squared test of goodness-

of-fit. Please see Table 3 for a summary of the analysis for each objective, outcome, and

corresponding hypothesis. All analyses will be performed using SAS version 9.2 (Cary, NC).

Variable/Outcome	Hypothesis	Outcome Measure (type of outcome)	Methods of Analysis
1) Primary • Upper extremity function	FES Intervention [I] is better than Conventional Therapy Control [C]	Spinal Cord Independence Measure III self-care subscale score (SCIM-SC)	ANCOVA
2) Secondary • Limb function	I is better than C	SCIM mobility subscale score	ANCOVA
• Upper limb function	I is better than C	Graded Redefined Assessment of Strength, Sensibility and Prehension(GRASSP) sub scales: Strength total score Sensibility total score Qualitative prehension total score Quantitative prehension total score	ANCOVA
• Upper limb function	I is better than C	Toronto Rehab Institute Hand Function Test (TRI-HFT) sub scales: Object manipulation score Wooden block score Cylinder torque Credit card force Wooden bar displacement length	ANCOVA
• Quality of life	I is better than C	Spinal Cord Injury-Quality of Life (SCI-QOL) subscales: Basic mobility score Fine motor score Manual wheelchair score Power wheelchair score Self-care score Independence score Pain behavior score	ANCOVA

19

		Pain interference score Satisfaction with social roles and activities score	
• Safety	I is better than C	Serious and non-serious adverse events, total number of each per group	Descriptive
• Healthcare resource utilization	Reduced healthcare resource utilization with I compared to C	Healthcare Resource Utilization Questionnaire, total number of minutes	ANCOVA
3) <u>Sensitivity Analyses:</u> • Per-protocol • Missing data based imputed based on LOCF • Adjusted analysis with key baseline characteristics: Age, baseline function and QoL	Results of analysis of primary analysis will remain robust	SCIM-SC score	ANCOVA, with multi-variable analysis for adjusted analysis

IMPORTANT REMARKS:
- In all analyses results will be expressed as coefficient, standard errors, corresponding 95% and associated p-values.
- Goodness-of-fit will be assessed by examining the residuals for model assumptions and chi-squared test of goodness-of-fit

ANCOVA - Analysis of Covariance; C – Control; FES - Functional Electrical Stimulation; I – Intervention; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; LOCF - Last Observation Carried Forward; QOL - Quality of Life; SCIM - Spinal Cord Independence Measure III; SCIM-SC - Spinal Cord Independence Measure III self-care sub-scale; SCI-QOL - Spinal Cord Injury-Quality of Life; TRI-HFT - Toronto Rehab Institute Hand Function Test

Table 3. Summary of the analysis for each objective, outcome, and corresponding hypothesis

Patient and public involvement

Patients were not involved in the design of this protocol. Collaborations will be developed with SCI community organizations to co-develop lay descriptions of the results of the trial for the public.

ETHICS AND DISSEMINATION

The study design is described according to the SPIRIT reporting guidelines.[39] This study has ethics approval from: MetroHealth System Institutional Review Board (IRB18-0751); University Health Network Research Ethics Board (REB17-6029); University of Texas Health Science Center IRB (HSC-MS-18-0862); Advarra IRB for HealthTech Connex Centre for Neurology Studies (Pro00030094); as well as approval from the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office

20

(HRPO). Any changes to the protocol will not be implemented until ethics approvals have been obtained. Amendments will be numbered in a sequential manner and assigned an amendment date and version.

Data collected as a part of the study will be maintained at Biostatistics Unit on behalf of the investigators. The initial evaluation of the clinical study results will be provided to the investigators and to MyndTec Inc. MyndTec Inc. will not prevent publication of the results regardless of the outcome of the study. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals. Participant confidentiality will be maintained in all analyses and presentations.

Author contributions

All of the authors made substantial contributions to study design; KDA, JRW, RK, JP, LT, and KM are involved in conduct; all authors were involved in drafting or revising this protocol manuscript for important intellectual content and gave final approval of the version to be published; KDA, JRW, RK, JP, MRP, LT, and KM will be involved in the analyses and reporting of results.

Funding

This trial is funded in part under the USAMRMC, award number W81XWH-16-1-0790, SC150251. MyndTec Inc. is responsible for training and distribution related to the MyndMove device and resolution of clinical and technical device-related issues throughout the study. MyndTec Inc provided additional funding for costs which were not covered by funding. In

21

addition, funding provided through the grant will be administered to the participating sites through

MyndTec Inc.

Competing interests

MyndTec Inc. is the Contracting Organization of this study and through funding provided by

USAMRMC, researchers are reimbursed for doing this study. All Investigators have an interest in

completing the study.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

All data from this work will be maintained at the Biostatistics Unit at St. Joseph's Healthcare

Hamilton. Data sharing and access to the trial dataset is incorporated into the Clinical Trial

Agreements between the MyndTec Inc. and each of the Principal Investigators and Sites according

to institutional requirements. Access to the trial dataset by individuals outside the study will be

reviewed on a case-by-case basis.

REFERENCES

1. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21:1371-83.

2. Noonan VK, Fingas M, Farry A, et al. Incidence and prevalence of spinal cord injury in Canada: a national perspective. *Neuroepidemiology* 2012;38:219-26.

3. Hoshimiya N, Handa Y. A master-slave type multi-channel functional electrical stimulation (FES) system for the control of the paralyzed upper extremities. *Automedica* 1989;11:209-20.

4. Handa Y, Handa T, Ichie M, et al. Functional electrical stimulation (FES) systems for restoration of motor function of paralyzed muscles--versatile systems and a portable system. *Front Med Biol Eng* 1992;4:241-55.

5. Nathan RH, Ohry A. Upper limb functions regained in quadriplegia: a hybrid computerized neuromuscular stimulation system. *Arch Phys Med Rehabil* 1990;71:415-21.

6. IJzerman MJS, Stoffers TS, in 't Groen FACG, et al. The NESS Handmaster orthosis: restoration of hand function in C5 and stroke patients by means of electrical stimulation. *J Rehabil Sci* 1996;9:86-9.

23

7. Snoek GJ, IJzerman MJ, in 't Groen FA, et al. Use of the NESS handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients. *Spinal Cord* 2000;38:244-49.

8. Prochazka A, Gauthier M, Wieler M, et al. The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch Phys Med Rehabil* 1997;78:608-14.

9. Popovic DS A, Pjanovic A, Radosavljevic S, et al. Clinical evaluation of the Bionic Glove. *Arch Phys Med Rehabil* 1999;80:299-304.

10. Popovic MR, Popovic DB, Keller T. Neuroprostheses for grasping. *Neurol Res* 2002;24:443-52.

11. Popovic MR, Thrasher TA, Zivanovic V, et al. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. *Neuromodulation* 2005;8:58-72.

12. Popovic MR, Thrasher TA, Adams ME, et al. Functional electrical therapy: retraining grasping in spinal cord injury. *Spinal Cord* 2006;44:143-51.

13. Rebersek S, Vodovnik L. Proportionally controlled functional electrical stimulation of hand. *Arch Phys Med Rehabil* 1973;54:378-82.

24

14. Peckham PH, Marsolais EB, Mortimer JT. Restoration of key grip and release in the C6 tetraplegic patient through functional electrical stimulation. *J Hand Surg Am* 1980;5:462-69.

15. Peckham PH, Mortimer JT, Marsolais EB. Controlled prehension and release in the C5 quadriplegic elicited by functional electrical stimulation of the paralyzed forearm musculature. *Ann Biomed Eng* 1980;8:369-88.

16. Kilgore KL, Peckham PH, Thrope GB, et al. Synthesis of hand grasp using functional neuromuscular stimulation. *IEEE Trans Biomed Eng* 1989;36:761-70.

17. Wuolle KS, Van Doren CL, Thrope GB, et al. Development of a quantitative hand grasp and release test for patients with tetraplegia using a hand neuroprosthesis. *J Hand Surg Am* 1994;19:209-18.

18. Mangold S, Keller T, Curt A, et al. Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. *Spinal Cord* 2005;43:1-13.

19. Beekhuizen KS, Field-Fote EC. Sensory stimulation augments the effects of massed practice training in persons with tetraplegia. *Arch Phys Med Rehabil* 2008;89:602-608.

20. Kowalczewski J, Chong SL, Galea M, et al. In-home tele-rehabilitation improves tetraplegic hand function. *Neurorehabil Neural Repair* 2011;25:412-422.

21. Teferra M. Functional electrical stimulation (FES): review. *IJLRET* 2017;3:95-101.

25

22. Popovic MR, Kapadia N, Zivanovic V, et al. Functional electrical stimulation therapy of voluntary grasping versus only conventional rehabilitation for patients with subacute incomplete tetraplegia: a randomized clinical trial. *Neurorehabil Neural Repair* 2011;25:433-42.

23. Nagai MK, Marquez-Chin C, Popovic MR. Why is functional electrical stimulation therapy capable of restoring motor function following severe injury to the central nervous system? In: Tuszynski MH, ed. Translational Neuroscience. New York, NY: Springer Science and Business Media 2016:479-98.

24. Kapadia N, Zivanovic V, Popovic MR. Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: pilot study. *Top Spinal Cord Inj Rehabil* 2013;19:279-87.

25. Scivoletto G, Tamburella F, Laurenza L, et al. The Spinal Cord Independence Measure: how much change is clinically significant for spinal cord injury subjects. *Disabil Rehabil* 2013;35:1808-13.

26. Scivoletto G, Tamburella F, Laurenza L, et al. Distribution-based estimates of clinically significant changes in the International Standards for Neurological Classification of Spinal Cord Injury motor and sensory scores. *Eur J Phys Rehabil Med* 2013;49:373-84.

26

27. Hebert DA, Bowens JM, Ho C, et al. Examining a new functional electrical stimulation therapy with people with severe upper extremity hemiparesis and chronic stroke: a feasibility study. *Br J Occup Ther* 2017;80:651-59.

28. Kapadia N, Moineau B, Popovic MR. Functional electrical stimulation therapy for retraining reaching and grasping after spinal cord injury and stroke. Front Neurosci Published online first: June 2020. doi:10.3389/fnins.2020.00718

29. Catz A, Itzkovich M, Agranov E, et al. SCIM--spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord* 1997;35:850-56.

30. Kalsi-Ryan S, Beaton D, McIlroy W, et al. Quantification of multi-modality sensation of the hand in cervical spinal cord injury. *J Spinal Cord Med*. 2006;29:311.

31. Kalsi-Ryan S, Beaton D, Curt A, et al. The Graded Redefined Assessment of Sensibility Strength and Prehension: reliability and validity. *J Neurotrauma* 2012;29:905-14.

32. Kalsi-Ryan S, Curt A, Verrier M, et al. Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia. *J Neurosurg Spine* 2012;17:65-76.

33. Kapadia N, Zivanovic V, Verrier M, et al. Toronto Rehabilitation Institute-Hand Function Test: assessment of gross motor function in individuals with spinal cord injury. *Top Spinal Cord Inj Rehabil* 2012;18:167-86.

27

34. Tulsky DS, Kisala PA, Victorson D, et al. Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system. *J Spinal Cord Med* 2015;38:257-69.

35. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons. 1987.

36. Zhang Y, Alyass A, Vanniyasingam T, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials. *J Clin Epid* 2017;88:67-80.

37. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol* 2013;13:92.

38. De Souza RJ, Eisen R, Perera S, et al. Best (but oft-forgotten) practices: sensitivity analyses in randomized controlled trials. *Am J Clin Nutr* 2016;103: 5-17.

39. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-07.

FIGURE LEGENDS

Figure 1. CONSORT diagram of study flow chart.

29

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1. Study Flow Chart

CONSORT diagram of study flow chart

215x279mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	21-22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21-22
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21-22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13,21

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6

Methods: Participants, interventions, and outcomes

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11-13

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7

Methods: Assignment of interventions (for controlled trials)

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9,10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9,10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9,10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14, 21

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol		18-20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		18-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)		18-19
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct		15-16
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		14
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval		20

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21-22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	16
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22

Appendices

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Protocol for a multi-center, single-blind randomized controlled trial comparing MyndMove neuromodulation therapy to conventional therapy in traumatic spinal cord injury

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039650.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Aug-2020
Complete List of Authors:	Anderson, Kim; MetroHealth System, Physical Medicine and Rehabilitation; Case Western Reserve University, Physical Medicine and Rehabilitation Wilson, James; MetroHealth System, Physical Medicine and Rehabilitation; Case Western Reserve University, Physical Medicine and Rehabilitation Korupolu, Radha; University of Texas Health Science Center at Houston, Physical Medicine and Rehabilitation; Institute for Rehabilitation and Research Pierce, Jacqueline; Health Tech Connex, Centre for Neurology Studies Bowen, James; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; University of Toronto, Toronto Health Economics and Technology Assessment (THETA) Collaborative O'Reilly, Daria; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; TELUS Health Kapadia, Naaz; University Health Network, Toronto Rehabilitation Institute; University of Toronto, Department of Physical Therapy Popovic, Milos; University Health Network, The KITE Research Institute; University of Toronto, Institute of Biomaterials and Biomedical Engineering Thabane, Lehana ; McMaster University Faculty of Health Sciences, Department of Health Research Methods, Evidence, and Impact; St. Joseph's Healthcare, Biostatistics Unit Musselman, Kristin; University Health Network, Toronto Rehabilitation Institute; University of Toronto, Physical Therapy
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	Neuromuscular disease < NEUROLOGY, REHABILITATION MEDICINE, Spine < ORTHOPAEDIC & TRAUMA SURGERY

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

BMJ

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protocol for a multi-center, single-blind randomized controlled trial comparing MyndMove neuromodulation therapy to conventional therapy in traumatic spinal cord injury

Authors:
Kim D. Anderson[1,2]; James R. Wilson[1,2]; Radha Korupolu[3]; Jacqueline Pierce[4]; James M. Bowen[5,8]; Daria O'Reilly[8,9]; Naaz Kapadia[6,10]; Milos R. Popovic[7,11]; Lehana Thabane[8,12]; Kristin Musselman[6,10]*

Affiliations:
[1]MetroHealth Rehabilitation Institute, MetroHealth System, Cleveland, OH, USA
[2]Department of Physical Medicine and Rehabilitation, Case Western Reserve University, Cleveland, OH, USA
[3]Department of Physical Medicine and Rehabilitation, McGovern Medical School, The University of Texas Health Science Center at Houston, TX, USA / The Institute of Rehabilitation & Research (TIRR) Memorial Hermann, Houston, TX, USA
[4]HealthTech Connex Centre for Neurology Studies/ Neuromotion Physiotherapy, Vancouver, BC, Canada
[5]Toronto Health Economics and Technology Assessment (THETA) Collaborative, [6]Toronto Rehabilitation Institute; [7]The KITE Research Institute, University Health Network, Toronto, ON, Canada
[8]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton ON, Canada
[9]Pharmacy Consulting TELUS Health, Toronto, ON, Canada
[10]Department of Physical Therapy, [11]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada
[12]Biostatistics Unit at St. Joseph's Healthcare, Hamilton, Hamilton ON, Canada

*corresponding author: Kristin Musselman, PT, PhD; 520 Sutherland Dr., Room 206-K, Toronto, ON, M4G 3V9, Canada; Kristin.Musselman@uhn.ca ; (416) 597-3422 x6190

Word count: 4000

1

Abstract

Introduction: This protocol is describing a multi-center, single-blind randomized controlled trial. The objective is to compare the efficacy of MyndMove therapy vs conventional therapy (CT) in improving upper extremity function in individuals with C4-C7 traumatic, incomplete spinal cord injury (SCI). It is being conducted in two US and two Canadian SCI rehabilitation centers.

Methods and analysis: Sixty people aged 18 or older with a C4-C7 incomplete (AIS B-D) SCI between 4 months to 8 years' post-injury are randomized to receive 40 sessions of MyndMove neuromodulation therapy or CT within a 14-week period of time. Therapy sessions are 1 hour in duration with a dose of 3-5 sessions per week. Assessments occur prior to randomization, after 20 sessions, after 40 sessions, and 10 weeks after the last session. The primary outcome measure is the efficacy of MyndMove therapy vs CT in improving upper extremity function as measured by Spinal Cord Independence Measure III: Self-Care sub score (SCIM-SC) after 40 sessions. Secondary outcomes include: 1) Improvements in the SCIM mobility sub score; 2) Upper limb functions measured by Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) and 3) Toronto Rehab Institute Hand Function Test (TRI-HFT); 4) To assess safety as measured by serious and non-serious adverse events recorded for participants in both groups of the study population over the duration of the study; 5) To compare the change in quality of life as measured by the Spinal Cord Injury-Quality of Life (SCI-QOL); and 6) To evaluate the impact on healthcare resource utilization.

Ethics and dissemination: All ethical approvals were obtained prior to enrolling any participants. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals

Registration: This trial is registered on www.ClinicalTrials.gov, study number NCT03439319.

2

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords: neuromodulation; upper extremity; spinal cord injury; conventional therapy

Article summary

Strengths and limitations of this study

- A strength of this study is that it is a properly powered randomized controlled trial designed to detect functionally meaningful change in participants with tetraplegia.

- This therapy requires the use of a device that is not currently part of standard rehabilitation for spinal cord injury and, as a result, the participant and treating therapist are not blinded.

- The assessing therapist is blinded to reduce the risk of bias.

- The statistical analysis team is blinded to the study group.

3

INTRODUCTION

Spinal cord injury (SCI) is a devastating, life altering event that can lead to significant disability, in addition to socioeconomic challenges for the individual, family, and community at large. A survey of people with SCI revealed that the majority of people with tetraplegia (which constitutes more than 50% of individuals with SCI) rated recovery of hand function as their highest priority.[1, 2] Currently, various approaches to improve hand function after SCI are used, for example: exercises, biofeedback, robotic therapy, task specific movement therapy, reconstructive surgeries, and functional electrical stimulation (FES) therapy. To date, FES therapy has been found to be one of the most promising approaches in improving voluntary hand function.[3-18] One school of thought proposes that FES can be used as a short-term therapeutic intervention to help improve voluntary grasping function. A number of FES systems have been used for this application, for example: NESS H200;[4-6] the Bionic Glove and its newer version HandEstim Wireless Hand Stimulator (HEWHS);[8-9] and the Complex Motion system .[12, 18] Emerging evidence in tetraplegia suggests that electrical stimulation and FES therapy improve arm and hand function more than conventional therapy, particularly when provided in combination with various types of conventional therapy. Recently a study demonstrated that the functional benefits of massed practice of conventional therapy were greater when augmented by sensory stimulation.[19] Another study demonstrated that exercise therapy combined with FES produced greater functional improvements compared to exercise therapy combined with traditional electrical stimulation.[20]

MyndMove therapy is a non-invasive FES neuromodulation therapy designed to restore voluntary reaching and grasping movements in individuals paralyzed by SCI or stroke. It is based on FES principles and therapeutic interventions[21] to provide clinically meaningful gains in both upper

4

extremity function and self-care functional independence.[22] The MyndMove system promotes development and reestablishment of neural pathways within the central nervous system (CNS) and between CNS and the upper extremities by engaging neuroplasticity following neurological injury.[23] Therapists use the device with surface electrodes to deliver proprietary electrical stimulation sequences to induce targeted muscle contractions leading to functional movements. Over multiple sessions, the treatments are thought to reconnect the signal from the brain to the muscles, restoring voluntary use of their arms and hands. MyndMove therapy is approved for sale by Health Canada (License Number 93158) and has been confirmed by the FDA (510(k) Number K170564). MyndMove therapy has also been confirmed by FDA to be a non-significant risk device and exempt from an IDE [reference file Q131135].

A pilot study comparing the effectiveness of FES neuromodulation therapy to conventional therapy (CT) has been conducted in individuals with cervical, incomplete SCI.[24] In that study, a small number of participants with chronic C4-C7 American Spinal Injury Association Impairment Scale (AIS) B-D SCI were randomized to FES neuromodulation therapy or CT and received 39 hours of therapy over 13-16 weeks. The FES neuromodulation therapy group improved 5-fold on the primary outcome measure (Toronto Rehabilitation Institute-Hand Function Test) compared to the CT group. However, because there were only 8 people enrolled and the study was open label, a larger randomized controlled trial (RCT) with blinded assessments was needed to definitively compare the effectiveness of the two interventions.

The protocol for this multi-center RCT in people with tetraplegia following traumatic SCI aims to (i) confirm the FES neuromodulation treatment effect as delivered by the MyndMove device across

5

multiple investigational sites, (ii) characterize the long term benefits and retention of function by including long-term follow up assessments, and (iii) compare the efficacy of MyndMove therapy to an equivalent number of hours of CT. The study will also evaluate the impact of MyndMove therapy on the quality of life for people with traumatic SCI (C4-C7) over the course of 24 weeks. Ultimately the data from these studies will assist in redefining clinical best practices in SCI rehabilitation.

METHODS AND ANALYSIS

Trial design and setting

This study is designed as a multicenter, parallel group, two arm, single-blind, randomized controlled trial to compare the clinical outcomes of MyndMove therapy to CT for individuals with C4-C7 traumatic incomplete SCI with upper extremity paresis. See Figure 1 for the study flow chart. The study is being conducted at four regional rehabilitation medical centers, in Canada and the United States, that specialize in providing neurorehabilitation to people with SCI. The first participant was enrolled in June 2019. It is estimated that the final participant will be enrolled by December 2020, but this may be negatively impacted by COVID-19.

Recruitment and retention

Each of the investigational sites has experience in recruiting individuals with SCI for clinical studies and each investigational site has a study coordinator assigned to the study who routinely reviews charts to identify potential study participants and to increase awareness of the planned clinical study within their community. Recruitment strategies include outreach to advocacy and support groups for individuals with SCI. Study coordinators will enhance retention of participants

6

by developing rapport with them during the active portion of the trial, then periodically communicating with participants during the follow-up portion of the trial.

Eligibility criteria

Inclusion criteria:

1. Traumatic incomplete (AIS B-D) C4-C7 SCI

2. Paralysis or paresis in both upper extremities

3. At least 4 months (120 days) and less than 96 months (2,920 days) post-traumatic SCI

4. Baseline SCIM-SC ≤ 10

5. From an inpatient (such as skilled nursing facility) or outpatient care setting

6. Able to understand and follow instructions

7. Able to tolerate being in a seated position for a least one hour required to deliver upper limb therapy

8. Willing to attend treatment sessions and all assessment sessions

9. Able to understand and provide informed consent

10. Male and female participants ≥ 18 years of age at the time of enrollment

Exclusion criteria:

1. Previous history of any other neuromuscular disorder or conditions that may affect motor response

2. Upper extremity injury or condition prior to SCI that limits the function of the hand or arm

3. Malignant skin lesion on the affected upper extremity

4. Rash or open wound at any potential electrode site

7

5. History of seizure disorder not effectively managed by seizure medications

6. An implanted metallic part (e.g. plates, screws or joint replacement) or electrical device (e.g. Implantable Cardiac Defibrillator, Pacemaker, Spinal Stimulation). (Note: If the participant has passive metallic implants, the therapy can be delivered if the implants are located in an area other than where the electrical stimulant is to be delivered.)

7. Complete denervation of muscles that are targeted by MyndMove such that MyndMove is unable to elicit tetanic muscle contraction when upper limits of stimulation intensity (of the device) for the targeted muscle are applied

8. Poorly controlled autonomic dysreflexia (as determined by the local site physician)

9. History of psychiatric illness requiring hospitalization within past 24 months

10. Active drug treatment for dementia

11. Life expectancy of less than 12 months due to other illness

12. In the judgment of the medical provider, participant has medical complications that may interfere with the execution of the study

13. Currently enrolled in another upper limb intervention study and/ or has received MyndMove therapy within the past 3 months

14. Enrolled, in the past six months, in a clinical study involving drugs or biologics

15. Currently dependent on a ventilator

16. Botulinum toxin injection into affected upper extremity and the muscle targeted by MyndMove therapy within 6 months prior to the study start. No botulinum toxin injections in the upper extremity during the study treatment and follow up period

17. Females who are pregnant or planning to become pregnant in the duration of the trial

8

18. Regional disorder of the upper extremities such as fracture, dislocation, or joint contractures to less than 50% of expected range of motion

Sample size

The sample size calculation is based on the test of the research hypothesis that the mean difference in SCIM -SC in the MyndMove intervention group is better than CT control group. The primary measure of effect is the difference in function measured using SCIM-SC at 14 weeks. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which implies that a mean difference in either direction will be interpreted. The sample was calculated using the *power procedure* in SAS 9.2 (Cary, NC). With the proposed sample size of 30 in each of the two groups (i.e. assuming a 1:1 allocation ratio) (i.e. total sample size of 60), the study will have power of at least 80% to yield a statistically significant result using T-test (assuming an intention-to-treat principle for the analysis) of the difference between mean SCIM-SC scores at 14 weeks adjusting for baseline SCIM-SC scores at alpha = 0.05. It is important to note that using the assumption of a T-test is more conservative in that an analysis of variance (ANCOVA) will lead to better power. This computation assumes that SCIM-SC scores are normally distributed, the mean difference is 3 points and the common within-group standard deviation is 4.05. These estimates are modified estimates from the pilot study[24] which account for the type of intervention planned for in this study. The assumed Minimal Clinically Important Difference is considered to correspond to a substantially meaningful improvement on the SCIM-SC, approximately 3 points,[25-26] and also represents a moderate effect of the intervention.

Allocation and blinding

9

Study participants will be stratified by rehabilitation site and will be allocated in a 1:1 ratio to the following two treatment arms:

1. MyndMove therapy: Participants will receive a minimum-maximum of 36-40 one-hour sessions per day of MyndMove therapy within a 14-week period of time.

2. CT: Participants will receive upper-limb conventional therapy of equivalent frequency, intensity, and duration to MyndMove therapy (i.e. a minimum-maximum of 36-40 one-hour sessions per day of CT within a 14-week period of time)

The randomization schedule will be generated and maintained by a statistician at the Biostatistics Unit. A 1:1 allocation occur as per a computerized randomization schedule stratified by site (to account for variation in rehabilitation programs between Canada and the US) using permutated blocks of random sizes and to ensure equal assignment of the MyndMove and the CT at each site. The block sizes will not be disclosed, to ensure concealment. Sufficient randomization sequence allocation, prior to study activation, will be generated to permit the enrollment and drop-out of at least 40% of the total sample size.

Participants who provide signed informed consent, meet all inclusion/exclusion criteria for the study, and complete the baseline visit will be randomly assigned to one of the two treatment arms requested directly from REDCap system. Through REDCap, the randomization allocation will be provided to the study coordinator. The study coordinator will then provide the information about treatment allocation to the participant and treating therapist. The therapist who is the outcome assessor will be blinded to the treatment allocation. All therapists (whether treating or assessing) will be licensed in physical or occupational therapy.

10

Intervention

Participants randomized to the MyndMove therapy group will receive FES therapy bilaterally at the therapist discretion based on clinical presentation/dominance and participant's goals. Treatment will be provided in one-hour sessions per day for a minimum-maximum of 36-40 sessions delivered no less than 3 times per week and up to 5 times per week within a 14-week period of time. Over the course of the sessions, the participants will progress through various movement sequences aimed at regaining natural, unassisted voluntary movements in the affected limb(s). The proposed volume of therapy is guided by discussions with clinicians experienced with delivery of MyndMove therapy along with previous clinical research studies.[27]

The type and frequency of protocols used will follow a standardized regimen in order to minimize co-intervention variation across sites.[27] Training for MyndMove will be provided prior to the initiation of the study. Guidance regarding protocol selection, sequence, and frequency of repetition will be provided as a part of the training by MyndTec. The selection of protocols used during each treatment session will be captured. During each treatment session, therapists will select from a menu of pre-programmed stimulation protocols to facilitate various task-specific movements (Table 1). Movement practice may be massed or distributed, depending on the tolerance of the participant (i.e. muscle fatigue).

Movement Practiced*	Muscles Stimulated with MyndMove®**
Palmar grasp^	- Flexor digitorum superficialis and profundus - Thenar muscles - Extensor digitorum
Lateral pinch grasp^	- Flexor digitorum superficialis and profundus - Thenar muscles - Extensor digitorum
Pinch grasp^	- Thenar muscles - Extensor digitorum

11

	- First lumbrical
Lumbrical grasp	- Thenar muscles - Extensor digitorum - First, second and third lumbricals
Tripod grasp	- Flexor digitorum superficialis - Thenar muscles - Extensor digitorum - Second dorsal interosseous
Side reach with finger extension	- Biceps - Triceps - Middle deltoid - Extensor digitorum - Extensor carpi radialis longus - Extensor carpi ulnaris
Forward reach and grasp	- Biceps - Triceps - Posterior deltoid - Anterior deltoid - Extensor digitorum - Extensor carpi radialis longus - Extensor carpi ulnaris - Flexor digitorum superficialis and profundus - Thenar muscles
Hand to mouth	- Biceps - Triceps - Anterior deltoid

*The movement is demonstrated for the participant by the therapist. The therapist then instructs the participant to voluntarily attempt the movement for about 10 seconds, after which electrical stimulation is provided with the appropriate MyndMove® protocol.[28] **muscles not listed in order of stimulation. ^Unilateral or bilateral stimulation may be used.

Table 1: Example MyndMove® Protocols

The CT intervention serves as an active control group and will use conventional rehabilitative therapy with control for the schedule, form, and intensity of participant-therapist interactions and therapeutic activities in the MyndMove therapy group. During each treatment session, participants will receive conventional therapy of equivalent duration to the one-hour sessions per day of MyndMove therapy. The type and frequency of interventions used will follow a standardized regimen developed by consensus across the centers for the CT in order to minimize intervention variation across sites. Conventional upper limb rehabilitation therapy, at the local institution, may include any or all of the following: a) facilitation of reaching or prehension movements; b) bilateral task-specific movement practice (distributed or massed, dependent on participant tolerance); c) range of motion and mobilization of joints; d) splinting; e) sensorimotor stimulation (ex. TENS,

12

acupuncture, muscle stimulation, biofeedback); f) electrical stimulation (for strength, not function); and g) reduction of edema, if needed. The use of other FES devices during the course of the study will not be permitted. The TiDieR checklist will be used to report results.

All other rehabilitation services will be provided throughout the intervention and follow-up period. This concomitant care, which may influence outcomes, will be captured throughout the study by self-report through the use of a healthcare resource utilization questionnaire, provided to the participant and confirmed by the study staff. During the intervention period, the questionnaire will be completed by the participant to record any rehabilitation services and provide a categorical description of the treatment provided and duration of treatment sessions. This information will be reviewed by study staff and verified with the participant.

For all treatment arms, adherence to therapy will be captured to document any missed research therapy visits. This will allow for the assessment of the effectiveness of the treatment and the practicality of daily administration of the treatment. A per-protocol analysis will be completed using only data from those participants completing at least 30 treatments, which corresponds to 75% of allocated treatments.

Data collection and management

The Biostatistics Unit will provide data management and analysis for the study. All data will be deidentified to maintain confidentiality and captured on paper case report forms. Key data will be entered at each site directly into the electronic database created in REDCap.

13

An independent Research Monitor will be appointed, with expertise consonant with the nature of risk(s) identified within the research protocol. The duties, authorities, and responsibilities of the independent Research Monitor will include: observation of recruitment and enrollment procedures and the consent process for individuals, overseeing study interventions and interactions, reviewing monitoring plans, and Unanticipated Problems Involving Risk to Subjects or Others reports; and overseeing data matching, data collection, and analysis. Monitoring activities will be performed both on- and off-site according to GCP guidelines. A MyndTec Study Monitor will conduct the site initiation visit, periodic site visits (with the independent Research Monitor), and a close-out visit for each site.

Schedule of data collection

A schedule of assessments and data collection is provided in Table 2.

Events	Screening Visit	Baseline Visit	Randomization	Treatment Period		Early Termination Assessment
				Interim Assessment (After 20th treatment session)	End of Treatment Assessment (After 40th treatment session / 14 weeks Post First Treatment Visit)	End of Study Follow-up Assessment (24 weeks Post First Treatment Visit)
Consent						
Informed Consent Form	X					
Eligibility						
Inclusion/Exclusion Criteria	X					
Enrollment			X			
Interventions						
MyndMove® Therapy						
Intensive Conventional Therapy						
Assessments						
Demographics and Social Status		X				
General Health History		X				

14

History of Injury Event		X				
Neurologic	X	X				
Blood Pressure	X	X*		X*	X*	X*
Functional Assessments						
SCIM	X	X		X	X	X
GRASSP		X		X	X	X
TRI-HFT		X			X	X
Participation and Quality of Life						
AE/SAE				X	X	X
SCI-QOL		X			X	X
Healthcare Resource Utilization Questionnaire		X		X	X	X
End of Therapy Questionnaire					X	

X* = Blood pressure is only required if the measurement is deemed abnormal or up to investigator's discretion. SCIM - Spinal Cord Independence Measure III; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; TRI-HFT - Toronto Rehab Institute Hand Function Test; SCI-QOL - Spinal Cord Injury-Quality of Life; AE - Adverse Event; SAE - Serious Adverse Event

Table 2. A summary of assessments and data collection.

Adverse Events and Serious Adverse Events

All adverse events (AE) will be recorded and used to assess participant safety. AE will be recorded on the appropriate case report forms from the time written informed consent is obtained until completion of the study or until resolution of the reportable event. Information to be collected includes the description of the AE, date and time of onset, severity, duration, causality, outcome, and relationship to the study procedure.

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1) leads to death, 2) is life threatening, or places the participant at immediate risk of death, 3) requires or prolongs inpatient hospitalization, 4) results in a significant, persistent, or permanent change, impairment, damage, or disruption in the participant's body function/structure, physical activities, and/or quality of life, 5) results in congenital anomaly/birth defect, or 6) any other serious or important event that may jeopardize the

15

participant and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

All AEs and Serious Adverse Events (SAE) will be followed until: 1) AE is resolved, 2) AE is declared clinically insignificant, 3) AE has stabilized, 4) participant is lost to follow-up or withdraws consent, 5) participant completes study, including required follow-up visits, or 6) study closure.

MyndTec Inc. shall reimburse all reasonable and necessary expenses incurred for medical care received by study participants, including hospitalization, in the treatment of any injury or illness sustained by a clinical trial participant as a result of receiving treatment with MyndMove therapy in the study.

Outcomes

Primary outcome

The primary outcome for the study is the change in SCIM-SC between baseline and end of treatment (14 weeks). This is the basis for the *a priori* sample size and sensitivity estimates. The SCIM is a disability scale that has been specifically developed to evaluate the functional outcomes of people with traumatic and non-traumatic SCI.[29]

Secondary outcomes

Additional secondary analyses of the SCIM self-care and mobility subscales will be performed at the interim, end of treatment, and end of study assessments (see Table 2 schedule of assessments).

16

The GRASSP test[30-32] is a multi-modality test designed to assess the integration of sensorimotor hand and upper limb impairment and function. The baseline scores for each of the GRASSP subscales will be compared to the scores at interim, end of treatment, and end of study assessments. The TRI-HFT[33] was developed to evaluate improvements in the gross motor function of the unilateral grasp due to FES for reaching and grasping treatment. The baseline scores for each of the TRI-HFT subscales will be compared to the scores at the end of treatment and end of study assessments. The SCI-QOL measurement system is a multifaceted system of measuring participants reported outcomes across a wide variety of functioning specifically targeted for individuals with SCI.[34] Participants will complete nine out of twenty-two areas of measure in the SCI-QOL (Table 3). The baseline scores for each of the SCI-QOL subscales will be compared to the scores at the end of treatment and end of study assessments. A healthcare resource utilization questionnaire to capture inpatient, outpatient, and community-based rehabilitation and healthcare services during the follow-up period will also be collected. The total number of minutes utilized from baseline to the end of study assessment will be compared between groups. Participants will be asked to complete an end of therapy questionnaire that consists of 3 open-ended questions to understand their acceptance and impression of the therapy they received in the trial. See Table 3 for the analysis plan for each secondary outcome.

Participant and disease characteristics (demographics, SCI info)

The following participant characteristics will be captured: AIS grade and neurologic level, concomitant medications, biologic sex, age, race, ethnicity, marital status, number of members in household, years of education, primary occupation, family income range, handedness, International SCI Upper Extremity basic data set, general medical history, cause of SCI, current

17

medical complications related to SCI, surgical history, current medical symptoms, smoking status, and alcohol consumption.

Data analysis plan

The analysis and reporting of the results with follow the CONSORT guideline [www.consort-statement.org]. The statistician/data analyst will be blinded to the study group. The process of participant selection and flow throughout the study will be summarized using a flow-diagram. The analysis results of participant demographics and baseline outcome variables (both primary and secondary) will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (interquartile range) for continuous variables and number (percent) for categorical variables. We will adopt an intention-to-treat principle to analyze all outcomes. We will also use multiple-imputation to handle missing outcome data.[35] Research has shown that this is the most optimal strategy for handling missing outcome data in trials under the assumption of missing at random.[36] All statistical tests will be performed using two-sided tests at the 0.05 level of significance. The overall level of significance will not be adjusted for multiple testing for secondary outcomes because these are exploratory. We will use analysis of covariance (ANCOVA) for the analyses of both primary and secondary outcomes, with treatment group as an independent variable and baseline values of each outcome as a covariate. For all models, the results will be expressed as mean difference, corresponding two-sided 95% confidence intervals and associated p-values. P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. We will conduct some sensitivity analyses to assess the robustness of the results: 1) Per-protocol analysis: this analysis will be based only on participants with complete data that completed study procedures as per-protocol; 2) Using last-observation-carried-forward

18

(LOCF) for missing data: this analysis will use the LOCF to impute missing data; 3) Adjusted

analysis: this analysis will adjust for some baseline variables that we think may impact the results

if not balanced. These include age, time post-injury, baseline function, baseline quality of life,

and, potentially, site. To the extent that these sensitivity analyses yield similar results to the main

analysis, inferences about the primary outcome will be strengthened.[37-38] Goodness-of-fit will

be assessed by examining the residuals for model assumptions and chi-squared test of goodness-

of-fit.   Please see Table 3 for a summary of the analysis for each objective, outcome, and

corresponding hypothesis. All analyses will be performed using SAS version 9.2 (Cary, NC).

Variable/Outcome	Hypothesis	Outcome Measure (type of outcome)	Methods of Analysis
1) Primary • Upper extremity function	FES Intervention [I] is better than Conventional Therapy Control [C]	Spinal Cord Independence Measure III self-care subscale score (SCIM-SC)	ANCOVA
2) Secondary • Limb function	I is better than C	SCIM mobility subscale score	ANCOVA
• Upper limb function	I is better than C	Graded Redefined Assessment of Strength, Sensibility and Prehension(GRASSP) sub scales: Strength total score Sensibility total score Qualitative prehension total score Quantitative prehension total score	ANCOVA
• Upper limb function	I is better than C	Toronto Rehab Institute Hand Function Test (TRI-HFT) sub scales: Object manipulation score Wooden block score Cylinder torque Credit card force Wooden bar displacement length	ANCOVA
• Quality of life	I is better than C	Spinal Cord Injury-Quality of Life (SCI-QOL) subscales: Basic mobility score Fine motor score Manual wheelchair score Power wheelchair score Self-care score Independence score Pain behavior score	ANCOVA

19

		Pain interference score Satisfaction with social roles and activities score	
• Safety	I is better than C	Serious and non-serious adverse events, total number of each per group	Descriptive
• Healthcare resource utilization	Reduced healthcare resource utilization with I compared to C	Healthcare Resource Utilization Questionnaire, total number of minutes	ANCOVA
3) <u>Sensitivity Analyses</u>: • Per-protocol • Missing data based imputed based on LOCF • Adjusted analysis with key baseline characteristics: Age, baseline function and QoL	Results of analysis of primary analysis will remain robust	SCIM-SC score	ANCOVA, with multi-variable analysis for adjusted analysis
IMPORTANT REMARKS: • In all analyses results will be expressed as coefficient, standard errors, corresponding 95% and associated p-values. • Goodness-of-fit will be assessed by examining the residuals for model assumptions and chi-squared test of goodness-of-fit			
ANCOVA - Analysis of Covariance; C – Control; FES - Functional Electrical Stimulation; I – Intervention; GRASSP - Graded Redefined Assessment of Strength, Sensibility and Prehension; LOCF - Last Observation Carried Forward; QOL - Quality of Life; SCIM - Spinal Cord Independence Measure III; SCIM-SC - Spinal Cord Independence Measure III self-care sub-scale; SCI-QOL - Spinal Cord Injury-Quality of Life; TRI-HFT - Toronto Rehab Institute Hand Function Test			

Table 3. Summary of the analysis for each objective, outcome, and corresponding hypothesis

Patient and public involvement

Patients were not involved in the design of this protocol. Collaborations will be developed with

SCI community organizations to co-develop lay descriptions of the results of the trial for the

public.

ETHICS AND DISSEMINATION

The study design is described according to the SPIRIT reporting guidelines.[39] This study has

ethics approval from: MetroHealth System Institutional Review Board (IRB18-0751); University

Health Network Research Ethics Board (REB17-6029); University of Texas Health Science Center

IRB (HSC-MS-18-0862); Advarra IRB for HealthTech Connex Centre for Neurology Studies

(Pro00030094); as well as approval from the U.S. Army Medical Research and Materiel Command

(USAMRMC), Office of Research Protections (ORP), Human Research Protection Office

20

(HRPO). Any changes to the protocol will not be implemented until ethics approvals have been obtained. Amendments will be numbered in a sequential manner and assigned an amendment date and version.

Data collected as a part of the study will be maintained at Biostatistics Unit on behalf of the investigators. The initial evaluation of the clinical study results will be provided to the investigators and to MyndTec Inc. MyndTec Inc. will not prevent publication of the results regardless of the outcome of the study. Dissemination of the results of the study will be made at peer reviewed academic meetings and through peer reviewed medical journals. Participant confidentiality will be maintained in all analyses and presentations.

Author contributions

All of the authors made substantial contributions to study design (KDA, JRW, RK, JP, JMB, DO, NK, MRP, LT, KM); KDA, JRW, RK, JP, LT, and KM are involved in conduct; all authors were involved in drafting or revising this protocol manuscript for important intellectual content and gave final approval of the version to be published (KDA, JRW, RK, JP, JMB, DO, NK, MRP, LT, KM); KDA, JRW, RK, JP, MRP, LT, and KM will be involved in the analyses and reporting of results.

Funding

This trial is funded in part under the USAMRMC, award number W81XWH-16-1-0790, SC150251. MyndTec Inc. is responsible for training and distribution related to the MyndMove device and resolution of clinical and technical device-related issues throughout the study. MyndTec Inc provided additional funding for costs which were not covered by funding. In

21

addition, funding provided through the grant will be administered to the participating sites through MyndTec Inc.

Competing interests

MyndTec Inc. is the Contracting Organization of this study and through funding provided by USAMRMC, researchers are reimbursed for doing this study. All Investigators have an interest in completing the study.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data sharing statement

All data from this work will be maintained at the Biostatistics Unit at St. Joseph's Healthcare Hamilton. Data sharing and access to the trial dataset is incorporated into the Clinical Trial Agreements between the MyndTec Inc. and each of the Principal Investigators and Sites according to institutional requirements. Access to the trial dataset by individuals outside the study will be reviewed on a case-by-case basis.

22

REFERENCES

1. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21:1371-83.

2. Noonan VK, Fingas M, Farry A, et al. Incidence and prevalence of spinal cord injury in Canada: a national perspective. *Neuroepidemiology* 2012;38:219-26.

3. Hoshimiya N, Handa Y. A master-slave type multi-channel functional electrical stimulation (FES) system for the control of the paralyzed upper extremities. *Automedica* 1989;11:209-20.

4. Handa Y, Handa T, Ichie M, et al. Functional electrical stimulation (FES) systems for restoration of motor function of paralyzed muscles--versatile systems and a portable system. *Front Med Biol Eng* 1992;4:241-55.

5. Nathan RH, Ohry A. Upper limb functions regained in quadriplegia: a hybrid computerized neuromuscular stimulation system. *Arch Phys Med Rehabil* 1990;71:415-21.

6. IJzerman MJS, Stoffers TS, in 't Groen FACG, et al. The NESS Handmaster orthosis: restoration of hand function in C5 and stroke patients by means of electrical stimulation. *J Rehabil Sci* 1996;9:86-9.

23

7. Snoek GJ, IJzerman MJ, in 't Groen FA, et al. Use of the NESS handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients. *Spinal Cord* 2000;38:244-49.

8. Prochazka A, Gauthier M, Wieler M, et al. The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch Phys Med Rehabil* 1997;78:608-14.

9. Popovic DS A, Pjanovic A, Radosavljevic S, et al. Clinical evaluation of the Bionic Glove. *Arch Phys Med Rehabil* 1999;80:299-304.

10. Popovic MR, Popovic DB, Keller T. Neuroprostheses for grasping. *Neurol Res* 2002;24:443-52.

11. Popovic MR, Thrasher TA, Zivanovic V, et al. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. *Neuromodulation* 2005;8:58-72.

12. Popovic MR, Thrasher TA, Adams ME, et al. Functional electrical therapy: retraining grasping in spinal cord injury. *Spinal Cord* 2006;44:143-51.

13. Rebersek S, Vodovnik L. Proportionally controlled functional electrical stimulation of hand. *Arch Phys Med Rehabil* 1973;54:378-82.

24

14. Peckham PH, Marsolais EB, Mortimer JT. Restoration of key grip and release in the C6 tetraplegic patient through functional electrical stimulation. *J Hand Surg Am* 1980;5:462-69.

15. Peckham PH, Mortimer JT, Marsolais EB. Controlled prehension and release in the C5 quadriplegic elicited by functional electrical stimulation of the paralyzed forearm musculature. *Ann Biomed Eng* 1980;8:369-88.

16. Kilgore KL, Peckham PH, Thrope GB, et al. Synthesis of hand grasp using functional neuromuscular stimulation. *IEEE Trans Biomed Eng* 1989;36:761-70.

17. Wuolle KS, Van Doren CL, Thrope GB, et al. Development of a quantitative hand grasp and release test for patients with tetraplegia using a hand neuroprosthesis. *J Hand Surg Am* 1994;19:209-18.

18. Mangold S, Keller T, Curt A, et al. Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. *Spinal Cord* 2005;43:1-13.

19. Beekhuizen KS, Field-Fote EC. Sensory stimulation augments the effects of massed practice training in persons with tetraplegia. *Arch Phys Med Rehabil* 2008;89:602-608.

20. Kowalczewski J, Chong SL, Galea M, et al. In-home tele-rehabilitation improves tetraplegic hand function. *Neurorehabil Neural Repair* 2011;25:412-422.

21. Teferra M. Functional electrical stimulation (FES): review. *IJLRET* 2017;3:95-101.

25

22. Popovic MR, Kapadia N, Zivanovic V, et al. Functional electrical stimulation therapy of voluntary grasping versus only conventional rehabilitation for patients with subacute incomplete tetraplegia: a randomized clinical trial. *Neurorehabil Neural Repair* 2011;25:433-42.

23. Nagai MK, Marquez-Chin C, Popovic MR. Why is functional electrical stimulation therapy capable of restoring motor function following severe injury to the central nervous system? In: Tuszynski MH, ed. Translational Neuroscience. New York, NY: Springer Science and Business Media 2016:479-98.

24. Kapadia N, Zivanovic V, Popovic MR. Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: pilot study. *Top Spinal Cord Inj Rehabil* 2013;19:279-87.

25. Scivoletto G, Tamburella F, Laurenza L, et al. The Spinal Cord Independence Measure: how much change is clinically significant for spinal cord injury subjects. *Disabil Rehabil* 2013;35:1808-13.

26. Scivoletto G, Tamburella F, Laurenza L, et al. Distribution-based estimates of clinically significant changes in the International Standards for Neurological Classification of Spinal Cord Injury motor and sensory scores. *Eur J Phys Rehabil Med* 2013;49:373-84.

26

27. Hebert DA, Bowens JM, Ho C, et al. Examining a new functional electrical stimulation therapy with people with severe upper extremity hemiparesis and chronic stroke: a feasibility study. *Br J Occup Ther* 2017;80:651-59.

28. Kapadia N, Moineau B, Popovic MR. Functional electrical stimulation therapy for retraining reaching and grasping after spinal cord injury and stroke. Front Neurosci Published online first: June 2020. doi:10.3389/fnins.2020.00718

29. Catz A, Itzkovich M, Agranov E, et al. SCIM--spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord* 1997;35:850-56.

30. Kalsi-Ryan S, Beaton D, McIlroy W, et al. Quantification of multi-modality sensation of the hand in cervical spinal cord injury. *J Spinal Cord Med*. 2006;29:311.

31. Kalsi-Ryan S, Beaton D, Curt A, et al. The Graded Redefined Assessment of Sensibility Strength and Prehension: reliability and validity. *J Neurotrauma* 2012;29:905-14.

32. Kalsi-Ryan S, Curt A, Verrier M, et al. Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): reviewing measurement specific to the upper limb in tetraplegia. *J Neurosurg Spine* 2012;17:65-76.

33. Kapadia N, Zivanovic V, Verrier M, et al. Toronto Rehabilitation Institute-Hand Function Test: assessment of gross motor function in individuals with spinal cord injury. *Top Spinal Cord Inj Rehabil* 2012;18:167-86.

27

34. Tulsky DS, Kisala PA, Victorson D, et al. Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system. *J Spinal Cord Med* 2015;38:257-69.

35. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons. 1987.

36. Zhang Y, Alyass A, Vanniyasingam T, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials. *J Clin Epid* 2017;88:67-80.

37. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol* 2013;13:92.

38. De Souza RJ, Eisen R, Perera S, et al. Best (but oft-forgotten) practices: sensitivity analyses in randomized controlled trials. *Am J Clin Nutr* 2016;103: 5-17.

39. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-07.

28

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

Figure 1. CONSORT diagram of study flow chart.

29

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1. Study Flow Chart

```
┌─────────────────────────────────┐
│          Recruitment            │
│  (rehabilitation, community)    │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│        Informed Consent         │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│         Screening Visit         │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│      Baseline Assessment        │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│      Randomization 1:1 ratio    │
└─────────────────────────────────┘
       │                 │
       ▼                 ▼
┌──────────────┐  ┌──────────────┐
│  MyndMove    │  │  Intensive   │
│  Therapy     │  │ Conventional │
│              │  │  Therapy     │
└──────────────┘  └──────────────┘
         │               │
          └──────┬───────┘
                 ▼
┌─────────────────────────────────┐
│ Interim Assessment (after 20th session) │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│   End of Treatment Assessment   │
│  (after 40th session / 14 weeks)│
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│  End of Study Follow-up Assessment │
│ (24 weeks Post First Treatment Visit) │
└─────────────────────────────────┘
```

CONSORT diagram of study flow chart

215x279mm (600 x 600 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	21-22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21-22
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21-22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	13,21

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5-6

Methods: Participants, interventions, and outcomes

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11-13

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7

Methods: Assignment of interventions (for controlled trials)

| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9,10 |

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9,10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9,10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9,10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14, 21

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-20	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-20	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-19	

Methods: Monitoring

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14	

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20	

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21-22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	16
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22

Appendices

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai