Official Title: Body-Weight Supported Balance-Perturbations for Post-Stroke Gait and Balance Training Rehabilitation: A Multisite Randomized Controlled Trial

Clinical Trial Number: NCT05110300

November 6, 2024

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

1. Methods

1.1. Study design

This will be a multisite randomized active-comparator controlled clinical trial. Due to the nature of the intervention, subjects and investigators will not be able to be masked to the intervention. The assessor will not be able to be masked to group assignments, as the presence or absence of certain variables in the dataset, namely the perturbation level, will immediately reveal group assignment.

Sample Size Estimation and Study Timeline: Using the pilot data, a Cohen's d effect size of 0.39 was calculated and a two-tailed power analysis (α=0.05) was conducted. For the observed effect size, an estimated sample size of 214 participants would achieve 80% power. Using this estimate, and the estimates of the participating sites of the number of potential subjects that could be recruited, enrollment is expected to last 12-18 months (Table 1).

Table 1. General Timeline

Year 1	Month											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Clinical Trial Registration[1]	X											
Purchasing[2]	X											
Staff Training/Check-in	X			X					X			
Steering Committee meeting	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment Target[3]		12	12	12	12	12	12	12	12	12	12	12
Completion Target[3]			12	12	12	12	12	12	12	12	12	12
Interim data analysis (25% and 50% recruitment)							X				X	
Year 2	**Month**											
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Staff Training/Check-in	X											
Steering Committee meeting	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment Target[3]	12	12	12	12	12	12	12					
Completion Target[3]	12	12	12	12	12	12	12	12				
Data analysis									X	X		
Manuscript preparation; Poster abstract submission										X	X	X
Clinical Trial Registration: Data updates[1]											X	X

[1]This study will be registered and maintained at clinicaltrials.gov; Registration will be completed prior to recruiting the first subject.
[2]If grant funding is able to be attained, purchasing outlined in the grant will be completed in month 1 of the award period.
[3]Enrollment and completion targets are estimates based on an 18 month enrollment period. For a 12 month enrollment period, the enrollment and completion targets would be 18 participants per month, with the completion target ending in month 13.

Participants, Settings, and Inclusion/Exclusion Criteria: To participate in this study, participants must be recruited at one of the three participating rehabilitation centers: Gaylord Specialty Healthcare (Wallingford, CT), MedStar National Rehabilitation Hospital (Washington, DC), or Spaulding Rehabilitation Hospital Cape Cod (Sandwich, MA).

To be eligible for study participation, subjects must meet the following *Inclusion Criteria*:

- Admitted to one of the listed study locations for inpatient rehabilitation following either

ischemic or hemorrhagic stroke and medically stable for the therapy program.
- Be 18 years of age or older.
- Discharge date of 10 days or longer at study consent
- Have at least a moderate fall risk or better, shown by an admission BBS score of 21/56 or greater.
    - Patients that score below 21 or are non-ambulatory will not be considered for this study.
    - Patients that are emergently re-admitted to acute care and subsequently re-admitted to the stroke rehabilitation program will be reassessed for appropriateness of continuation in the study on a case by case basis.
    - Patients that progress to a BBS score of 21 or greater during their stay, and have a set discharge date of 10 days or longer, can be approached for study recruitment.
- Appropriate cognition
    - Able to read and understand the consent, in English or a language available by translator services, based on the judgment of the clinical team, either by using outcomes measures, i.e. SLUMS ≥ 20, or through clinical evaluations and team discussion. Eligibility will ultimately be decided by the treating physician and/or in combination with the participant's clinical team.
- Ability to tolerate and actively participate in at least 2 and up to 6 study related BWSS therapy sessions.
    - Study related therapy sessions will last a minimum of 15 minutes, up to 30 minutes in the BWSSs.

Those who present with one or more of the following *Exclusion Criteria* will not be eligible for study participation:
- Cognitive deficits that would disrupt the ability to provide informed consent as described above
- Active enteric infection control precautions
    - Subjects would be eligible once precautions are lifted
- Ongoing orthostasis
- Uncontrolled hyper/hypotension
- Active seizures
- Spinal stabilization with the use of Halos
- Unstable skin structures (i.e. skin grafts)
- Chest tubes
- Unstable rib or lower extremity fractures
- Severe osteoporosis
- Subjects where pressure around the abdomen, thighs, groin, or shoulders is contraindicated
- New limb amputations
- Vestibular disorders that may impact balance
- Premorbid conditions that may impact balance
- Patients requiring more than 50% high flow oxygen as consistent with inpatient therapy guidelines
- Subjects who weigh more than 450 pounds, per the structural limitations of the ZeroG system
- Anyone belonging to a vulnerable population as described below, including subjects under the age of 18 and who are or might be pregnant

Equipment and Instruments: Several pieces of equipment and outcome instruments will be needed for this study. The ceiling-track mounted, FDA listed, ZeroG body weight support system

BWSS (Aretech LLC, Ashburn, VA) and the Training Responses in Postural Rehabilitation (TRiP) balance perturbation module (Aretech LLC, Ashburn, VA) will be the primary pieces of equipment required to complete this study. All study locations already have the ZeroG BWSS and TRiP module installed.

In addition to the equipment, several outcome measurements will be collected throughout the study duration. Balance specific measurements that will be collected include the BBS, an objective balance measure, and the Activities Specific Balance (ABC) scale, a subjective patient reported measure. When appropriate for the patient, an admission BBS is collected within 72 hours of admission at all study locations by the patient's primary therapist. This admission evaluation will be used to initially identify potential subjects with an admitting BBS of 21 or greater; this will be used as the pre-intervention assessment (pre-assessment) during data analysis. When patients are discharged, a follow-up BBS is typically collected at all study locations. However, discharge may not always occur in a timely fashion after the conclusion of the study. To address this, a post-intervention assessment (post-assessment) will be collected within 48 hours of the last study session if not already collected by the participant's primary therapist during that time. The patient reported ABC scale will be collected during the informed consent process and immediately following the last study session.

To evaluate gait, the objective self selected 10 Meter Walk Test (10MWT) assessment will be conducted. If not already conducted during the participant's admission evaluation, a 10MWT pre-assessment will be conducted by site investigators within 48 hours prior to the first study session. A post-assessment 10MWT will be collected within 48 hours of the last study session if not already collected by the participant's primary therapist during that time.

Subject identification, recruitment, and pre-assessments: As described above, qualifying patients will initially be screened/identified through internal reports generated at each study site summarizing admission BBS scores for recently admitted patients. Screening will continue until the target number of participants have completed the study and/or the pre-determined statistical guidelines have been met. After initial screening, the additional inclusion/exclusion criteria will be considered with attending physician approval and the patient approached for consent. After collecting informed consent, participants will be asked to complete an ABC scale pre-assessment. If it was not already conducted by the participant's primary physical therapist at admission, a 10MWT pre-assessment will be conducted within the 48 hours prior to the first treatment session. The admission BBS score will be counted as the participants' BBS pre-assessment. Study procedures and assessments will be conducted according to the general timeline shown in **Table 2**.

Table 2. Schedule of Study Procedures and Assessments

Procedure	Admission	Screening	Pre-Intervention	Treatment Sessions						Post-Intervention
				1	2	3	4	5	6	
BBS	X									X
Report generation	X									
Informed consent		X								
Participant group assignment			X							
Collection of demographic and other secondary information as described below[1]			X							X
Additional stroke information[1]			X							X
ABC scale			X							X
10MWT			X							X
BWSS Control Intervention				X	X	X	X	X	X	
BWSS-P Intervention				X	X	X	X	X	X	
TRiP/Perturbation level recording				X	X	X	X	X	X	
System on-time/off-time recording				X	X	X	X	X	X	
Data transfer										X

[1]The described information can be collected, as available, any time after the subject has consented to the study, but before de-identified data is transferred to the Lead Site.

Subject assignment: Consented subjects will be assigned to either the BWSS Standard Intervention (Control) Group or BWSS with Balance Perturbations (BWSS-P) Intervention Group according to a pre-generated randomized assignment sheet. Each randomized assignment sheet will consist of equal BWSS Control and equal BWSS-P assignments whose order has been randomized using the random list generator at https://www.random.org/lists/. Co-Investigators at each site, who will not be delivering the study interventions directly, will be given a unique list with a number of assignments that is in proportion to the number of subjects expected to be recruited at the site; additional assignment lists will be generated if needed. These co-Investigators will be responsible for communicating group assignments to study therapists delivering the intervention, and for ensuring that randomization and treatment order is maintained. It is expected that if the assignment scheme is not maintained for whatever reason, that they will report the incident to the steering committee, described below, and how it was/or still needs to be rectified. No matter group assignment, all consented subjects will be asked to conduct all pre- and post-assessments.

BWSS Standard Intervention Control Group: The BWSS control group will conduct at least 2 and up to 6 study related therapy sessions. Study related therapy sessions will last a minimum of 15 minutes up to 30 minutes. Study sessions will be completed over a 2 to 3 week period as part of the subject's inpatient therapy program. Each session must have an active time of at least 15 minutes in the system to be included, up to 30 minutes for each session. To be as pragmatic and clinically relevant as possible, treatment sessions will be incorporated directly into the participants' normal care. Furthermore, we are allowing participants to complete 2 to 6 sessions as dictated by short or unexpected changes to the discharge planning timeline. During each session, participants will conduct balance exercises, including: marching, side-stepping, retro-ambulation, step-taps, and step-ups. They will also conduct various standard gait exercises, including: ambulation over the ground, going up and down stairs, and performing sit-to-stand transitions. Each of the 2 to 6 study sessions will be part of the subject's normal course of therapy. As this is an active clinical comparison, clinical parameters and progression, other than those described

above, will be determined by the treating therapist (i.e. percent body weight support and use of assistive devices) to ensure success and appropriate challenge to the subject.

BWSS-P Intervention Group: The BWSS-P intervention group will also conduct 2 to 6 study sessions over a two-week period. Each session must have an active time of at least 15 minutes in the system, up to 30 minutes for each session. Participants in the BWSS-P group will conduct the same balance and gait exercises as the control group, however, these sessions will include eight perturbations, two in each direction (lateral left, lateral right, anterior, and posterior). Perturbations will occur while static/standing (lateral, anterior, posterior) and dynamically while ambulating (anterior, posterior). Each of the 2 to 6 study sessions will be part of the subject's normal course of therapy. As this is an active clinical comparison, clinical parameters and progression, other than those described above, will be determined by the treating therapist (i.e. percent body weight support and use of assistive devices) to ensure success and appropriate challenge to the subject. The TRiP or perturbation level will be progressed to the point of loss of balance, or very near loss, without recovery. The perturbation level should then be then decreased by one level for treatment. All 8 perturbations will occur at this level until it is clinically appropriate to progress again. The intensity of TRiP perturbation ranges from level 1 to 10, minimal to maximum, respectively.

Post-Assessments: After the completion of the subjects' final BWSS session before discharge, investigators will conduct an ABC and 10MWT post-assessment no longer than 48 hours following the final session. Follow-up BBS are often completed prior to discharge as part of patient/participant's standard of care. However, in the case that there is an unexpected delay or there is a significant length of time until the participant's discharge, a post-assessment BBS will be conducted no longer than 48 hours following the last session.

Data Analysis: Data were analyzed using GraphPad Prism (version 10; GraphPad Software, Boston, MA) and RStudio (version 4.2.2, Posit Software, PBC, Boston, MA]) using the *car* package.[1]

Descriptive data is reported as mean (95% confidence interval). If hypothesis testing was done, data were reported with a p-value, and significance was set at α=.05. The primary outcome measures used in our analyses were the BBS, ABC, 10MWT, CMS GG0130 Mobility scores, and CMS GG0170 Self-care scores. Data were determined to be missing completely at random and were dealt with via complete case analysis and mixed-effects analysis as applicable. Data were also assessed for violations in assumptions of their given tests, and were dealt with via non-parametric analysis as necessary.

Categorical data was analyzed using Chi-square testing. Unpaired t-tests or Mann-Whitney U tests were utilized as necessary to evaluate between-group differences in continuous outcome variables.

Analysis of covariance (ANCOVA) was used to account for between group differences while controlling for covariates.[2,3] To evaluate if there were differences between pre- and post-intervention data, a 2-way analysis of variance (ANOVA) was utilized, with mixed-effects analysis being utilized when data was missing. Differences in average improvement by number of sessions completed were evaluated using a 2-way ANOVA. Differences in outcome measure between testing sites were analyzed using one-way ANOVA or Kruskal-Wallis testing. Multiple comparisons were analyzed using, Fisher's, Dunn's, Tukey's multiple comparison tests as appropriate.

References:

1. Fox J, Weisberg S. An R companion to applied regression. Third edition. Los Angeles London New Delhi Singapore Washington, DC Melbourne: SAGE; 2019.

2. Parametric ANCOVA and the Rank Transform ANCOVA When the Data are Conditionally Non-Normal and Heteroscedastic - Stephen F. Olejnik, James Algina, 1984 [Internet]. [cited 2024 Apr 4]. Available from: https://journals.sagepub.com/doi/10.3102/10769986009002129

3. Conover WJ, Iman RL. Analysis of Covariance Using the Rank Transformation. Biometrics [Internet]. [Wiley, International Biometric Society]; 1982 [cited 2024 Apr 4];38(3):715–724. Available from: https://www.jstor.org/stable/2530051