Statistical Analysis Plan

NCT03760016

Moderate-Intensity Exercise Versus High-Intensity Interval Training to Recover Walking Post-Stroke

Finalized on 08-07-2020. Uploaded to ClinicalTrials.gov on 04-13-2021, prior to completion of data collection and prior to any outcome data analysis.

Overall Statistical Methods

SAS will be used for data analysis, and the study statistician will remain blinded to study group. Data related to baseline variables, intervention fidelity and concurrent outside interventions will be compared between groups using t-tests and X^2. If a baseline prognostic factor is found to differ between groups, it will be considered for inclusion as a covariate during hypothesis testing. The primary analysis will follow intent-to-treat methods and any missing data will be handled with the maximum likelihood method, assuming that patterns of missingness do not violate the missing at random assumption.[1] To test robustness of different ways to handle missing data, sensitivity analyses will be used.

Hypothesis Testing

Hypothesis 1: To test our primary hypothesis that, compared with 4 weeks of MAT, 4 weeks of HIT will elicit significantly greater improvement in the 6MWT distance, a general linear model will be used. In this model, we will use fixed effects for group (HIT, MAT), time (PRE, 4-WK, 8-WK, POST), [group x time], site (UC, KUMC, UD), [site x time], baseline speed category (<0.4, ≥0.4 m/s), and [baseline speed category x time] with an unstructured covariance matrix. This hypothesis will be tested by the significance of the [group x time] contrast from the PRE to 4-WK for the 6MWT at $\alpha=0.05$. Secondary outcomes will be tested separately using this same model to identify the most sensitive measures to carry forward into future studies.[2] The Benjamini-Hochberg procedure[3] will be used to control the false discovery rate for the secondary

outcomes, which include: comfortable gait speed, fast gait speed, VO_2 at the ventilatory threshold and the PROMIS-Fatigue Scale total score.

Hypothesis 2: To test the hypothesis that, compared with 4 and 8 weeks of HIT, 12 weeks of HIT will elicit significantly greater improvements in walking capacity and increased benefit over MAT, the same general linear model described above will be used. The hypothesis that 12 weeks of HIT will elicit greater improvements in primary and secondary outcomes compared to 4 and 8 weeks of HIT will be tested by the significance of the respective time contrasts within the HIT group. The hypothesis that HIT will elicit significantly greater improvements in primary and secondary outcomes from PRE to 8-WK and PRE to POST compared to MAT will be tested by the significance of the respective [group x time] contrasts. False discovery rate control will be applied for secondary outcomes.[3]

Prognostic Factor Testing

We will also test for baseline cofactors that may influence a stroke survivor's response to the interventions in this study. To do this, we will utilize a multivariate prognostic model that includes comfortable gait speed, lower extremity Fugl-Meyer motor scores, and scores on the Activities-Specific Balance Confidence Scale. These measures were selected based on previous studies suggesting that comfortable gait speed,[4-9] lower limb Fugl-Meyer motor scores,[9-11] and balance abilities[12] may influence response to gait rehabilitation interventions in individuals with chronic stroke. Other potential cofactors will also be explored to inform future studies.

Safety Data Analysis

We expect a similar rate of non-serious adverse events (AEs) between HIT and MAT (e.g. temporary exercise-related soreness and fatigue), without any study-related serious AEs. In the unexpected event of one or more serious adverse events (SAE), the SAE rate will be compared between groups to confirm that there is no significant difference in major safety risk between HIT and MAT. A logistic regression model will be used for this analysis with SAE (yes/no) as the dependent variable and fixed effects for group, site, and baseline gait speed category. If there are SAE(s) in one group only, a continuity correction (0.5 SAEs added to each group) will still allow the odds ratio to be calculated.[13]

References

1. Fitzmaurice G, Laird N, Ware J. *Applied longitudinal analysis.* 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2011.
2. Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. *Neurorehabil Neural Repair.* 2009;23(3):197-206.
3. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological).* 1995;57(1):289-300.
4. Dean CM, Ada L, Lindley RI. Treadmill training provides greater benefit to the subgroup of community-dwelling people after stroke who walk faster than 0.4m/s: a randomised trial. *J Physiother.* 2014;60(2):97-101.
5. Dean CM, Rissel C, Sherrington C, et al. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomized trial. *Neurorehabil Neural Repair.* 2012;26(9):1046-1057.
6. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. *Stroke.* 2008;39(6):1786-1792.
7. Kim DK, Oh DW. Repeated Use of 6-min Walk Test with Immediate Knowledge of Results for Walking Capacity in Chronic Stroke: Clinical Trial of Fast versus Slow Walkers. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.* 2019;28(11):104337.
8. Salbach NM, Mayo NE, Wood-Dauphinee S, Hanley JA, Richards CL, Côté R. A task-orientated intervention enhances walking distance and speed in the first year post stroke: a randomized controlled trial. *Clin Rehabil.* 2004;18(5):509-519.
9. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. *Archives of physical medicine and rehabilitation.* 2002;83(5):683-691.
10. Bowden MG, Behrman AL, Neptune RR, Gregory CM, Kautz SA. Locomotor rehabilitation of individuals with chronic stroke: difference between responders and nonresponders. *Archives of physical medicine and rehabilitation.* 2013;94(5):856-862.
11. Burke E, Dobkin BH, Noser EA, Enney LA, Cramer SC. Predictors and biomarkers of treatment gains in a clinical stroke trial targeting the lower extremity. *Stroke.* 2014;45(8):2379-2384.
12. Dobkin BH, Nadeau SE, Behrman AL, et al. Prediction of responders for outcome measures of locomotor Experience Applied Post Stroke trial. *J Rehabil Res Dev.* 2014;51(1):39-50.
13. Boyne P, Dunning K, Carl D, et al. High-Intensity Interval Training and Moderate-Intensity Continuous Training in Ambulatory Chronic Stroke: Feasibility Study. *Physical therapy.* 2016;96(10):1533-1544.