**Official Title:** Adaptive Ankle Robot Control System to Reduce Foot-drop in Chronic Stroke

**NCT02483676**

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**Statistical Analysis Plan for the study of**
**Ankle Robot to Reduce Foot Drop in Stroke**

This document lays out the analysis plan we intend to use for the study of whether robot-assisted treadmill training will result in greater improvements in gait and balance among chronic stroke survivors with foot drop impairment.

## 1.0 Brief description of the design of the parent study.

After baseline data collection, eligible patients were randomized to receive either treadmill with anklebot (TMR) or standard treadmill TM alone. Randomization was based on permuted blocks in two strata defined by baseline gait speed. Subjects in each group were be expected to attend 3 sessions per week for six weeks. Follow-up data collection will occur at the end of the training session. Durability of the improvements will be measured by also collecting data 6 weeks and 6 months after the end of the intervention. The primary outcomes will be the outcomes measured immediately after the end of training.

## 2.0 Statistical Test of the Primary Hypotheses.

**2.1 Outcomes.** The main outcomes to be considered will be::

AIM 1

- peak DF swing angle (Var="Pk DF P-ank) (Primary Outcome)
- DF angle at foot strike (Var="AIC") (2nd Primary Outcome)
- Mean Gait Velocity (Var="Prefered Gaid Velocity w/o AD")
- A-P GRF Propulsion (Var="AP impulse")

AIM 2

- Extent of Postural Sway (Var="EO Sway Area" or "EC Sway Area")
- Peak paretic A-P forces during push-off nonparetic gait initiation (Primary Outcome for Aim 2. (Var="Gait Initiation Peak NP A-P force") (Not collected for last 10-15 patients)

All these outcomes will be treated as quantitative random variables.

**2.2 Analysis Sample.** The primary analysis will be based on the principle of intention to treat. That is, in the analysis, patients will be included in the group to which

they were randomized, irrespective of whether they actually received the intervention. This provides anunbiased estimate of the causal impact of assigning a patient to TMR vs. assigning them to TR. The principle of intention-to-treat will be violated to the degree that outcomes for some patients at some timepoints are missing. The implications of missing data and how we will handle that are discussed below. Secondary analyses (described below) will be performed to using different analysis samples to estimate different causal parameters.

**2.3 Statistical Model.** To estimate the impact of TMR vs TR, for each outcome, we will fit the following model:

$$E(\text{Outcome})=\beta_0 + \beta_1 F1 + \beta_2 F2 + \beta_3 F3 + \beta_4 F1(TMR) + \beta_5 F2(TMR) + \beta_6 F3(TMR) + \boldsymbol{\beta}(\text{Covariates})$$

where F1, F2, and F3 are indicators for the three follow-up measures, and TMR is an indicator that the patient was in the TMR group. In this model, $\beta_4$ , $\beta_5$, and $\beta_6$ stand for the difference between TMR and TR at each of the three follow-up time points. The primary analysis will be based on $\beta_4$. This model will be fit using restricted maximum likelihood, allowing for different variancs at each time point, and different covariances between any two time points (this is sometimes refered to as an "unstructured" variance/covariance assumption). We will allow a different variance/covariance structure in each intervention group. However, if the differences in the estimated variance/covariance structures are not statistically significant (based on a likelihood ratio test), we will assume a common variance/covariance structure in the final model.

This model will provide valid inference if the distribution of outcomes does not markedly depart from normality. If an outcome appears to depart from normaility by exhibiting a great deal of positive skewness (e.g., skewness coefficient greater than 3.0), I will fit the above model using a log-tranformed version of the outcome.

**2.4 Covariates**. Covariates will be included in the model if they are statistically significant ($p<0.05$) predictors of the outcome. This will reduce residual variation and increase power. Up to 3 covariates will be included in the model based on the strength of their statistical significance, chosen in a forward stepwise manner. Covariate will be chosen from the following candidate variables.

Time Since Stroke
Age
Sex
Wearing an AFO
Non-AFO AD
SIS mobility
Baseline Gait Velocity (cm/sec)
Baseline Peak Paretic DF Swing Angle (deg)
Baseline Paretic DF Angle at Foot Contact (deg)
Baseline Paretic A-P Propulsion in Late Stance (N-s)
Baseline CoP Sway Area (cm2)
Baseline Standing asymmetry (NP/P vertical forces)
Baseline Peak Paretic A-P force during gait initiation (N)

**2.5 Impact of Missing Outcomes.** The methods described above will result in unbiased estimates of the impact of being assigned toTMR assuming that the data are missing at random, given all observed data. That means, essentially, that conditional on all observed outcomes, the distribution of the missing outcomes is not different than the distribution of the observed outcomes. However, if there are departures from the missing-at-random assumption (e.g., if those with the worst outcomes are the ones who fail to return for follow-up visits), then the estimated rates of improvement may be biased. Note, however, that the estimated treatment effect would only be biased if there were differential degrees of departure from the missing-at-random assumption in the two treatment groups.

The proposed approach is somewhat resistant to biases due to missing data because it is based on maximum likelihood estimation and takes into consideration all the observed data. Thus, for example, if a patient has missing outcomes for the second follow-up visit, but has been observed at other time points, the estimation of the outcomes at the second follow-up will be implicitly imputed based on the observed outcomes and the included covariates.

## 3.0 Secondary Analyses

**3.1 Intention to treat analysis of secondary outcomes.** Similar analyses will be performed to explore the impact of TMR on the following secondary outcomes:

AIM 1

- Single support duration (Var=”P-SS%”)
- Double support duration (Var=”DS%”)
- Timing of peak fexion (Var=”PK DF P-ank %cyc”)
- Pareti foot vertical clearance (Var=”p-foot clearance”)
- Steps/day in two consecutive days (Var=”48 hr Step Count “) (There seems to have been a lot of non-adherence regarding this measure and it may not be usable)
- Stroke Impact Scale (Var=”SIS Mobility”)

AIM 2

- coP trajectories of APAs during gait initiation by leg (Not measured)
- Berg Balance Scale (Var=”Berg Balance”)
- DGI scale (Var=”DGI”)
- ABC Scale (Var=”ABC”)

**3.2 Per Protocol Analysis.** In a secondary set of analyses, we will perform all of the above described analyses after including only those patients who attended at least 15 sessions in their assigned group. This results in an estimate of the causal impact of the TMR (relative to TM) among those willing and able to come to most of the sessions. We would expect to see a somewhat greater effect of TMR in this analysis because it will remove those who did not attend the TM sessions.