Improving Physical Activity and Gait Symmetry After Total Knee Arthroplasty
Statistical Analysis Plan

NCT number NCT04090125
Document Date 10/6/2022

Statistical Design and Power

Overall Strategy, Study Design and Rationale

The Specific Aims of this study involve collection of preliminary data on the efficacy of a new Physical Activity and Symmetry (PAS) intervention, following total knee arthroplasty (TKA), and assessment of the feasibility and acceptability of the PAS intervention. To accomplish these aims, we will propose an exploratory randomized controlled trial with 60 patients equally allocated to the PAS intervention or an attention control group. Patients will be the unit of randomization. We will aim to enroll patients approximately 8 weeks 72from the initiation of outpatient PT, allowing time for randomization and notification of the treating physical therapist before PT is complete. Follow-up assessments will be conducted 8 weeks after randomization (corresponding to the end of the PAS intervention), as well as after 6 months (sustainability end point). (Longer term outcomes will be included in a larger trial.)

This study design will allow us to answer clinical questions regarding the efficacy of the PAS intervention through testing the following hypotheses:

H_1: The PAS group will have greater improvement in objectively assessed physical activity at the 8-week and 6-month assessments, compared to the attention control group. The main co-primary metric of interest is minutes of Moderate to Vigorous Physical Activity (MVPA); other secondary metrics will include step count, minutes of any physical activity, and sedentary minutes.

H_2: The post-TKA exercise group will have greater improvement in peak load symmetry during walking at the 8-week and 6-month assessments, compared to the attention control group. The main co-primary outcome of interest will be the limb symmetry index during level walking; secondary outcomes will be limb symmetry index values during additional physical performance tasks.

Analyses appropriate for randomized clinical trials, described below, will be used to test each of these hypotheses. Regarding feasibility and acceptability of the PAS intervention, simple analyses (also described below) will be used to describe metrics related to recruitment, retention, intervention delivery, and outcome assessment.

Statistical Methods

Sample Size and Power Calculations

MVPA and peak joint loading symmetry during gait will be treated as co-primary outcomes. However, no adjustment for multiplicity is made due to the pilot nature of this study, with an objective of generating estimates suitable for the power analysis for the subsequent large-scale trial. Also owing to the pilot nature of this exploratory trial, we do not necessarily expect to have a highly powered study; rather, the large-scale trial that follows will aim to accomplish this objective. In the Table below we demonstrate a range of effect sizes (in standard deviation units) and the corresponding statistical power that would apply for a comparison of intervention versus control group means at the two-sided 0.05 significance level, for the projected total of n=54 participants (n=27 per group) with complete data. Due to expected attrition of 10%, we will enroll n=60 participants into the trial. This sample size is reasonable to enroll within the time frame of this exploratory trial, and it will allow sufficient experience with intervention delivery to inform the larger trial. Our analytic strategy (described below) will also accommodate dropout, missed visits, and loss-to-follow-up. Information regarding the actual observed extent of dropout, missed visits, and loss-to-follow-up in this study will also be useful for the subsequent large-scale trial.

Statistical power according to effect size, assuming 27 patients per group					
Effect Size (SD units)					
0.5	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
0.44	0.58	0.71	0.82	0.90	0.95

Analytic Techniques and Handling of Missing Data

Preliminary analyses will include generating descriptive statistics for demographic variables, as well as baseline characteristics and follow-up measures. This includes means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Ranges will also be examined for outliers and to ensure data integrity. Demographics and baseline characteristics will also be described separately by randomized group. Statistical tests will be performed to compare each of these by randomized group to determine the extent of random imbalance by t-test of chi-square testing, as appropriate. However, the p-values generated by these tests are considered as descriptive rather than as inferential. We would

expect some imbalance between the groups by random chance, owing to the limited sample size. Variables exhibiting imbalance may be considered as covariates in the statistical models described below.

The co-primary outcome of MVPA will be analyzed across the follow-up time points through a general linear mixed model (GLMM). Specifically, the MVPA values at 8 weeks and at 6 months for a given patient will form their response vector for this model. Fixed effects for the primary model will include an indicator for PAS group, an indicator for the 6-month follow-up time point, their interaction (group by time), and baseline MVPA value; a supporting model will also include any covariates that exhibit random imbalance between groups at baseline. Random effects for patients will account for the within-patient correlation induced by the repeated measures design. Formal statistical testing of the group by time interaction term will provide assessment for whether efficacy varies by follow-up time point. A term representing the interaction of PAS-by-baseline value will be included and tested to explore whether participants' starting point might impact how much they improve; it will be removed if non-significant attention. Statistical contrasts will be constructed in order to estimate the effect of PAS versus attention control, separately at 8 weeks and at 6 months; these estimates will inform the sample size estimation of the subsequent trial. Estimated correlations among follow-up time points will also be useful in this regard.

The approach outlined above will be repeated for the co-primary outcome of peak joint loading symmetry during gait, through fitting a separate GLMM. The main difference will be to include walking speed as an additional covariate, as justified in the research strategy. Secondary outcomes will also be analyzed using the same approach, each with its own GLMM.

An exploratory analysis will include Knee injury and Osteoarthritis Outcome Score (KOOS) pain scores as a (time-dependent) main effect, as well as their interaction with PAS, to evaluate whether this variable has an impact on intervention effects. This exploratory analysis will be repeated, but using participant-specific changes in KOOS pain scores, to examine how our primary outcomes (MVPA and peak load symmetry during walking) are associated with those changes.

If any of the co-primary or secondary outcomes exhibit distributions that deviate markedly from normality, alternatives will be considered. First, transformations, such as the natural logarithm, will be applied in an attempt to normalize the distribution. If this is not successful in remedying the non-normality, alternatives such as categorizing the variable and applying appropriate categorical data analysis, such as logistic mixed models (with a similar specification as described above for the GLMMs) or logistic models utilizing generalized estimating equations methodology can be fitted.

A two-sided 0.05 significance level will be applied to each co-primary outcome, as well as each secondary outcome; no adjustment for multiple comparisons will be applied. This is consistent with the trial's objective as a pilot study to generate estimates useful for the large-scale trial to follow.

An additional advantage to using the GLMM approach is its ability to accommodate missing data (including dropouts, missed visits, and lost-to-follow-up) under a missing at random paradigm. All available follow-up data will be utilized in an intent-to-treat manner. If a participant is missing one of the follow-up time points, that participant is not completely excluded from the analysis. A supportive analysis will be conducted using multiple imputation to produce multiple datasets that have complete data for all n=60 participants, where missing values (due to dropouts, missed visits, and lost-to-follow-up) have been imputed. The statistical models will be fitted to each of the complete datasets; results of each model will be synthesized in a manner that accounts for both between and within imputation variation to produce final estimates to address the research questions.

Feasibility metrics will be computed as proportions, along with 95% confidence intervals to describe the level of uncertainty of the estimates. Lower confidence bounds of these proportions will be useful in considering worst-case scenarios when planning the subsequent large-scale trial. Acceptability data are primarily open-ended questions, and responses will be summarized to inform appropriate modifications to the PAS intervention. For the brief questionnaires on acceptability, appropriateness, and feasibility [1,2], we will calculate mean and median scores and distributions across each domain.

REFERENCES

1. Lewis CC, Weiner BJ, Stanick C, Fischer SM. Advancing implementation science through measure development and evaluation: a study protocol. *Implement Sci.* 2015;10:102.
2. Weiner BJ, Dorsey C, Stanick CF, Halko HM, Powell BJ, Lewis CC. Psychometric assessment of three newly developed implemenation outcome measures. 9th Annual Conferene on the Science of Dissemination and Implementation; 2016; Washington, DC.