A Novel Physical Therapist Administered Physical Activity Intervention after TKR

IRB Protocol Number: 946165-4
National Clinical Trial (NCT) Identified Number: NCT03228719
Principal Investigator (PI): Daniel K. White
Sponsor: University of Delaware
Funded by: National Institutes of Arthritis and Musculoskeletal and Skin Disease
Date of SAP: 3/28/2023

Version	Date	Summary of Revisions
1.1	3/28/23	• Revised Figure: Study flow-chart to fix typo for primary outcome • Clarification in section 7.2.1 that the primary efficacy includes ActiGraph monitors worn for valid times only
1.0	3/16/23	• First full version
Preliminary Version		• Only included statistical plan.

Statistical Analysis Plan

1 SAP Signatures

I give my approval for the attached SAP entitled A Physical Therapist-Administered Physical Activity Intervention after Total Knee Replacement dated 3/15/23

Statistician (Author)
Name: Barry Bodt, PhD

Signature: Barry Bodt

Date: 3/28/2023

Principal Investigator
Name: Daniel White, PT, ScD, MSc

Signature:

Date: 3/28/2023

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3 Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
SAP	Statistical Analysis Plan
PT	Physical Therapy
TKR	Total Knee Replacement
MVPA	Moderate to Vigorous intensity Physical Activity
UDPT	Delaware Physical Therapy Clinic at the University of Delaware

4 Introduction

4.1 Preface

Total Knee Replacement (TKR) is the most successful intervention to address pain from knee osteoarthritis. However, most resume a sedentary lifestyle gain weight and subsequently remain at high risk for poor health outcomes after surgery. There is a critical need for people after TKR to adopt an active lifestyle. Outpatient Physical therapy (PT) is an ideal, low-cost setting for a physical activity intervention for people after TKR given that physical therapists are experts at prescribing and personalizing exercises to meet patients' abilities over multiple outpatient visits. Unfortunately, little study has been devoted to the efficacy of a physical therapist delivered physical activity intervention. The objective of this paper is to evaluate the preliminary efficacy over 12 months of a physical therapist-delivered physical activity intervention. The intervention starts with providing a Fitbit™ monitor at admission to PT. Next, the physical therapist provides face-to-face feedback on current activity levels and recommends step goals personalized to previous activity levels. The intervention is integrated into standardized outpatient PT for TKR.

4.2 Scope of the analyses

These analyses will assess the efficacy of standardized outpatient PT plus a Physical Therapist-administered physical activity intervention versus standardized outpatient PT alone with change in Moderate to Vigorous intensity Physical Activity (MVPA) over 6 months in adults after TKR.

5 Study Objectives and Endpoints

5.1 Study Objectives

The purpose of this study is to conduct a randomized, controlled trial to examine the effectiveness of a Physical Therapist-administered physical activity intervention in adults who received a TKR and sought care in an outpatient physical therapy (PT) clinic compared to outpatient PT alone.

5.2 Endpoints

The primary endpoint of our study is to examine the efficacy of a Physical Therapist-administered physical activity intervention and standardized outpatient PT to increase MVPA

over 6 months after discharge from outpatient PT compared to a control group that received standardized outpatient PT.

The secondary analyses endpoint of our study is to examine the efficacy of a Physical Therapist-administered physical activity intervention and standardized outpatient PT to increase MVPA over 12 months after discharge from outpatient PT compared to a control group that received standardized outpatient PT. We will examine the number of steps/day over 6- and 12- months. Lastly, we will examine as an exploratory analysis to what extent baseline characteristics and treatment condition interact with study outcomes (MVPA and steps/day).

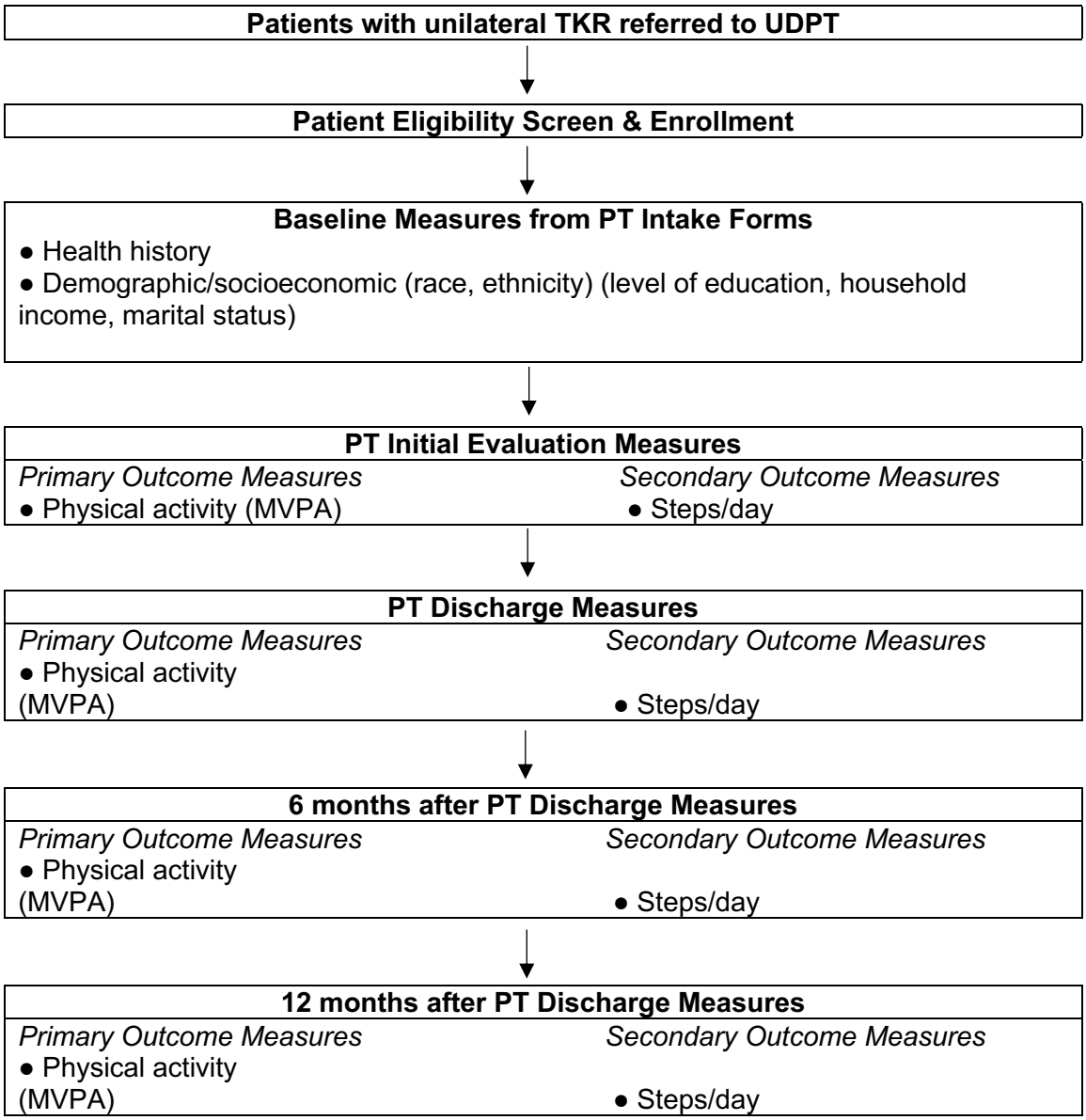
6 Study Methods

6.1 General Study Design and Plan

(ICH E3;9)

We conducted a pragmatic randomized controlled trial with a 2-group, superiority, parallel-design. The intervention group received a Physical Therapist-administered physical activity intervention and standardized outpatient PT while the control group received standardized outpatient PT. The study was assessor-blinded, i.e., all members of the research team who were involved with the assessment of the primary and secondary outcomes were blinded. Study participants and treatment physical therapists were not blinded to group assignment.

Figure: Study flow-chart



6.2 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

We recruited individuals who met the following inclusion criteria: 1) aged 45 years or older, 2) seeking outpatient physical therapist services for a unilateral TKR, and 3) were interested in increasing their PA. We excluded individuals who 1) had any comorbidities that made it unsafe for them to engage in PA, as instructed by a physician; 3) had a lower extremity surgery in the 6 months prior to study enrollment, or were planning a surgery in the 6 months after study enrollment; or 4) previously received a PA intervention at the Delaware Physical Therapy Clinic.

6.3 Randomization and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

Participant-level randomization was performed to assign each participant to either the Intervention group or the Control group using a simple randomization schedule from the RAND() function in Microsoft Excel. Randomization occurred after participants provided signed informed consent to participate in the study and a research assistant determined they met study criteria. Randomization could have occurred after study participants started standardized outpatient PT.

A researcher not involved in recruitment or outcome assessment accessed the schedule, informed participants of their group assignment, and group assignment was concealed from the remaining members of the research team. This included blinding all members of the research team who were involved in the assessment of primary and secondary outcomes, or in statistical analysis of study outcomes. Participants and treating PTs were not blinded to their group assignment.

6.4 Study Assessments

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Visit Description	Patient Eligibility Screen and Enrollment	Randomization		Discharge	Follow-up Period	
Study visit: Study Day (Range of assessment periods)	**Visit 1: Day 0 (+/- 14 days)**	**Visit 2: Day 7 (-2, +8 days)**	**Treatment Period[1]**	**Visit 3: Day[2] (-14, +30 days)**	**Visit 4: 180 Days after Discharge (6 month) (-30, +60 days)**	**Visit 5: 360 Days after Discharge (12 month) (-30, +60 days)**
Informed Consent/HIPAA	X					
Demographics/ Medical History	X					
Accelerometer	X			X	X	X
Randomization		X				
Adverse Events			X	X	X	X
	1 – Study intervention will be delivered when the study participant visit PT. The total number of visits will be based on the number of PT visits during the PT episode of care. The number of visits will be based clinically on physical therapist discretion in accordance with standard physical therapy guidelines. 2 – The study visit day varies depending on the duration of outpatient PT					

Data collected outside of the time windows listed above will be classified as the intended visit the data was to reflect and noted as being outside the time window. Such data will be included in the primary analyses, however we will also perform a secondary analyses excluding data collected outside the time window.

Study Variable	Description	Endpoints	Interpretation
Age	Age of study participant in years	Minimum 45 years	N/A
Gender	Self-reported Sex of study participant	Male/Female	N/A
BMI	Body Mass Index calculated from weight and height.	N/A	N/A
Race	Self-reported race	White, Black or African American, Asian, American Indian or Alaskan Native, Hawaiian, more than one race, other	N/A
Hispanic	"Do you consider yourself to be Hispanic or Latino?"	Yes/No	N/A
Health History Questionnaire	The number of comorbidities from a list of 54 possible conditions	N/A	N/A
Moderate to Vigorous intensity Physical Activity (MVPA)	MVPA calculated from a monitor (ActiGraph GT3x)	Continuous measure. Minimum value 0 minutes/day	Higher values indicate greater time in MVPA
Steps/Day	Steps/day calculated from a monitor (ActiGraph GT3x)	Continuous measure. Minimum value 0 steps/day	Higher values indicate greater steps taken/day
Adverse Event	Defined as any unfavorable or unintended diagnosis, sign, symptom, or disease that is associated with the study and that may or may not be related to the intervention.	Continuous number of adverse events	N/A

7 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)
The sample size was N=120 study participants.

General Analysis Considerations

7.1 Timing of Analyses

Final analyses will be performed when data collection is completed. In particular, the final analyses will be performed when all enrolled study subjects have completed the 12 month follow up or dropped out prior to the 12 month follow up. The final analysis will be performed on data transferred to a file from RedCap, having been documented as meeting the cleaning and approval requirements after the finalization and approval of this SAP document. In particular data cleaning will involve checking physical documents for errors/discrepancies, ensuring all responses are correctly entered into REDCap, and then performing a quality check to ensure answers were entered accurately. For the ActiGraph, we will ensure data was recorded at 60Hz, that data fell within the expected wear time range, and that included participants met our wear time criteria of at least 4 days and at least 10 hours on those days.

7.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

7.2.1 Full Analysis Sample (Intention to Treat)

- *All subjects who were randomized*
- *The ActiGraph monitor was worn for ≥ 4 days of 10 hours of wear time each time point (baseline, discharge, and 6 months).*
- *This sample will be the primary efficacy sample*

7.2.2 Per Protocol Sample

- *All subjects who adhere to the major criteria in the protocol*
    - *Subjects who did not drop out*
        - *Completed Physical Therapy*
        - *Did not drop out over the 12 months of follow up after discharge from physical therapy*
    - *The ActiGraph monitor was worn ≥ 4 days at each time point (baseline, discharge, 6 months, and 12 months).*

The exact process for assigning the statuses (Full Analysis Sample and Per Protocol Sample) will be defined and documented prior to breaking the blind along with any predefined reasons for eliminating a subject from a particular population.

7.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

We have identified three covariates that are expected to have an important influence on our study outcomes, i.e., age, sex, and body mass index. We will adjust for these covariates in all analyses. In particular, age and body mass index will be treated as continuous variables, and sex as a categorical variable. We will perform separate subgroup analyses to examine evidence for a difference in treatment effects based on 1) Age (< and ≥ 65 years), 2) Sex (men and women), and 3) BMI (< and ≥ 32 kg/m2).

7.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

Missing data will be given careful attention in the analysis. In this RCT we have two treatment arms and four fixed times tied to the recovery process for measurements. It is anticipated that drop-outs from the study will be limited because all have elected to undergo knee replacement surgery and would be working toward recovery. However, it is possible that participants may not attend all follow-ups. Drastically fewer participants in the final analysis would affect study sensitivity and excessive missed follow-ups would potentially bias model parameter estimates. Under the assumption of limited data that is missing completely at random (MCAR) or missing at random (MAR), the mixed-effect model using restricted maximum likelihood estimation is a full information approach and leads to unbiased model parameter estimates. Selection between two common covariance structures, Toeplitz and AR(1), will be accomplished using the Akaike Information Criterion (AIC).

In the event that assumptions are not met regarding missing value frequency, MAR, or MCAR and missing values are occurring with higher frequency or are truly missing not at random (MNAR), the analysis may be biased. To test the missingness assumptions, missing data will first be summarized by group, time, each design cell, and each of the three covariates, age, sex and body mass index in an effort to graphically or tabularly detect patterns in the variation of missingness. More formally, missing/nonmissing will be taken as a dichotomous outcome in a logistic regression for continuous covariates and will be compared with between and within factors and sex using chi-square tests. Significant logistic regression coefficients or significant chi-square tests indicate a pattern of missingness variation that will be identified and reported and whose impact on the analysis will be explained if possible.

7.5 Interim Analyses and Data Monitoring (as applicable)

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 “Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics”)

7.5.1 Purpose of Interim Analyses

The interim analyses were performed due to uncertainty about some aspect or aspects of the treatment or treatments and the interim will allow learning to influence the subsequent design of the study. This included the simple uncertainty about safety aspects and the primary endpoint treatment effect that leads to early termination for futility of efficacy.

7.5.2 Planned Schedule of Interim Analyses

An interim analysis was performed after half of the participant’s 6-month follow-up visits were completed.

7.5.3 Scope of Adaptations and Stopping Rules

If the effect size of the intervention vs control exceeded 3.0 with a 95% CI of 2.5 to 3.5, then the intervention was to be deemed to be effective and study was to stop. As well, study participants who had not yet completed the intervention, i.e., were in physical therapy, and were in the control condition would have been offered the intervention. As well, we tallied the number of AEs, and compared that number between the intervention and control groups. If the intervention group was found to have more than three times the odds of AEs with a 95% CI of 2.5 to 3.5 compared with the control, then the study was to be stopped. Neither of

these events (efficacy or excessive AEs) occurred in the interim analyses.

7.5.4 Practical Measures to Minimize Bias

The interim analysis was performed by a single research assistant. This research assistant was the only person to see the data. She presented the results to the study's principal investigator to make decisions. This analyses was not made publicly available.

The final analyses will be performed by a statistician who will be blinded to group assignment. In particular, the study's principal investigator will draft mock tables for the statistician to fill out with data. Note the groups will be described as group 1 and group 2. Only after the tables are completely filled out, will the study's principal investigator become unblinded to determine which group (intervention vs control) is assigned to group 1 and group 2, and edit the tables accordingly.

8 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, and standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

8.1 Subject Disposition

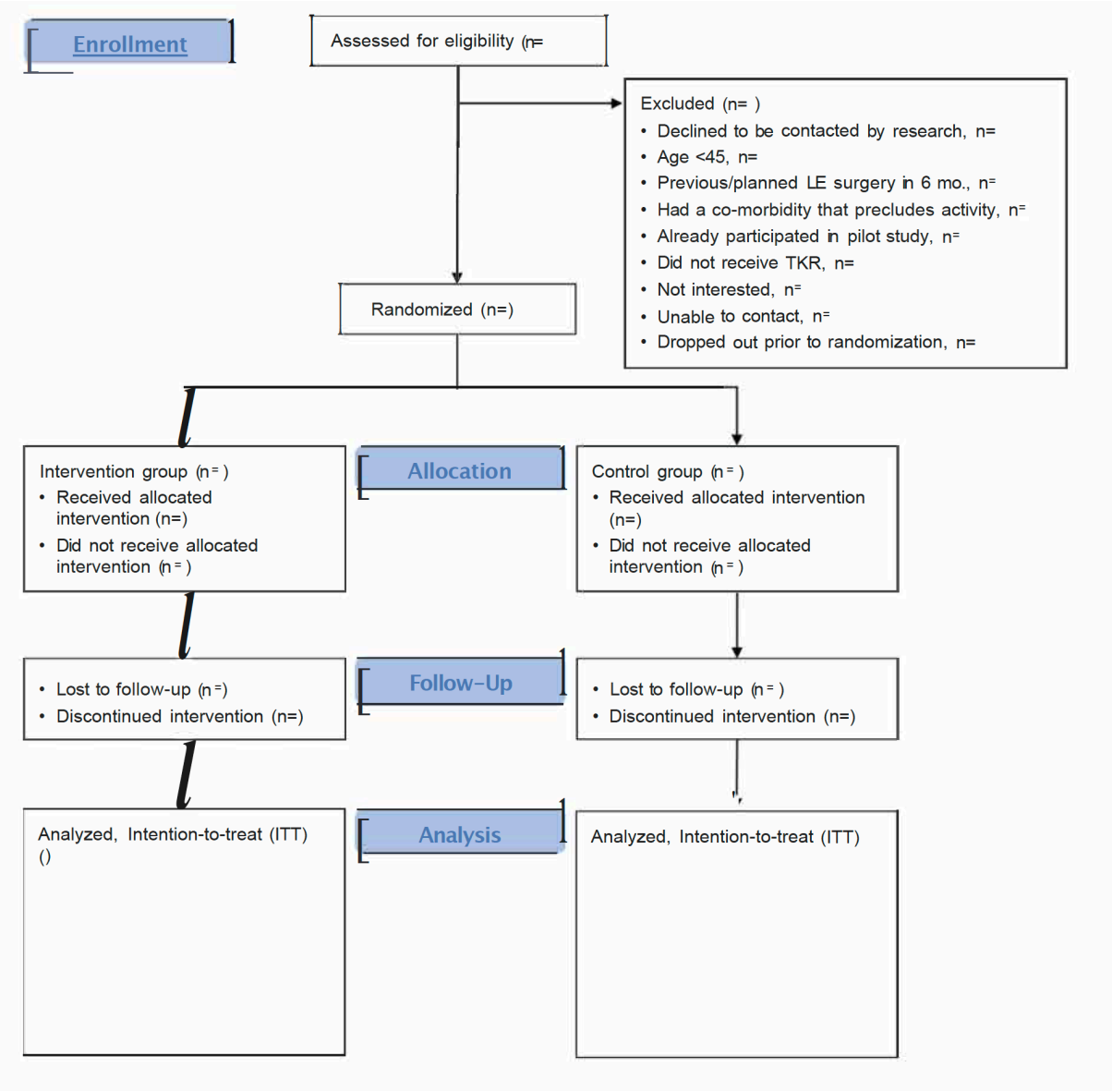
We establish how many subjects reached the various stages of the trial (Enrollment, Allocation, Follow-up, and Analysis) using the following list:

Enrollment:
- Declined to be contact by research
- Age < 45
- Previous or planned surgery
- Comorbidity that precludes physical activity
- Already participated in a Delaware ACTIVE Lab study
- Did not receive a TKR
- Not interested
- Unable to contact
- Dropped out prior to randomization

Allocation:
- Did not receive allocated intervention

Follow-up:
- Lost to Follow-up
- Discontinued the intervention

CONSORT Diagram Template



8.2 Demographic and Baseline Variables

Characteristic [mean ± SD or n (%)]	All *n*=	Intervention *n*=	Control *n*=
Age (years)			
Gender (female)			
BMI (kg/m^2)			
Race (Non-White)			

Comorbidity (Health History Questionnaire)			
MVPA at baseline (minutes/day)			
Steps/day at baseline			
Days between TKR and PT Evaluation			

8.3 Treatment Compliance

Characteristic [mean ± SD or n (%)]	All *n*=	Intervention *n*=	Control *n*=
Days Randomization to Discharge			
Days Eval to Discharge			

Characteristic [mean ± SD or n (%)]	Intervention *n*=
Percent of days in PT in the study that the Fitbit was checked (recorded or checked on HEP):	
Percent of weeks in PT in the study that a step goal was recorded:	

9 Efficacy Analyses

The primary and secondary outcomes will be summarized stratified by treatment group at each study timepoint (baseline, discharge, 6-month, 12-month). Our primary analysis will use an intention-to-treat (ITT) analysis that includes all participants who wore the monitor for ≥4 days at baseline. The statistical model underlying the analysis a mixed-effects model to examine the main and interaction effects of *group* (Intervention vs. Control) and *time* (BL, DC, 6M, and 12M) on MVPA (minutes/day). We will adjust this model for age, sex, and body mass index. The null hypothesis is that there is no difference in change in MVPA in the intervention group compared to the control group. The alternative hypothesis is that there is a difference between groups. The nature of the hypothesis is confirmatory as this study has been powered to detect a difference should one exist. The mixed-effect model will be used to calculate the mean and 95% Confidence Interval time in MVPA at each study time point. We will also calculate difference in means and 95% Confidence Intervals between the intervention and control group at each study time point. We will also calculate 2-sided p-values to determine statistical significance of differences between groups by time in MVPA.

- Methods and assumptions for handling longitudinal data or missing data.

Mixed-effect modeling will be used to estimate MVPA over time. The mixed-effect model using restricted maximum likelihood estimation is a full information approach and leads to unbiased model parameter estimates in the presence of MCAR or MAR missingness. Selection between two common covariance structures, Toeplitz and AR(1), will be accomplished using the Akaike Information Criterion (AIC).

9.1 Primary Efficacy Analysis

The primary endpoint of our study is to examine the efficacy of a Physical Therapist-administered physical activity intervention and standardized outpatient PT to increase MVPA over 6 months after discharge from outpatient PT compared to a control group that received standardized outpatient PT.

The statistical model underlying this analysis is a mixed-effects model to examine the main and interaction effects of *group* (Intervention vs. Control) and *time* (BL, DC, and 6M) on MVPA (minutes/day). We will adjust this model for age, sex, and body mass index.

9.2 Secondary Efficacy Analyses

9.2.1 Secondary Analyses of Primary Efficacy Endpoint

The per protocol sample, instead of the ITT sample will be used for the analysis of the primary efficacy endpoint.

9.2.2 Analyses of Secondary Endpoints

The secondary analyses endpoint of our study is to examine the efficacy of a Physical Therapist-administered physical activity intervention and standardized outpatient PT to increase MVPA over 12 months after discharge from outpatient PT compared to a control group that received standardized outpatient PT. We also examined the number of Steps/day over 6 and 12 months. The statistical model underlying this analysis is a mixed-effects model to examine the main and interaction effects of *group* (Intervention vs. Control) and *time* on MVPA (minutes/day) and Steps/day in separate models. We will adjust these models for age, sex, and body mass index.

9.3 Exploratory Efficacy Analyses

We will explore possible statistical interaction of study group with age (< and $\geq$ 65 years), obesity (< and $\geq$ 32 kg/m2), and sex (male/female) in separate analysis.

10 Safety Analyses

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.

- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold (for example, 5 %) within any arm of the clinical study, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

10.1 Adverse Events

We will report on the number of adverse events that are possibly or definitely related to the

study.

10.2 Deaths, Serious Adverse Events and other Significant Adverse Events

We will report on the number of serious adverse events and deaths that are possibly or definitely related to the study.

11 Reporting Conventions

P-values ≥0.01 will be reported to 2 decimal places; p-values less than 0.01 will be reported as “<0.01”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 2 significant figures.

12 Summary of Changes to the Protocol and/or SAP

We have modified the primary and secondary study endpoints from the original study protocol (version v.4 20 August 2018). Namely, the original study protocol listed MVPA taken at baseline, discharge, 6 months and 12 months as our primary study outcome. We have since modified this to MVPA taken at baseline, discharge, and 6 months. As well, the original study protocol listed fidelity, safety, and physical function as secondary outcomes. We have decided to investigate these outcomes in a secondary publication/manuscript separate from the primary paper. We will examine changes in steps/day as a secondary outcome in the primary paper. Lastly, we did list tertiary outcomes including self-efficacy for exercise and fear of movement in the study protocol. We will investigate these in secondary papers, and not as part of the primary paper.

13 Listing of Tables, Listings and Figures

This section is to give precise details for each table, listing or figure to be produced.

Mock Table 1: MVPA at each study time point using the ITT sample

	Baseline	Discharge	6 month	12 month
Control				
Intervention				
Control-Intervention				

Mock Table 2: Steps/day at each study time point using the ITT sample

	Baseline	Discharge	6 month	12 month
Control				
Intervention				
Control-Intervention				

Mock Table 3: MVPA at each study time point using the per-protocol sample

	Baseline	Discharge	6 month	12 month
Control				
Intervention				
Control-Intervention				

Mock Table 4: Steps/day at each study time point using the per-protocol sample

	Baseline	Discharge	6 month	12 month
Control				
Intervention				
Control-Intervention				