Statistical Analysis Plan

Delaware Physical Exercise and Activity for Knee osteoarthritis

(Delaware PEAK)

IRB Protocol Number: 1730922

National Clinical Trial (NCT) Identified Number: NCT04980300

Principal Investigator (PI): Daniel K. White

Sponsor: University of Delaware

Funded by: Rheumatology Research Foundation

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Version	Date	Summary of changes
v0.01	**07/14/2023**	**Original**
v0.02	**8/7/2023**	**Clarified analysis section 8.2.1 and 8.2.2**
v0.03	**8/16/2023**	**Revised section 6.4 and clarified section 8.2.1 and 8.2.2**
V1.00	**9/25/2023**	**Revised section 8.2.1 to clarify the ITT sample would include only those with complete baseline monitor data. Added a 24 week follow up to analyses described in sections 10.2.2 and 10.3**
V1.1	**12/19/2023**	**Revised the study flow chart and the per protocol sample sets 1 and 2 to a single per protocol sample. Clarified that valid ActiGraph data includes those who wore the monitor for ≥ 4 days in section 6.4 instead of in section 8.2. Clarified an index knee for VAS Pain for analysis. Revised secondary data analysis sample (8.2.3) to only include the per protocol analysis and report on outcomes measured with the ActiGraph. Clarified in 8.2.2 that the per protocol sample is a subset of the ITT sample. We clarified in section 5.2 that we are examining health beliefs in physical exercise and physical therapy. We added additional exploratory outcomes. We added exploratory measures from section 5.2 into Table 1 in section 6.4 and removed adverse events as these are listed in section 11.1. We clarified that the EARS will be collected at 12 and 24 weeks in section 6.4. We clarified that both the ITT and per protocol samples will be used for analyses for secondary and exploratory outcomes separately in sections 10.2./10.3. Mock tables in section 16 were revised.**
V1.2	**7/2/2024**	**Modified table 5 collapsing urban area and urban cluster. Replaced**

		supplemental table 4 for tables 4A and 4B. Renumbered section 9.4 as Efficacy Analysis. **Modified supplemental table 5. Added supplemental table 6. Section 9.3 table 6 modified and added supplemental table 8 to describe treatment fidelity to exercise and education. Added supplementary table 10 for treatment expectations before and after randomization.** **Renamed the expanded intervention group as the intervention and the Brief intervention group as the control.**

1 SAP Signatures

I give my approval for the attached SAP entitled “Delaware Physical Exercise and Activity for Knee osteoarthritis (Delaware PEAK)” dated 06/14/2023

Statistician (Author)
Name: Barry A. Bodt

Date: July 14, 2023

Statistician Reviewer (As applicable)
Name:

Date: _____

Principal Investigator
Name: Daniel K. White

Date: 7/14/2023

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3 Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
SAP	Statistical Analysis Plan
PT	Physical Therapy
EARS	Exercise Adherence Rating Scale
MVPA	Moderate-to-Vigorous intensity Physical Activity
SED	Sedentary Behaviors
LPA	Light Intensity Physical Activity
NICE	National Institute for Health and Care Excellence
IPAQ	International Physical Activity Questionnaire
VAS	Visual analogue scale
CCI	Charlson Comorbidity Index
PEAK	Physical Exercise and Activity for Knee osteoarthritis

4 Introduction

4.1 Preface

Knee Osteoarthritis (OA) is a serious disease. In 2010, OA moved up from 15th to 11th in rankings for global burden of disease,[1] and the most common weight-bearing joint affected by OA is the knee.[2] More than 15 million Americans currently have symptomatic knee OA.[3] The estimated annual cost to treat knee OA is $27 billion,[4] which is similar to the cost to treat stroke (~$34 billion[5]). The incidence of knee OA is expected to increase with the aging and obese US population.[6] Walking difficulty is the primary functional limitation in people with knee OA that, in turn, makes OA the leading cause of disability among older adults.[7] Not only is walking difficulty related to disability, but it is also associated with a 55% higher risk of premature death.[8,9] Without a cure, treatment for knee OA focuses primarily on managing pain and reducing disability.

Treatment guidelines for knee OA champion the use of supervised exercise. The recently released 2019 ACR/Arthritis Foundation guidelines for the treatment of OA strongly support the use of supervised exercise.[10] These recommendations are consistent with those of the Osteoarthritis Research Society International (OARSI), which promote exercise, self-management, and education.[11] Both guidelines (ACR and OARSI) come from the robust and pervasive research findings that exercise reduces pain and improves physical function in adults with knee OA.[8]

Few adults with knee OA try supervised exercise to manage their OA. For example, less than 10% of adults with knee OA exercise regularly,[12,13] and only one-in-ten patients are seen for supervised exercise 5 years before a knee replacement.[14] Health claims data show a similar trend, with a doubling in the prescription of opioids and a 50% reduction in referrals for Physical Therapy (PT) in the past decade.[15] Hence, few adults with knee OA are utilizing physical activity and/or supervised exercise to address their symptoms of knee OA.

The objective of this study is to examine the efficacy of Delaware PEAK to increase physical activity in adults with knee OA compared to a control group receiving web-based resources about knee OA and exercise. The rationale for our study is that there is a need to examine whether Delaware PEAK can directly target the mismatch between OA recommendations and practice patterns. Our central hypothesis is that Delaware PEAK will increase physical activity and will increase the belief that exercise is helpful and not harmful, compared with a control group receiving web-based OA treatment resources. Successful completion of this proposal will provide the evidence necessary to scale up this low-cost intervention, with the goal of increasing the number of adults who use exercise to manage their knee OA and thus reducing the burden of disease.

4.2 Scope of the analyses

These analyses will assess the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK) versus a control group receiving web-based resources about knee OA and exercise regarding change in Moderate-to-Vigorous intensity Physical Activity (MVPA) over 12 weeks in adults with knee OA.

5 Study Objectives and Endpoints

5.1 Study Objectives

The purpose of this study is to examine the efficacy of Delaware PEAK to increase physical activity in adults with knee OA compared to a control group receiving web-based resources about knee OA and exercise.

5.2 Endpoints

The primary endpoint of our study is to examine the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK) to increase MVPA over 12 weeks compared to a control group receiving web-based resources about knee OA and exercise.

The secondary analyses endpoint of our study is to examine the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK) to increase health beliefs in Physical Exercise and Physical Therapy, light physical activity (LPA), and steps per day, over 24 weeks compared to a control group receiving web-based resources about knee OA and exercise. We also will assess change in MVPA over 24 weeks.

Our exploratory endpoints include change in pain, symptoms, function in activities of daily living, function in sport and recreation, and quality of life over 12 weeks and 24 weeks. We will also examine change in treatment expectations before and after randomization. Lastly, we will examine change in treatment adherence from 12 to 24 weeks among those in the intervention group.

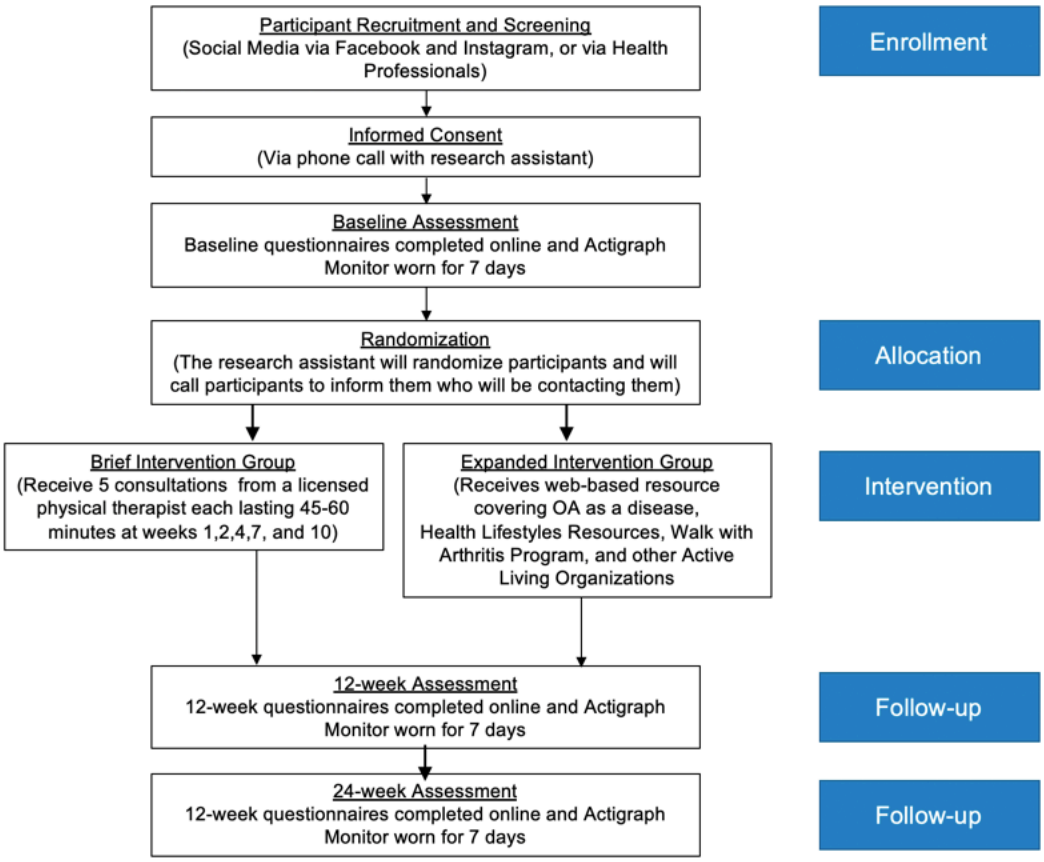
6 Study Methods

6.1 General Study Design and Plan

(ICH E3;9)

We will conduct a pragmatic randomized controlled trial with a 2-group, superiority, parallel-design. The intervention group will receive a physical therapist-delivered exercise intervention (Delaware PEAK), i.e., the Intervention, while the control group will receive web-based resources about knee OA and exercise. 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. Participants will not be blinded to group assignment but will not be informed about study hypotheses until study completion. The physical therapist will not be blinded to group assignment.

Figure 1: Study flow-chart



6.2 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of an electronically signed and dated informed consent form
2. ≥45 years of age,
3. Resides in the contiguous United States
4. Available for the duration of the intervention portion of the study (12 weeks) and willing to wear physical activity monitors
5. Looking to move more, i.e., be more active.
6. Knee OA diagnosis by the NICE criteria
7. Comfortable participating in a program delivered in English
8. Is able to safely participate in moderate-intensity exercise as determined by a pre-exercise screen questionnaire,[29]
9. Has either a smartphone or a laptop/desktop computer with an internet connection.
10. Has a working email address.

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Regularly exercise for more than 60 minutes/week.
2. Has a scheduled knee or hip joint replacement
3. Has had physical therapy for knee OA in the past 6 months
4. Participated in a strength training program for the lower extremities in the past 6 months

6.3 Randomization and Blinding

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

Participant-level randomization will be performed to assign each participant to either the Intervention group (referred to as the Intervention) or the Control group using block randomization schedule with block sizes of 4. Randomization was performed using REDCap's built-in randomization function and will occur after participants sign the informed consent and complete baseline data collection. Participants will be randomized into one of two groups: (1) the Intervention group, who will receive the Delaware PEAK program with a physical therapist, or (2) the control group, who will receive pre-recorded, web-based resources.

Participants will not be blinded to group allocation; however, they will not be informed about the study hypotheses until the study is completed, at which time they will be provided a lay summary of findings. The treating physical therapist will not be blinded to group assignment, as they are delivering the Intervention. Research team members responsible for outcome data management will be blinded to group assignment. As all outcomes are collected either through a physical activity monitor or online questionnaires, this study is thus considered assessor-blinded for our primary outcome, physical activity. Statistical analyses will be performed in a blinded manner.

6.4 Study Assessments

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Table 1: Timeline of Assessments

	STUDY PERIOD								
	Enrollment/BL	**Randomization**	**Intervention**					**Follow-Up**	
Timepoint	*-t_1*	*0w*	*1w*	*2w*	*4w*	*7w*	*10w*	*12w*	*24w*
Enrollment:									
Screening Form	X								
Verbal Eligibility Form	X								
Informed Consent	X								
General Information (Demographics)	X								
Randomization		X							
Intervention:									
Intervention			X	X	X	X	X		
Control			X	X	X	X	X		
Assessment:									
Primary outcome									
Physical activity (MVPA via Actigraph)	X							X	X
Secondary outcomes									
Treatment Beliefs of Physical Therapy	X							X	X
Treatment Beliefs of Physical Exercise	X							X	X
Physical activity (steps/day, LPA via Actigraph)	X							X	X
Exploratory measures									
Knee Pain (Visual Analogue Scale)	X							X	X
Knee Injury and OA Outcome Score (KOOS) subscales: Pain, Symptoms, function in activities of daily living, function in sport and recreation, quality of life	X							X	X
Treatment Expectations Question	X	X							
Exercise Adherence Rating Scale (EARS)*								X	X
Other measures									
Adverse Events		X	X	X	X	X	X	X	X
Charlson Comorbidity Index	X								
*Collected in the those randomized to the intervention group									

Table 2: Analysis Time Windows

Visit (target day)	**Lower bound (days)**	**Upper bound (days)**
Enrollment (0)	n/a	n/a
Baseline (14, post-enrollment)	n/a	n/a

12-week Follow-up (84, post-randomization)	-7 days	+28 days
24-week Follow-up (168, post-randomization)	-7 days	+28 days

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. While the spacing of follow-up assessments makes it unlikely that multiple data collections will occur during the same window, the first valid set of assessments will be used for the corresponding timepoint.

Descriptions of each outcome, timepoint of collection, and score range are described below. A table is also provided that summarizes this information.

MVPA: Objectively-measured physical activity will be collected using the Actigraph GT3x at the baseline, 12-week, and 24-week timepoints. Minutes/week of MVPA can range from 0 minutes/week to 10,080 minutes/week (7 days x 24 hours x 60 minutes). Valid data includes those who wore the ActiGraph for $\geq$ 4 days.

LPA, Daily Walking: Data collected using the ActiGraph GT3x activity monitor will also be used to assess change in minutes/week of LPA and average steps/day between baseline and both follow-up timepoints. Minutes/week of LPA can range from 0 minutes/week to 10,080 minutes/week (7 days x 24 hours x 60 minutes). Steps/day can be any value greater than or equal to 0. Valid data includes those who wore the ActiGraph for $\geq$ 4 days.

Health Beliefs: Health beliefs will be measured with the Treatment Beliefs of OA: Physical Therapy (TOA-PT) and Treatment Beliefs of OA: Physical Exercise (TOA-PE) questionnaires, collected at the baseline, 12-week, and 24-week timepoints. The TOA provides separate scores for positive and negative treatment beliefs. We will measure change in TOA-PT and TOA-PE scores from baseline to 12 weeks and baseline to 24 weeks. The TOA-PT negative beliefs scores range from 4 to 16, TOA-PT positive scores range from 7 to 28, TOA-PE negative beliefs scores range from 4 to 16, TOA-PE positive scores range from 7 to 28. For all scales, a higher score indicates a greater amount of positive or negative treatment beliefs.

Charlson Comorbidity Index (CCI): The Charlson Comorbidity Index (CCI) is a 17-item questionnaire that creates a weighted score based on a range of common, comorbid conditions. This questionnaire will be collected at the baseline timepoint and scores range from 0 to 29, with a higher CCI score indicating greater levels of comorbidity.

Visual Analog Scale (VAS) Pain: Change in knee pain will be measured using a single-item Visual Analog Scale (VAS) question in which the participant will indicate their pain in each knee. Scores range from 0-100 where 0 is no pain and 100 is the worst pain imaginable. An index knee to be used for analysis is defined as the knee with worse pain at baseline.

Knee Injury and Osteoarthritis Outcome Score (KOOS): The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a 42-item questionnaire that assesses five domains, including pain, symptoms (other than pain), function in activities of daily living, function in sport and recreation, and quality of life. The KOOS has subscale scores for Pain, Symptoms, ADL Function, Sport & Recreation Function, and Quality of Life. Scores are transformed to a 0-100 scale with 0 indicating extreme knee problems and 100 indicating no knee problems.

Treatment Expectations Question: The participant will complete a Treatment Expectations Question, which asks the participant how effective they expect the intervention to be for their knee. This question will be collected at the baseline timepoint: right before and right after randomization. Answers will be expressed as frequencies and percentages for each of the following categories: No effect at all, Minimal improvement, Moderate improvement, Large improvement, and Complete recovery, as well as reported as an increase, decrease, or no change in treatment expectations.

Exercise Adherence: For the Intervention, adherence to strengthening exercises and physical activity will be measured using the Exercise Adherence Rating Scale (EARS). The EARS includes 6 items whose total score ranges from 0 to 24, where a higher score indicates greater adherence. The EARS will be collected at 12 and 24 weeks.

Adverse Events (AE): Information on potential adverse events (AE) will be collected by the treating physical therapist at the beginning of each session in the intervention, by a Research Assistant during follow-up reminder phone calls in the Control, or by spontaneous report on the part of the participant (e.g., reaching out to the study team by phone or email). AEs will be reported as frequencies and percentages.

General Information Form: The participant will complete a General Information Form that collects height, weight, date of birth, gender, race, ethnicity, veteran status, highest level of education attained, employment status, and approximate household income. This form will be collected at the baseline timepoint. Continuous variables will be expressed as means and standard deviations while categorical variables will be expressed as frequencies and percentages.

Table 3: Outcome Timepoints and Scoring

Outcome	**Timepoints collected**	**Scoring**
MVPA	Baseline, 12-week, 24-week	0 to 1044 minutes/day
TOA (PT and PE)	Baseline, 12-week, 24-week	4 to 16 for negative 7 to 28 for positive
EARS	12-week, 24-week	0 to 24
Light intensity physical activity (LPA)	Baseline, 12-week, 24-week	0 to 10,080 minutes/week
Daily Walking (steps/day)	Baseline, 12-week, 24-week	At least 0 steps/day
VAS Pain	Baseline, 12-week, 24-week	0 to 100
KOOS Subscales	Baseline, 12-week, 24-week	0 to 100 for each subscale
General Information Form	Baseline	n/a
Treatment Expectations	Baseline (x2)	n/a
CCI	Baseline	0 to 29
Exercise Adherence (EARS)	12-week and 24-week	0-24

Adverse Events	Throughout	n/a

7 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

The sample size is n = 100 randomized participants. In order to be randomized, participants must complete baseline assessments.

8 General Analysis Considerations

8.1 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 24-week follow up timepoint or dropped out prior to the 24-week timepoint. 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. Data cleaning will involve checking REDCap surveys for errors/discrepancies, ensuring all responses are correctly scored REDCap, and then performing a quality check to ensure answers were scored 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. As well, we will cross-reference the date the monitor was worn from the Actigraph is between the dates the monitor was send the received from REDCap. We will also check that the file names and dates of the Actigraph files correspond to names and dates from REDCap.

8.2 Analysis Populations

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

8.2.1 Full Analysis Sample (Intention to Treat)

- *All subjects who were randomized*
- *This will be the primary efficacy sample*

8.2.2 Per Protocol Sample

- *Of those in the Full Analysis sample in 8.2.1, we will include all subjects who adhere to the major criteria in the protocol*
    - *Completed their respective intervention group*
        - *For Intervention group $\geq$ 3 of 5 consultations*
        - *For Control group, accessed the website.*

8.2.3 Secondary Data Analysis Sample

- *We will repeat the Per Protocol analysis for outcomes measured with the ActiGraph excluding participants on those who worn their ActiGraph monitor outside of our established visit windows.*

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.

8.3 Covariates and Subgroups

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

Baseline demographics will be assessed for group assignment differences after randomization. Covariates will be determined based on the presence of group differences.

8.4 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 three fixed times for assessment. It is anticipated that drop-outs from the study will be at random because study participants were considered treatment-seeking. 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 models with two common covariance structures, Toeplitz and independent errors 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/non-missing 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. Model residuals will be evaluated for normality using the Shapiro-Wilk test, homogeneity of variance using Levine's test, and transformations, if necessary, will be chosen from among the Box-Cox transformations.

9 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, Intervention) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

9.1 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:
- Regularly exercise > 60 min/wk
- Scheduled knee replacement
- Received physical therapy or prescribed an exercise program in past 6 months
- Did not receive medical clearance after failing the Adult Pre-Exercise Screening System questionnaire
- < 45 years of age
- No activity related knee pain
- Morning stiffness > 30 min
- Reside outside of the contiguous United States
- Not comfortable with a program delivered in English
- Not seeking to be more physically active
- Did not have a smartphone/ computer with internet access
- Did not complete the baseline data collection

Allocation:
- Did not receive allocated intervention

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

Figure 2: CONSORT Diagram Template

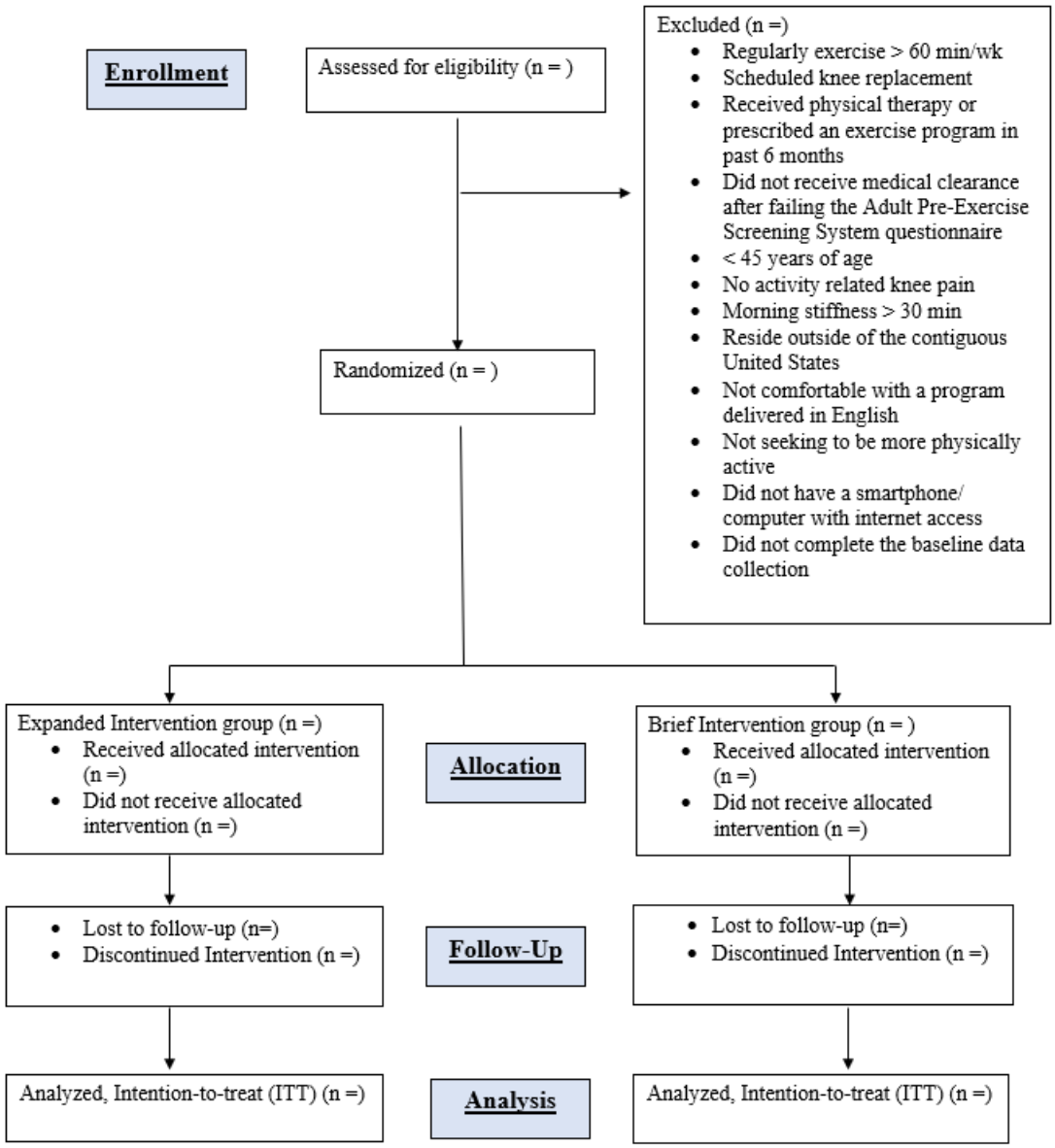


Table 4: Anticipated Recruitment Schedule

	ANTICIPATED	
Month	# to Randomize/month	Cumulative Total
July 2021	1	1
August 2021	4	5
September 2021	5	10
October 2021	6	16
November 2021	6	22
December 2021	6	28
January 2022	6	34
February 2022	6	40
March 2022	6	46
April 2022	6	52
May 2022	6	58
June 2022	6	64
July 2022	6	70
August 2022	6	76
September 2022	6	82
October 2022	6	88
November 2022	6	94
December 2022	6	100

9.2 Protocol Deviations

Potential protocol deviations include: follow-up assessments collected outside of preset time window, participants delaying assessment due to unforeseen circumstances, or the activity monitors not being sent/being lost in the mail. All would be considered missing data and would be handled in the manner described in the Missing Data section of this document.

9.3 Demographic and Baseline Variables

Table 5: Demographic and Baseline Characteristics

Characteristic [mean (sd) or n (%)]	All Study Participants (n=)	Intervention (n=)	Control (n=)
Age (years)			
Weight (kg)			
Height (m)			
Body Mass Index (kg/m^2)			
Gender			
Women			
Men			

Non-binary			
Race			
White			
Black			
Asian			
Native American or Alaskan Native			
Hawaiian or Pacific Islander			
More than one race			
Ethnicity (n/N)			
Hispanic			
Annual household income ($)			
< 5,000			
≥5,000 to < 25,000			
≥25,000 to < 50,000			
≥50,000 to < 75,000			
≥75,000 to < 100,000			
≥100,000			
Education			
< High School			
High school			
Associate's degree			
Bachelor's degree			
Master's degree			
Doctoral degree			
Other			
Number of comorbidities			
Work			
Full-time			
Part-time			
Unemployed or laid off			
Retired			
Keeping house or raising children			
Community Type			
Rural			
Urban			

Treatment Compliance

Table 6: Treatment Compliance Measures

	Control	Intervention
Number of physical therapy consultations (0-5), mean (SD)	-	
Number of physical therapist consultations, n (%)		
0	-	
1	-	
2	-	
3	-	
4	-	
5	-	
Duration of physical therapist consultations (mins), mean (SD)		
Initial	-	
Follow-ups	-	
PT discussed steps/day n/N (%)		
1st consultation	-	
2nd consultation	-	
3rd consultation	-	
4th consultation	-	
5th consultation	-	
PT discussed step goals n/N (%)		
1st consultation	-	
2nd consultation	-	
3rd consultation	-	
4th consultation	-	
5th consultation	-	
Self-reported adherence to exercises (EARS)[1]		
12 weeks	-	
24 weeks	-	
Website access, n/N (%)		
Never		-
≥ 1 visit		-

[1] EARS (Exercise Adherence Rating Scale) range 0-24 with higher scores representing more adherence.

9.4 Efficacy Analyses

The primary and secondary outcomes will be summarized stratified by treatment group at each study timepoint (baseline, 12-week, 24-week). Our primary analysis will use an intention-to-treat (ITT) analysis that includes all participants who wore the monitor for ≥4 days for 10 hours/day 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, 12-week) on MVPA (minutes/day). 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 the 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. Data will be summarized by intervention group. Means, Standard Deviations, Minimums and Maximums will be used to summarize continuous variables. Categorical variables will be summarized as frequencies and percentages.

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 models with two common covariance structures, Toeplitz and independent errors, will be accomplished using the Akaike Information Criterion (AIC).

9.5 Primary Efficacy Analysis

The primary endpoint of our study is to examine the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK, referred to as the Intervention) to increase MVPA over 12 weeks compared to a control group receiving web-based resources about knee OA and exercise (referred to as the Control).

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* (baseline, 12-week) on MVPA (minutes/day).

9.6 Secondary Efficacy Analyses

9.6.1 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.

9.6.2 Analyses of Secondary Endpoints

The secondary analyses endpoints are to examine the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK, referred to as the Intervention) to increase treatment beliefs, increase LPA, and increase steps/day over 12 weeks and 24 weeks compared to a control group receiving web-based resources about knee OA and exercise (referred to as the Control). Additionally, we will examine the efficacy of the intervention to increase MVPA over 24 weeks. Both ITT and per protocol samples will be used for separate analyses.

9.7 Exploratory Efficacy Analyses

Further, we will explore the efficacy of a physical therapist-delivered exercise intervention (Delaware PEAK, referred to as the Intervention) to decrease VAS pain and increase KOOS subscale scores over 12 weeks and 24 weeks compared to a control group receiving web-based resources about knee OA and exercise (referred to as the Control). Both ITT and per protocol samples will be used for separate analyses. We also will explore the change in exercise adherence from the 12-week to 24-week follow-up timepoints in the Intervention group only. Lastly, we will examine changes in treatment expectations between group from before to after randomization.

10 Safety Analyses

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with frequencies and percentages of such events in each Intervention group will be reported.

- Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with frequencies and percentages of such events in each Intervention group will be reported.

- 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 of 5% within either Intervention group, grouped by organ system, with frequencies and percentages of such events in each Intervention group will be reported.

10.1 Adverse Events

We will report on the frequencies and percentages 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 frequencies and percentages of deaths, serious adverse events, and other significant adverse events that are possibly or definitely related to the study.

11 Reporting Conventions

P-values ≥0.01 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. 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 be reported to one decimal place.

12 Quality Assurance of Statistical Programming (As Applicable)

At the time of this writing, data will be stored on REDCap, a password-protected 2-factor authentication, data management platform hosted by the Center for Human Research Coordination at the University of Delaware.

At the time of this writing, data analysis will be performed using JMP, Version 17.0.0. SAS Institute Inc., Cary, NC, USA.

For quality assurance, all summary score calculations will be performed by REDCap software and checked by a research assistant for accuracy.

13 Summary of Changes to the Protocol and/or SAP

Rationale for Adjustments of Statistical Analysis Plan from Protocol (March 12, 2023)
The changes from the protocol-specified definitions of aims, outcomes and statistical analytic approaches are outlined below. These changes reflect an error in data collection during the trial. Questionnaires are collected via automated survey in REDCap, and the automated survey did not include the SEE for the 12-week and 24-week follow-up timepoints. Therefore, SEE was only collected at the baseline timepoint and cannot be assessed for change after the intervention.

V0.02 changes: We clarified the definition of adherence to the control and interventions to be included in the per-protocol analysis.

V0.03 changes: We revised section 6.4 to remove a time window for the baseline data collection for the Actigraph since this would not impact follow up time. We removed language around drop outs in section 8.2.1 and 8.2.2 since these subjects would be excluded anyways since they would not have monitor data. Also, we clarified in Table 2 the number of days post-enrollment and post-randomization for follow-up.

V1.0 changes: Revised section 8.2.1 to clarify the ITT sample would include only those with complete baseline monitor data. Added a 24 week follow up to analyses described in sections 10.2.2 and 10.3

V1.1 changes: Revised the study flow diagram. Revised the per protocol sample sets 1 and 2 to a single per protocol sample. Clarified that valid ActiGraph data includes those who wore the monitor for $\geq$ 4 days in section 6.4 instead of in section 8.2. Clarified an index knee for VAS Pain for analysis. Revised secondary data analysis sample (8.2.3) to only include the per protocol analysis and report on outcomes measured with the ActiGraph. Clarified in 8.2.2 that the per protocol sample is a subset of the ITT sample. We clarified in section 5.2 that we are examining health beliefs in physical exercise and physical therapy. We added additional exploratory outcomes. We added exploratory measures from section 5.2 into Table 1 in section 6.4 and removed adverse events as these are listed in section 11.1. We clarified that the EARS will be collected at 12 and 24 weeks in section 6.4. We clarified that both the ITT and per protocol samples will be used for analyses for secondary and exploratory outcomes separately in sections 10.2. and 10.3. Mock tables in section 16 were revised to reflect what is planned for the manuscript.

V1.2 changes: We combined urban area and urban cluster in table 5 since the 2020 Census combined these geographical categories. Replaced supplemental table 4 with tables 4A and 4B, which adds descriptive baseline values (table 4A) in addition to within and between group changes (table 4B). Added a column for non-

randomized to modified supplemental table 5. Added supplemental table 6 to describe sample that had valid MVPA data compared to those who did not have MVPA data. Section 9.3 table 6 modified and added supplemental table 8 to describe treatment fidelity to exercise and education. Renumbered section 9.4 as efficacy analysis and added a calculation of effect sizes for analyses. Added table 4 and supplementary table 9 for effect sizes from the ITT and per protocol analyses, respectively. Added supplementary table 10 for treatment expectations before and after randomization.

14 References

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account for why people with or at high risk of knee osteoarthritis do not meet physical activity guidelines? Arthritis Rheum. 2013;65(1):139-147.
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15 Listing of Tables, Listings and Figures

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

PEAK Tables

Table 1: Participant characteristics

Characteristic [mean (sd) or n (%)]	All Study Participants (n=)	Intervention (n=)	Control (n=)
Age (years)			
Weight (kg)			
Height (m)			
Body Mass Index (kg/m^2)			
Gender			
Women			
Men			
Non-binary			
Race			
White			
Black			
Asian			
Native American or Alaskan Native			
Hawaiian or Pacific Islander			
More than one race			
Ethnicity (n/N)			
Hispanic			
Annual household income ($)			
< 5,000			
≥5,000 to < 25,000			
≥25,000 to < 50,000			
≥50,000 to < 75,000			
≥75,000 to < 100,000			
≥100,000			

Education			
< High School			
High school			
Associate's degree			
Bachelor's degree			
Master's degree			
Doctoral degree			
Other			
Number of comorbidities			
Work			
Full-time			
Part-time			
Unemployed or laid off			
Retired			
Keeping house or raising children			
Community Type			
Rural			
Urban			

Table 2: Mean (sd) scores for study outcomes across time by treatment groups

Outcome [mean (sd) or n (%)];n	Baseline		12 weeks		24 weeks	
	Intervention	Control	Intervention	Control	Intervention	Control
Primary Outcome						
MVPA[2] (min/day)						
Secondary Outcomes						
Light Intensity Physical Activity						
Steps/day						
Treatment Beliefs						
TOA-PE[3] positive						
TOA-PE negative						
TOA-PT[4] positive						
TOA-PT negative						
Exploratory Outcomes						
VAS pain						
KOOS Subscales						
Pain						
Symptoms						
Activities of daily living						
Sports and recreation						
Quality of life						

[2] MVPA: Moderate to Vigorous Intensity Physical Activity
[3] Treatment Beliefs of OA: Physical Exercise
[4] Treatment Beliefs of OA: Physical Therapy

Table 3: Change within and between groups

Outcome [mean (sd) or n (%)]	Mean (sd) change within groups				Change between groups (Intervention – Control)	
	Baseline – 12 weeks		Baseline – 24 weeks		Baseline – 12 weeks	Baseline – 24 weeks
	Intervention Group	Control	Intervention Group	Control	Mean difference (95% CI)	Mean difference (95% CI)
Primary Outcome						
MVPA[5] (min/day)						
Secondary Outcomes						
Light Intensity Physical Activity						
Steps/day						
Treatment Beliefs						
TOA-PE[6] positive						
TOA-PE negative						
TOA-PT[7] positive						
TOA-PT negative						
Exploratory Outcomes						
VAS pain						
KOOS pain[8]						
KOOS ADL[9]						
Exercise Adherence						

[5] MVPA: Moderate to Vigorous Intensity Physical Activity
[6] Treatment Beliefs of OA: Physical Exercise
[7] Treatment Beliefs of OA: Physical Therapy
[8] Knee Injury and Osteoarthritis Outcome Score Pain subscale
[9] Knee Injury and Osteoarthritis Outcome Score Activities of Daily Living subscale

Supplemental Tables

Supplemental Table 1: Participant characteristics who were included in the per protocol analyses.

Characteristic [mean (sd) or n (%)]	All Study Participants (n=)	Intervention (n=)	Control (n=)
Age (years)			
Weight (kg)			
Height (m)			
Body Mass Index (kg/m^2)			
Gender			
Women			
Men			
Non-binary			
Race			
White			
Black			
Asian			
Native American or Alaskan Native			
Hawaiian or Pacific Islander			
More than one race			
Ethnicity (n/N)			
Hispanic			
Annual household income ($)			
< 5,000			
≥5,000 to < 25,000			
≥25,000 to < 50,000			
≥50,000 to < 75,000			
≥75,000 to < 100,000			
≥100,000			
Education			
< High School			
High school			
Associate's degree			
Bachelor's degree			
Master's degree			
Doctoral degree			
Other			
Number of comorbidities			
Work			
Full-time			
Part-time			
Unemployed or laid off			
Retired			
Keeping house or raising children			
Community Type			
Rural			
Urban			

Supplemental table 2: Per protocol sample mean (sd) scores for study outcomes across time by treatment group

Outcome [mean (sd) or n (%)];n	Baseline	12 weeks	24 weeks	P value
Primary Outcome				
MVPA[10] (min/day)				
Secondary Outcomes				
Light Intensity Physical Activity				
Steps/day				
Treatment Beliefs				
TOA-PE[11] positive				
TOA-PE negative				
TOA-PT[12] positive				
TOA-PT negative				
Exploratory Outcomes				
VAS pain				
KOOS Subscales				
Pain				
Symptoms				
Activities of daily living				
Sports and recreation				

[10] MVPA: Moderate to Vigorous Intensity Physical Activity
[11] Treatment Beliefs of OA: Physical Exercise
[12] Treatment Beliefs of OA: Physical Therapy

Supplemental table 3: Per protocol sample change within and between groups

Outcome [mean (sd) or n (%)]	Mean (sd) change within groups				Change between groups	
	Baseline – 12 weeks		Baseline – 24 weeks		Baseline – 12 weeks	Baseline – 24 weeks
	Intervention Group	Control Group	Intervention Group	Control Group	Mean difference (95% CI)	Mean difference (95% CI)
Primary Outcome						
MVPA[13] (min/day)						
Secondary Outcomes						
Light Intensity Physical Activity						
Steps/day						
Treatment Beliefs						
TOA-PE[14] positive						
TOA-PE negative						
TOA-PT[15] positive						
TOA-PT negative						
Exploratory Outcomes						
VAS pain						
KOOS Subscales						
Pain						
Symptoms						
Activities of daily living						
Sports and recreation						
Quality of life						

[13] MVPA: Moderate to Vigorous Intensity Physical Activity
[14] Treatment Beliefs of OA: Physical Exercise
[15] Treatment Beliefs of OA: Physical Therapy

Supplemental table 4A: Secondary Data Analysis Sample (Per protocol sample excluding those who wore the ActiGraph monitors outside of the established visit windows) sample adjusted mean (se)

Outcome [adjusted mean (se)];n	Baseline	12 weeks	24 weeks	P value
Primary Outcome				
MVPA[16] (min/day)				
Secondary Outcomes				
Light Intensity Physical Activity				
Steps/day				

Supplemental table 4B: Secondary Data Analysis Sample (Per protocol sample excluding those who wore the ActiGraph monitors outside of the established visit windows) scores for study outcomes across time change within and between groups

Outcome	Adjusted Mean (se) change within groups				Adjusted Mean (se) change between groups	
	12 weeks – Baseline		24 weeks – Baseline		12 weeks – Baseline	24 weeks – Baseline
	Intervention Group	Control Group	Intervention Group	Control Group	(Intervention – Control)	(Intervention – Control)
Primary Outcome						
MVPA (min/day)						
Secondary Outcomes						
Light Intensity Physical Activity						
Steps/day						

[16] MVPA: Moderate to Vigorous Intensity Physical Activity

Supplemental table 5: Safety Analyses

Participants n/N (%)	Intervention Group	Control Group
Discontinued participation because of adverse events		
Serious Adverse Event (related or unrelated)		
Hospitalizations (related)		
Hospitalizations (unrelated)		
Deaths (related)		
Deaths (unrelated)		
Nonserious Adverse Event (related or unrelated)		
Back (related)		
Back (unrelated)		
Hip/Thigh (related)		
Hip/Thigh (unrelated)		
Knee (related)		
Knee (unrelated)		
Ankle/Foot (related)		
Ankle/Foot (unrelated)		
Other (related)		
Other (unrelated)		

Supplemental table 6: Comparison of included study participants with valid MVPA data (n=) vs those excluded from this analysis (n=)

Characteristic [mean (sd) or n (%)]	Study Participants with valid MVPA data (n=)	Study participants excluded from MVPA analysis (n=)
Age (years mean (sd))		
Weight (kg mean (sd))		
Height (m mean (sd))		
Body Mass Index (kg/m^2 mean (sd))		
Gender (n (%))		
Women		
Men		
Non-binary		
Race (n (%))		
White		
Black		
Asian		
Native American or Alaskan Native		
Hawaiian or Pacific Islander		
Other		
More than one race		
Ethnicity (n (%))		
Hispanic		
Not Hispanic		
Did not know		
Annual household income (n (%))		
< 5,000		
≥5,000 to < 25,000		
≥25,000 to < 50,000		
≥50,000 to < 75,000		
≥75,000 to < 100,000		
≥100,000		
Don't know		
Education (n (%))		
< High School		
High school		
Associate's degree		
Bachelor's degree		
Master's degree		
Doctoral degree		
Other		
Number of comorbidities (mean (sd))		
Work (n (%))		
Full-time		
Part-time		
Unemployed or laid off		

Retired		
Keeping house or raising children		
Looking for work		
Community Type (n (%))		
Rural		
Urban		

Supplemental table 7: Attendance at consultations and self-rated adherence to intervention
Table 6: Treatment Compliance Measures

	Control	Intervention
Number of physical therapy consultations (0-5), mean (SD)	-	
Number of physical therapist consultations, n (%)		
0	-	
1	-	
2	-	
3	-	
4	-	
5	-	
Duration of physical therapist consultations (mins), mean (SD)		
Initial	-	
Follow-ups	-	
PT discussed steps/day n/N (%)		
1st consultation	-	
2nd consultation	-	
3rd consultation	-	
4th consultation	-	
5th consultation	-	
PT discussed step goals n/N (%)		
1st consultation	-	
2nd consultation	-	
3rd consultation	-	
4th consultation	-	
5th consultation	-	
Self-reported adherence to exercises (EARS)[17]		
12 weeks	-	
24 weeks	-	
Website access, n/N (%)		
Never		-
≥ 1 visit		-

[17] EARS (Exercise Adherence Rating Scale) range 0-24 with higher scores representing more adherence.

Supplemental table 8: Fidelity check for components of the intervention being completed at each consultation

Consultation Session [n/N (%)]	1	2	3	4	5
PT prescribed ≥ 3 strengthening exercises					
PT recorded sets, repetitions, and resistance band used for strengthening exercises					
PT reviewed Educational information					
PT discussed barriers to exercise					
Participant recorded exercises in log book					

Supplemental table 9: Treatment Expectations[18]

	Control	Intervention
Pre-randomization (%(n))		
No effect at all		
Minimal Improvement		
Moderate Improvement		
Large Improvement		
Complete Recovery		
Post-randomization		
No effect at all		
Minimal Improvement		
Moderate Improvement		
Large Improvement		
Complete Recovery		

[18] Study participants were asked to rate their expectations for treatment before and after randomization as 1: No effect at all, 2: Minimal Improvement, 3: Moderate Improvement, 4: Large Improvement, 5: Complete Recovery