Virtual Exercise Rehabilitation In-home Therapy: A Randomized Study (VERITAS)

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Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

VERITAS

ANALYSIS PLAN REVIEW and APPROVAL
Protocol Number: VERITAS Version 1.4

I have reviewed and agree to the planned analyses as set forth by this Statistical Analysis Plan for the VERITAS clinical trial.
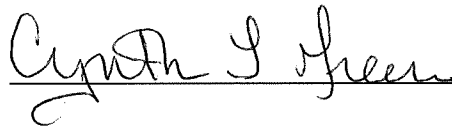
Reviewed and Approved by:

DCRI:

_____   _____

Janet Prvu Bettger, ScD, FAHA   Date
Associate Professor, Orthopedic Surgery
Primary Investigator

DCRI: *Cynth S Green* _____   08-MAY-2018

Cynthia Green, PhD   Date
Assistant Professor, Biostatistics & Bioinformatics
Statistical Investigator

Reflexion, Health, Inc.:   *Joe M Smith (A)*

_____   _____

Joe Smith   Date
Chief Executive Officer

Statistical Analysis Plan

VERITAS

Virtual **E**xercise **R**ehabilitation **I**n-home **T**herapy: **A** Randomized **S**tudy

Protocol Number
VERITAS Version 1.4

Protocol History
Original   March 2, 2017

Study Intervention
VERA™ in the home with virtual PT support

Sponsor
Reflexion Health, Inc.

SAP Version: 1.2

Date: May 8, 2018

Prepared by
Cynthia L Green, PhD
Assistant Professor of Biostatistics
Duke Clinical Research Institute

CONFIDENTIAL

ANALYSIS PLAN REVIEW and APPROVAL
Protocol Number: VERITAS Version 1.4

I have reviewed and agree to the planned analyses as set forth by this Statistical Analysis Plan for the VERITAS clinical trial.

Reviewed and Approved by:

DCRI: _____   _____

        Janet Prvu Bettger, ScD, FAHA   Date
        Associate Professor, Orthopedic Surgery
        Primary Investigator

DCRI: _____   _____

        Cynthia Green, PhD   Date
        Assistant Professor, Biostatistics & Bioinformatics
        Statistical Investigator

Reflexion Health, Inc.: _____   5/10/2018

        Joe Smith   Date
        Chief Executive Officer

1   MODIFICATIONS TO ORIGINAL SAP

- Section 9.10 (page 23): Corrected costs assigned to PT visits in Control group cost formula from $210 to $133, to match costs listed in table above

2 LIST OF ABBREVIATIONS

Abbreviation	Description
6MWT	Six minute walk test (i.e., distance walked in 6 minutes)
AE	Adverse Event
ANOVA	Analysis of Variance
BMI	Body Mass Index
CRF	Case Report Form
D/C	Discharge
DCRI	Duke Clinical Research Institute
DMC	Data Monitoring Committee
DUMC	Duke University Medical Center
ER	Emergency Room
GCP	Good Clinical Practice
IC	Informed Consent
IRB	Internal Review Board
ITT	Intent-to-Treat
KG	Kilogram
KOOS	Knee Injury and Osteoarthritis Outcome Score
M	Meter
MCID	Minimal Clinical Improvement Difference
MITT	Modified Intent-to-Treat
PI	Principal Investigator
POST-OP	Postoperative
PT	Physical Therapy / Physical Therapist
PROMIS	Patient-Reported Outcomes Measurement Information System
QC	Quality Control
QOL	Quality of Life
ROM	Range of Motion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Statistical Operating Procedure
TKR	Total Knee Replacement
US	United States
Vera™	Virtual Physical Therapy Delivery System

3   QUALITY CONTROL

All tables, listings, and graphs will be reviewed by the lead and faculty statisticians before considered final. The quality control process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. While independent programming (second verification) will not be done, tables will be reviewed for accuracy, consistency with this analysis plan, consistency within tables, and consistency with corresponding output.

4   PURPOSE AND SCOPE OF STATISTICAL ANALYSIS PLAN

The purpose of this analysis plan is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous manner. Specifically, this plan will:

- Give a brief overview of the protocol, study design and study objectives

- Outline the types of analyses and presentations of data that are relevant to the primary and secondary study objectives (efficacy and safety)

- Explain how the data are analyzed, adhering to commonly accepted standards and practices of statistical analysis

The scope of this plan applies to the analyses as presented in the clinical protocol only and does not include any analyses for exploratory purposes. Documents used in the preparation of this statistical analysis plan include the study protocol (Final Protocol dated March 2, 2017) and Case Report Forms (CRF) including Randomization (dated August 17, 2016), Baseline Data (October 17, 2016), Baseline Survey (dated August 17, 2016), Discharge (dated August 17, 2016), 6-week Data (dated August 17, 2106), 6-week Survey (dated February 5, 2017), 3-month Survey (dated February 5, 2017), and Patient Diary (dated August 17, 2016). The statistical plan described is an *a priori* plan and no analyses or data review by randomized treatment group prior to the preparation of this plan have been conducted. The Duke Clinical Research Institute (DCRI) will oversee all statistical analyses detailed in this analysis plan. This document defines the populations to be analyzed and provides full details of the statistical analyses, data displays, and algorithms to be used for data derivations to aid in the production of the statistical output.

5 OVERVIEW

As background for the statistical methods presented below, this section provides an overview of the study objectives and design. It must be understood that this overview is a summary only, and that the protocol is the definitive reference for all matters discussed in what follows.

5.1 Rehabilitation for Total Knee Replacement

Physical therapy (PT) is an important component of care for patients who have total knee replacement (TKR) surgery. The focus of this rehabilitative care is to promote mobilization and the achievement of functional goals. A meta-analysis evaluating the effectiveness of post-surgical PT in 18 randomized clinical trials for a total of 1,739 patients with primary TKR concluded that patients who received PT had improved physical function and decreased pain at 3-4 months after hospital discharge, and the benefit extended to 6 months in some studies.[1] In the United States, PT after hospital discharge is provided in rehabilitation facilities, in the home by home health therapists, and in community-based clinics. Although widely supported as the standard of care with evidence of effectiveness, there is significant variation in what is provided, to whom, and for what duration. Post-acute care including utilization of PT for joint replacement is the single largest driver in the variation of Medicare spending.[2]

Gaps exist in the ability of PT to support all patients in need, including a projected nationwide shortage of therapists, few therapists available in underserved areas, and limited numbers of PT visits covered by insurance for those who have it. These gaps make it necessary to develop other effective, low-cost and accessible options to help patients regain physical function after TKR, and improve pain and other patient-centered outcomes.

5.2 Study Purpose

This randomized clinical trial will compare the costs and clinical effectiveness of traditional PT versus a technology-supported home-based PT rehabilitation program for patients with TKR. The primary aim of this project is to determine if a technology-supported home-based PT rehabilitation program is a cost-saving approach and at least clinically equivalent to traditional PT.

5.3 Study Rationale

The use of digital technology where the patient and therapist can interact both in real-time and asynchronously (e.g., patient completes recommended activities and therapist reviews performance at different times) can alleviate scheduling issues for both the therapists and patients, allowing therapists to potentially manage more patients (higher case load) and patients to follow recommendations and complete activities when most convenient. Having the PT program entirely available to the patient via technology may be cost efficient for both the patient and health system as more therapy sessions could be completed by the patient on their own schedule, without co-pays, and requiring less real-time PT supervision over time.

6 OVERVIEW

6.1 Synopsis

This is a multi-center, randomized, clinical trial to evaluate the costs and clinical effectiveness of technology-supported home-based physical therapy (PT) compared with traditional PT in the home or clinic. Duke University and Duke Clinical Research Institute (DCRI), along with the sponsor, Reflexion Health, Inc., will be responsible for the design, implementation, and leadership of the VERITAS study. Data analysis and publications will be managed according to a written plan designed to maintain appropriate scientific oversight and rigor by the DCRI. A Data Monitoring Committee (DMC) will not be used.

This trial will include subjects scheduled for a total knee replacement (TKR), as defined by protocol inclusion and exclusion criteria. All subjects will receive standard of care as defined by current site-specific and local guidelines for the management of TKR.

A total of 300 randomized subjects are planned for this study. Subjects will be randomized in a 1:1 ratio, stratified by site, to receive either tele-rehab-supported PT or traditional home and/or clinic-based PT.

6.2 Study Objectives

6.2.1 Primary Objective:

The primary objective is to compare the effects of tele-rehab-supported PT versus traditional home and/or clinic-based PT for TKR on health service use costs at 12-weeks postoperative.

Hypothesis (Superiority Test): Patients who receive tele-rehab-supported PT will have lower total episode of care costs compared with patients in the traditional PT group at 12-weeks.

6.2.2 Secondary Objective:

The secondary objectives are to compare tele-rehab-supported PT and traditional PT on patient-centered outcomes as follows:

a. Effectiveness hypothesis (Non-Inferiority Test): The tele-rehab intervention will be non-inferior to traditional PT at 6 weeks (differences between groups <5% for clinical and patient-reported outcomes) and 12 weeks (difference <5% patient-reported outcomes).

b. Safety hypothesis (Non-Inferiority Test): The tele-rehab intervention will be non-inferior to traditional PT at 12 weeks (pain, falls, and self-reported number of re-hospitalizations).

6.2.3 Exploratory Objectives:

The final objectives (exploratory analyses) are to determine if superiority between PT methods exist for the endpoints primarily tested for non-inferiority, determine whether individual patient characteristics are associated with differential improvement from 6 to 12 weeks assessed by patient-reported outcomes, and to determine the cost for the VERA system such that the cost between the control group and intervention groups is cost-neutral, assuming that the intervention group is determined to cost less.

7 Study Design

7.1 Overview

VERITAS (Virtual Exercise Rehabilitation In-home Therapy: A Randomized Study) is a multi-center randomized clinical trial aimed at evaluating both the costs and clinical effectiveness of technology-supported home-based physical therapy (PT) compared with traditional PT in the home or clinic. Patients in both groups will be prescribed exercises by a physical therapist. The trial is focused on the delivery of the PT program: VERA™ in the home with virtual PT support compared to PT provided through traditional methods (e.g., home health, clinic, or printed instructions). This study will recruit patients at approximately 6 surgical practice groups (either one site or group of local sites) to enroll 300 patients with unilateral total knee replacement (TKR) who are planned to return home after hospital discharge.

Once authorized to begin, sites will pre-screen patients scheduled for TKR for eligibility. The baseline study visit will be completed at least 10 days prior to surgery. After informed consent is obtained, patients will complete the baseline assessments and be randomized to either tele-rehab supported PT (Vera™) or traditional PT. Intervention group patients will have the tele-rehab system installed in their home prior to surgery, virtually meet the physical therapist, receive recommendations for a pre-operative exercise program ("prehab"), and continue the recommended tele-rehab PT program after hospital discharge until discharged by the physical therapist. Control group patients will follow the clinical team's recommendations for PT as organized and delivered in traditional care (home health, clinic, paper instructions). There are no differences in risk to patients between the two study arms.

Data will be collected at the following time points, and is detailed in Table 1 below:

- Pre-enrollment: Screening log (monthly submission)
- Baseline (≥10 days prior to surgery): Randomization CRF, patient contact information and medical record release, patient surveys, and baseline case report form (CRF)
- Hospital discharge: CRF
- 6 weeks after surgery: CRF, patient surveys, and patient diary (collected by DCRI Call Center)
- 12 weeks after surgery: Patient surveys and patient diary (collected by DCRI call center), as well as chart review for service utilization (among select sites)

Activity	Screening	Enrollment / Baseline	D/C	6 weeks post-op	12 weeks post-op
Table 1: Schedule of Assessments					
Complete screening log for all patients	X[1]				
Invite patient to participate via letter or other IRB-approved method	X[2]	X[2]			
RAPT score and living situation assessment	X[2]	X[2]			
Consent and randomization		X[3]			
Medical record release, patient contact form		X			
Gait speed measurement		X[4]	X[4]	X[4]	
Range of motion measurement				X[4]	
Data collection form entered in DCRI Registry System		X	X	X	
Chart review for health resource use					X
Patient-reported health outcomes*					
KOOS		X[5]		Call Ctr	Call Ctr
PROMIS Global Health		X[5]			Call Ctr
Satisfaction with Physical Function		X[5]			Call Ctr
Adherence to PT regimen				Call Ctr	Call Ctr
Pain[6]			X[4,6]	Call Ctr[6]	
Falls		X[5] (in prior 3m)	X[4]	Call Ctr	Call Ctr
Physical activity		X[5]		Call Ctr	Call Ctr
Healthcare encounters / service use		X[5] (hosp. in prior 3m)		Call Ctr (pt diary)	Call Ctr (pt diary)
Thoughts about tele-rehab system[7]					Call Ctr

* Two additional outcomes were incorporated into the 6 and 12 week interviews, addressed in elsewhere in the protocol: return to work and personal recovery goal.

[1] Submitted monthly via email to DCRI Coordinating Center.

[2] Completed at either time point as approved by local IRB.

[3] If surgery date is unknown at time of consent, randomization may be delayed, but must occur no less than 10 days prior to surgery.

[4] Results recorded in medical record and entered on data collection form in DCRI Registry System.

[5] Baseline assessments collected by study site and faxed to DCRI Call Center.

[6] Collected using pain scale from PROMIS survey when full PROMIS is not administered.

[7] Collected only among patients randomized to tele-rehab.

7.2 Study Effectiveness and Safety Endpoints

7.2.1 Primary Effectiveness Endpoint

The total health service use costs at 12-weeks postoperative will be compared between patients who receive tele-rehab-supported PT versus traditional home and/or clinic-based PT for TKR.

For this analysis, the cost for each group will be determined by assigning pre-determined costs for activities collected in the patient's diary. A diary form will be given to each patient after randomization, as a method to support recall of healthcare interactions during the 6- and 12-week follow-up interviews. Patients will be instructed to use the diary to collect any interactions with the healthcare system that occur after they are discharged from the

hospital following their surgery. Encounters of interest will include in-person PT visits, doctor visits, phone calls or emails to a PT or doctor, visits to an urgent care center or emergency room, and hospitalizations. Data recorded on the diary will be collected from the patient verbally by the DCRI Call Center during the planned follow-up interviews

7.2.2   Secondary Endpoints Compared at 6 Weeks Postoperative for Non-inferiority

Standard clinical follow-up for TKR patients occurs approximately 6 weeks after surgery. At this routine visit, patients will be administered standard clinical assessments for gait speed and range of motion (ROM) in the operated knee. The DCRI call center also captures patient-reported outcome measured 6 weeks after surgery.

Non-inferiority effectiveness endpoints:

1.   Survey regarding health [Knee Injury and Osteoarthritis Outcome Score (KOOS)] for pain, symptoms, activities of daily living, function in sports and recreation, and knee-related quality of life (QOL)
2.   Knee ROM [lower (extension) and upper range of motion (flexion)]
3.   Gait Speed

7.2.3   Secondary Endpoints Compared at 12 Weeks Postoperative for Non-inferiority

At approximately 12 weeks after surgery, the patient will be contacted again by the DCRI Call Center to collect the following data via telephone interview:

Non-inferiority effectiveness endpoints:

1.   Survey regarding health (KOOS)

Non-inferiority safety endpoints:

1.   Pain score
2.   Any fall reported between hospital discharge and 12-week follow-up (yes/no)
3.   Re-hospitalizations since hospital discharge (total count)

7.3 Additional Secondary Endpoints

Additional secondary endpoints are collected at 6 and/or 12 weeks post-operatively that are not part of non-inferiority testing for effectiveness or safety. Superiority testing will be completed for all non-inferiority endpoints and these additional secondary endpoints below.

Endpoints collected and compared at 6 weeks:

1. KOOS subdomain scores
2. Physical activity (duration of moderate exercise in total minutes per week)
3. Return to work by 6 weeks (yes, modified schedule, or no)

Endpoints collected and compared at 12 weeks:

1. KOOS subdomain scores
2. Patient-Reported Outcomes Measurement Information System (PROMIS) – Physical Health (PH)
3. Patient-Reported Outcomes Measurement Information System (PROMIS) – Mental Health (MH)
4. Satisfaction with Physical Function (questionnaire)
5. Physical activity (duration of moderate exercise in total minutes per week)
6. Return to work by 12 weeks (yes/modified schedule/no)
7. Satisfaction with tele-rehab platform (*intervention patients only thus just tabulated*)

Endpoints collected at both 6 weeks and 12 weeks post-operatively but compared only at 12 weeks (*patient diary and interview data that need to be combined to represent the entire 12 weeks*):

1. Adherence to prescribed PT regimen (# days per week, adherence [5 categories], and reasons for not done as prescribed)
2. Healthcare encounters – 8 types (total PT visits, calls/emails to PT, MD office visits, MD phone calls/emails, re-hospitalizations, urgent care or ER visit, inpatient re-habilitation stay, and skilled nursing facility stay)
3. Progress toward personal recovery goal [actual score, score=10 (yes/no), and time to meeting goal]

7.4 Exploratory Endpoints

Exploratory endpoints will include effectiveness endpoints evaluated for superiority, as well as comparison of change over time for endpoints assessed at multiple time points both within and between treatment groups.

Effectiveness and safety endpoints evaluated for superiority:

1. ROM (upper and lower) at 6 weeks
2. Gait speed (6 weeks)
3. Pain score (6 and 12 weeks)
4. KOOS overall score (6 and 12 weeks)

Effectiveness and safety endpoints evaluated for change over time:

1. Change in KOOS (baseline-6 weeks, 6-12 weeks and baseline-12 weeks)
2. Change in gait speed (hospital discharge to 6 weeks)
3. Change in pain score over time (discharge to 6 weeks, 6-12 weeks, and discharge to 12 weeks)

Other secondary endpoints evaluated for change from baseline to 12 weeks:

1. Progress toward recovery goal
2. PROMIS Global and Mental Health
3. Satisfaction with Physical Function
4. Physical activity

7.5 Randomization

It is anticipated that a total of 306 subjects will be randomized to one of the two treatment groups. Once a subject has provided informed consent and eligibility criteria have been confirmed, the site-designee will access the secure, study website to randomize the subject and receive the subject's assignment number. While the subjects, Investigator, and Sponsor are not blinded to treatment assignment due to study implementation requirements, aggregated data will remain blinded to all until the database is locked.

Subjects will be randomized by site in a 1:1 ratio to receive either tele-rehab-supported PT or traditional home and/or clinic-based PT. In either case, randomization must occur no less than 10 days prior to the patient's surgery date, or the patient will be considered ineligible.

8 DATA SOURCES

8.1 DCRI Registry System

Enrollment and randomization of subjects will be handled by a secure, password protected web-based electronic data collection tool (DCRI Registry System) for site coordinators to abstract medical record information about each patient after informed consent is obtained. Collection time points include randomization, baseline (enrollment visit), hospital discharge, and 6 weeks after discharge.

8.2 DCRI Call Center

DCRI Call Center staff will contact all patients via telephone approximately 6 and 12 weeks after hospital discharge to administer the follow-up surveys/assessments and collect details from the patient diary.

8.3 Adverse Events

Reporting of any adverse events discovered during the course of the study will be the responsibility of care providers at the local site and should be made using the appropriate mechanism (e.g., FDA Medwatch).

8.4 Final Study Report

The final study report will be based on data collected either through the DCRI Registry System (CRF data) or DCRI Call Center (survey/questionnaire and patient diary data).

9 GENERAL METHODOLOGY

Descriptive statistics will be grouped into three categories: Tele-rehab PT, Traditional PT, and Overall. Continuous variables will be summarized by the number of observations and the mean, standard deviation, median, minimum, and maximum values. For categorical data, the counts, denominators and percent per category will be presented within non-missing observations. Subjects with a missing value for a variable will not be included in the calculation for that variable. All continuous data will be summarized with one more significant digit than in the dataset. Percentages will be rounded to one digit to the right of the decimal. Subjects with missing categorical data will not be included in calculations of percentages for that variable unless otherwise specified. No imputation will be made for missing values. Both the frequency and the associated denominator will be shown to facilitate review of missing categorical data. Categorical responses of "Unknown" will be set to missing.

It is anticipated that both the 6- and 12-week follow-up calls will not occur exactly at 6 and 12 weeks post-op, respectively, for every patient. However, the DCRI Call Center is instructed to contact subjects as close as possible to the appropriate time since postoperative discharge date. Data needed for the primary endpoint will be prioritized if patients agree to spend only a limited time on the follow-up call.

All statistical tests will be one-sided (non-inferiority) or two-sided (superiority) with a significance level of 0.05, unless otherwise documented. Tests for differences between treatment groups for endpoints that are not protocol-specified may be performed. Unless otherwise stated, continuous variables will be compared between groups with two-sample student t-test or with Wilcoxon's rank-sum test depending on normality assumptions.

When it is necessary to detect differences between groups, unless it is stated otherwise, categorical values will be compared using the chi-square test or Fisher's exact test. The chi-square test will be used when all cells in the table of the categorical comparison have an expected value of 5 or above. Otherwise, a Fisher's exact test will be performed.

All tables will be presented with summary statistics overall and by treatment group unless otherwise specified.

All analyses will be completed using SAS version 9.4 or higher.

9.1 Data Management

The final transfer to the sponsor will include all tables, listings, graphs supported by this analysis plan in PDF format. All analysis datasets and documentation (analysis dataset programming specs) that support statistical analyses included in this analysis plan will be made available upon request from the sponsor. All data and documents requested will be transferred to the sponsor by using a secure transfer method.

9.2 Analysis Populations

Modified Intent-to-Treat: All safety and effectiveness measures will be analyzed on a modified intent-to-treat basis. Modified means that only patients who complete the TKR

procedure will be analyzed according to the treatment in which they were randomized, regardless of whether or not they completed all protocol requirements. As such, all randomized and TKR surgical patients will be included in the Modified Intent-To-Treat (MITT) Population. The exception will be if a patient withdraws consent to participation and requests in writing that all data previously collected be removed from the study.

Subjects who are randomized but do not have a TKR procedure will be noted in subject-specific listings but will not be included in tabulated results. This will include subjects who have not received their surgery at the cut-off time designated by the study team, so that close-out procedures and statistical compilation of data can be done.

9.3   Data from Multiple Sites

The VERITAS study is a multi-center clinical trial within sites in the United States. Approximately six orthopedic surgical practice groups will be selected to enroll patients in the trial. Sites will be identified and approached based on estimated surgery volume, and the availability of staff resources to support successful participation. Site selection will be limited geographically to a 50-mile radius around the Durham-Chapel Hill Comprehensive Joint Replacement (CJR) bundle region to minimize the variation of in-hospital costs. Site start-up may be staged to allow for controlled run-in of the first patients at each site.

The site where a subject was randomized is included as part of the randomization strata. Exploratory analyses will include assessing the influence of site on treatment effects for both the primary and secondary endpoints. This will be done by adding a fixed-effect main site effect and interaction term between randomization strata (site) and treatment in a generalized linear model used to analyze the primary and secondary endpoints. This is described in more detail in Section 9.12 of this document.

9.4   Accounting for Missing Data

Missing data will not be imputed. We will analyze only available information.

9.5   Randomization Form

A randomization summary will be completed overall and by treatment group. This list will include the total patients randomized by site, as well as the number of site months (time from first consented patient until the date of database lock) for each site and treatment group. Additional items collected at randomization will include enrollment information, as well as inclusion and exclusion criteria.

Data within the Randomization CRF will be tabulated using counts and percentages overall and by treatment group. No formal statistical comparisons will be done.

The consent date for patient ID "04-119" will be recoded as 2/23/17 in the randomization dataset.

9.6 Baseline Data Collection Form

9.6.1 Demographics

Baseline demographic and patient characteristic data (including age, sex, height, weight, race, ethnicity, marital status, work status and insurance) will be tabulated overall and compared by treatment group. Race will also be categorized as White, Black, Other or Multiple races for statistical comparative purposes. Body mass index (BMI) will be computed using height and weight [BMI = weight (kg) / height^2 (m^2)].

9.6.2 Medical History and Physical Assessments

Medical history and comorbidities will be summarized overall and compared by treatment group using frequency counts and percentages. Continuous assessments including height, weight, 10-meter gait speed (if collected), heart rate and blood pressure and will be summarized overall and by treatment group as n, mean, standard deviation (SD), median, 25th and 75th percentiles, min and max with comparisons between groups using the appropriate method based on the variable distribution.

9.6.3 Baseline Patient Survey

Self-reported history and activity level will be summarized overall and by treatment group and will be compared between treatment groups using appropriate statistical methods.

Additional survey data collected will include personal recovery goals (goal and current score), the Satisfaction with Physical Function Survey, the PROMIS Global Health Survey, and the KOOS Knee Survey Questionnaire. Responses will be tabulated overall and by treatment group for each individual question response; however, no statistical comparisons will be done.

The overall scores generated from each of the Satisfaction, PROMIS and KOOS surveys (overall and subdomain scores) at baseline will be compared between treatment groups using the appropriate statistical procedure to evaluate baseline balance.

9.7 Discharge Data Collection Form

Summary of patient disposition will include time from consent until time of surgery (TKR) and time from surgery until discharge, both measured in days. Other data that will be summarized overall and by treatment group include discharge status, procedure completion status, pain score, 10-meter gait speed, and falls during the hospital stay. Discharge destination will also be summarized as home vs. other for statistical comparative purposes.

9.8 Follow-up Data Collection Forms

9.8.1 6-Week Data Collection

Standard clinical follow-up for TKR patients occurs approximately 6 weeks after surgery. At this routine visit, patients will be administered standard clinical assessments for gait speed and range of motion (ROM) in the operated knee. Six-week data captured will

include the time from surgery until the date of the 6-week visit in days. Ten-meter gait speed and range of motion (ROM) upper and lower scores will be tabulated overall and by treatment group. Comparisons between treatment groups will be based on an analysis as described Sections 9.11 and 9.12.

9.8.2   6-Week Patient Survey

The DCRI call center captures patient-reported outcome measured 6 weeks after surgery, including fallen since hospital discharge (yes/no), pain score, physical activity (frequency and duration of exercise) and return to work (yes/no, and if yes, same or modified schedule). These 6-week variables will be summarized overall and by treatment group.

The KOOS Knee Survey Questionnaire will also be administered at 6-weeks. Responses will be tabulated overall and by treatment group for each question response as well as for the total score; however, no statistical comparisons will be done on the individual responses. The KOOS junior can be used at the 6-week visit. The overall KOOS scored will be evaluated for both superiority and non-inferiority at 6-weeks, while the KOOS subdomain scores will only be compared for superiority as part of the exploratory analyses.

9.8.3   3-Month Patient Survey

At this visit, patients will be again be contacted by the DCRI call center to capture patient-reported outcomes, including fallen since last interview (yes/no), pain score, total re-hospitalizations since discharge, physical activity (frequency and duration of exercise) and return to work (yes/no, and if yes, same or modified schedule).

Additional survey data collected will include the Satisfaction with Physical Function Survey, the PROMIS Global Health Survey, the PROMIS Global Mental Survey, and the KOOS Knee Survey Questionnaire. Responses will be tabulated overall and by treatment group for each question response; however, no statistical comparisons will be done for the individual responses. The overall KOOS score and individual subscale scores will be compared. The KOOS junior cannot be used at the 3 month time point for efficacy analysis but can be used to evaluate change from 6 weeks to 3 months.

The Net Promoter Score (how likely it is that you would recommend virtual physical therapy) will also be summarized within the subjects randomized to virtual rehab on a scale from 0 (not likely) to 10 (likely).

Additional variables collected at both 6- and 12-weeks but compared only at 12-weeks include healthcare encounters, adherence to prescribed PT regimen ((# days per week, adherence [5 categories], and reasons not done as prescribed) and progress toward personal recovery goal will be summarized using both categorical and continuous variables. Each type (PT visit, PT call/email, doctor visit, doctor call/email, urgent care visit, ER visit and hospitalization) will be summarized as incidence rate (Yes/No) and the number of encounters.

9.9 Power and Sample Size Calculations

The primary aim of this study is to assess the difference in outpatient post-surgical costs between the control and intervention groups at 12-weeks post-operative. The exact post-procedure cost estimates under study are unknown; however, we can estimate that an effect size of approximately 0.33 can be detected with 150 subjects per group with at least 80% power. The effect size is the ratio of the mean difference over the standard deviation (SD) assumed for each population. Lower variability would enable detection of a smaller cost difference, or the detection of a larger difference with fewer patients. The sample size estimates were made assuming a two-sample t-test with equal variance and a significance level of 0.05. Thus, with 300 subjects we can detect an effect size of 0.33 which represents a whole scenario of cost differences that can be detected with at least 80% power that is dependent on the variability of the costs under study. The below table illustrates some example cost differences that could be detected based on the assumed SD of the costs.

Standard Deviation (SD)	Mean Cost Difference ($)		Standard Deviation (SD)	Mean Cost Difference ($)
100	32.50		800	259.60
200	64.90		900	292.10
300	97.40		1000	324.50
400	129.80		1100	357.00
500	162.30		1200	389.50
600	194.70		1300	421.90
700	227.20		1400	454.40
750	243.40		1500	486.80

9.10 Primary Effectiveness Analysis

The total health service use costs at 12-weeks post-operative will be compared between patients who receive tele-rehab-supported PT (virtual group) versus traditional home and/or clinic-based PT (control group) for TKR. The primary cost comparisons will be done using an analysis of variance (ANOVA) method for continuous variables if (1) the dependent variable is normally distributed or (2) can be normalized using a transformation such as the logarithm or square root. The underlying assumptions of the statistical test procedure will be verified through non-normality tests and plots. If there is strong evidence that the assumptions are not met or cannot be met with an appropriate distribution, the nonparametric Wilcoxon Rank sum test will be used.

The total health service use costs at 12-weeks post-operative will be the primary effectiveness endpoint for this study. This will be calculated using a fee-for-service model and assigned costs. Tele-health for rehabilitation services was not a reimbursable service at the start of the trial, and thus a total intervention cost, including direct and indirect time with physical therapy and any in-person visits, is assigned using the following units and costs:

Healthcare Encounter	Unit	Cost
Intervention	Total (all interactions)	$600
Home health PT	<5 visits (cost per visit) ≥5 visits (single cost per 60-day episode)	$133 $2,325
Outpatient clinic PT	Single visit	$90
PT call/email	Single interaction	n/a
Doctor's office	Single visit	$150
Doctor's office call/email	Single interaction	n/a
Urgent care or ER visit	Single visit	$250
Re-hospitalization	Full length of one inpatient stay	$7,825
Inpatient rehab facility	Full length of stay	$10,720
Skilled nursing facility	Full length of stay	$6,510

Intervention Group Patients: Total costs will be calculated as the assigned cost of the intervention plus assigned costs for any reported doctor's office visits, urgent care or ER visits, re-hospitalizations, and inpatient rehabilitation or skilled nursing facility stays in the 12 weeks following discharge from the surgical hospital stay. The formula is as follows:

> **Cost** = intervention cost + (# of doctors office visits * $150) + (# of ER/UC visits * $250) + (# of re-hospitalizations * $7,825) + (# of skilled nursing facility stays * $6,510) + (# of inpatient rehabilitation facility stays * $10,720)

The cost formula for the intervention group is computed under the assumption that intervention patients do not require home health or outpatient clinic PT visits and that the costs of virtual PT are negligible. Based on the diary data collected, we can't distinguish the costs between in-person or virtual PT without additional data collected from PT therapist reports or external data sources.

Control Group Patients: Total costs will be computed using data obtained from the 6-week and 3-month patient diaries reported to the call center based on PT visits, doctor's office visits, urgent care or ER visits, re-hospitalizations, and inpatient rehabilitation or skilled nursing facility stays. The formula is as follows:

> **Cost** = (confirmed home health and dates of service and then (1) # PT visits within those dates * $133, if # PT visits <5 or (2) Single cost per 60-day episode of $2,325, if # PT visits ≥5) + (confirmed outpatient clinic and dates of service and then # of PT visits within those dates * $90) + (# of doctors office visits * $150) + (# of ER/UC visits * $250) +(# of re-hospitalizations * $7,825) + (# of skilled nursing facility stays * $6,510) + (# of inpatient rehabilitation facility stays * $10,720)

Additional "cost formula rules" when assigning cost are as follows:

1) For healthcare encounters occurring **in between** a transition of care **stop date and start date or the start date is missing**, assign the location of care to the prior interval care location.

2) For healthcare encounters occurring **on the same day** as the **stop date and start date** for a transition of care interval, assign the location of care to the prior interval care location.

3) For healthcare encounters with known month and year, but unknown day of the healthcare encounter date, assign healthcare encounter to the first active care type of the month.

4) Healthcare encounter for patient ID "04-116" occurring on 4/31/2017 will be removed from the healthcare encounter dataset.

5) Home health visits within one week of the 60-day episode window were counted as within the 60-day episode of care to account for errors in self-reporting.

The null hypothesis for the primary endpoint is that there is no treatment difference between patients who receive tele-rehab-supported PT versus traditional home and/or clinic-based PT. The alternative hypothesis is that a treatment difference exists between patients who receive tele-rehab-supported PT versus traditional home and/or clinic-based PT.

Let μ_T and μ_C be the average total health care costs for the virtual and control PT groups, respectively. The null hypothesis and the alternative hypothesis will be as follows:

$$H_0: \mu_T = \mu_C$$
$$H_A: \mu_T \neq \mu_C$$

The primary statistical method for the hypothesis test will be t-test, and the mean difference between groups will be presented with a 95% confidence interval (CI). The test is two-sided even though we are more interested in determining that the intervention group is superior to the control group to allow for a possible negative significant difference.

Let $\bar{X}_T$ and $\bar{X}_C$ be the sample mean costs for the virtual and control groups, respectively, and let S_T^2 and S_C^2 be the sample variance for the virtual and control samples, respectively. The equality of the variances of the two samples will be tested using the Folded *F*-test (i.e., F=Max$(S_T^2, S_C^2)/\min(S_T^2, S_C^2)$). If there is not strong statistical evidence to say that the variances of the two samples are different (insignificant *F*-test and 4-fold variance difference), then the alternative hypothesis for total cost will be concluded when the associated *t*-test statistic assuming equal variance is less than the 2.5th percentile of the Student's *t* distribution with $n_T + n_C - 2$ degrees of freedom, where n_T is the number of subjects in the virtual group and n_C is the number of subjects in the control group. Otherwise, the *t*-test will be computed assuming the variances are unequal.

If a parametric method is determined not to be possible through normality checks (Shapiro-Wilks test) or transformations, a Wilcoxon rank-sum test will be performed for the primary effectiveness endpoint and a 95% CI for the median difference presented.

9.11 Secondary Analyses for Effectiveness and Safety

The secondary effectiveness and safety endpoints will include both clinical and patient-reported outcomes at 6-weeks and 12-weeks postoperatively. The secondary objectives are to compare tele-rehab-supported PT and traditional PT on patient-centered outcomes as follows.

9.11.1 Effectiveness hypothesis (Non-Inferiority Test)

The tele-rehab intervention will be non-inferior to traditional PT at 6 weeks (differences between groups <5% for clinical and patient-reported outcomes) and 12 weeks (difference <5% patient-reported outcomes). The secondary objectives are to compare tele-rehab-supported PT and traditional PT on patient-centered outcomes as follows:

- 6 Weeks:

    - KOOS: Total score based on a normalized scale of 0-100 (worst to best). The minimal perceptible clinical improvement difference (MCID) for non-inferiority that we will use is 10 points.

    - ROM: This is reported to reflect both extension (lower) and flexion (upper) range of motion. An MCID is not available and based on recent literature we will use 6.3 degrees for extension and 9.6 degrees for flexion.

    - Gait Speed (m/sec): MCID is 0.1 m/s

- 12 Weeks:

    - KOOS: The minimal perceptible clinical improvement difference (MCID) for non-inferiority will be 10 points.

Analyses for each endpoint will be similar to those considered in Section 9.10 for the primary cost endpoint, except the tests will be one-sided for non-inferiority. A one-sided 95% confidence interval for the mean difference between intervention groups will be completed using parametric methods if possible; otherwise, the median difference will be utilized.

Non-inferiority will be determined if the upper bound of the difference indicative of treatment benefit in the control group is less than the MCID for each endpoint. No adjustment for multiple comparisons is necessary since all tests must be significant to determine non-inferiority (intersection-union multiple testing rule) for effectiveness.

9.11.2 Safety hypothesis (Non-Inferiority Test)

The tele-rehab intervention will be non-inferior to traditional PT at 12 weeks using the following endpoints at 12 weeks:

- Pain: The minimal perceptible clinical improvement difference (MCID) for non-inferiority will be 1.7

- Re-hospitalizations: The total number of re-hospitalizations will differ by no more than 1.

- Falls: The percentage of subjects reporting any fall from index hospital discharge until 12 weeks postoperative will differ by no more than 10% (reported at 6 and 12 weeks as a categorical yes/no response).

A one-sided 95% confidence interval for the mean difference between intervention groups will be completed using parametric methods if possible; otherwise, the median difference will be utilized. Non-inferiority will be determined if the upper bound of the difference indicative of a treatment benefit in the control group is less than the MCID for each endpoint. No adjustment for multiple comparisons is necessary since all tests must be significant to determine non-inferiority (intersection-union multiple testing rule) for the safety hypothesis.

9.12 Other Exploratory Analyses

The final objectives (exploratory analyses) are to determine if superiority between PT methods exist for the endpoints primarily tested for non-inferiority, determine whether individual patient characteristics are associated with differential improvement from 6 to 12 weeks assessed by patient-reported outcomes, and to determine the cost for the VERA system such that the cost between the control group and intervention groups is cost-neutral, assuming that the intervention group is determined to cost less. The secondary endpoints that will be considered are detailed in Sections 7.2-7.4.

An appropriate regression model may be considered for the primary cost endpoint to adjust for baseline variables found to be imbalanced or to assess the influence of site on treatment effects. This will be done by adding a fixed-effect main site effect and interaction term between randomization strata (site) and treatment in a generalized linear model. Assuming the average cost for the intervention group is lower than the control group, we will also determine the cost for the VERA system such that the cost difference between the control group and the intervention group is cost-neutral.

If the endpoints tested for non-inferiority between PT methods are found to be non-inferior, then additional analyses to control for baseline covariates or site effects may be done using methods previously described to determine if the PT group is superior to the control group after adjustment.

To determine whether individual patient characteristics are associated with differential improvement, we will evaluate the change over time (0-6, 0-12 and/or 6-12 weeks) for endpoints measured at multiple time points using parametric or non-parametric methods previously discussed. When both 6 and 12-week assessment are made, the Sidak alpha-correction method will be used to correct for multiple comparisons. The correction method is given by $1-(1-\alpha)^{1/k}$, where k is the number of comparisons considered. If adjustments for baseline covariates are necessary, generalized repeated measures models will be used to assess main effects of intervention group and time, as well as the interaction between time and intervention groups.

Progress toward recovery goal will be compared between PT groups using either a chi-square or Fisher's exact test for categorical responses (score=10 yes/no), Wilcoxon rank sum test for actual score and change from baseline score, and as time until meeting recovery goal (score=10) using the nonparametric log-rank test or Cox proportional hazards model.

9.13 Interim analysis

No interim efficacy or safety analysis will be performed for this study.

10 CHANGES IN ANALYSIS PLAN FROM ORIGINAL PROTOCOL

The secondary objectives within the protocol are to compare tele-rehab-supported PT and traditional PT on patient-centered outcomes using non-inferiority tests that evaluate whether or not differences between treatment groups are <5% for each effectiveness and safety endpoint. We propose instead to establish a non-inferiority margin for each endpoint as given in Section 9.11 based on previous literature and clinical experience.

11 FIGURES, TABLES AND LISTINGS

Table shells will be provided in a separate document.

12 REFERENCES FOR MCID

- KOOS
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC280702/
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC161802/

- Pain Score (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3779528)

- ROM (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958082)