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

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VERITAS

Virtual Exercise Rehabilitation In-home Therapy: A Randomized Study

Protocol

Version 1.4
March 2, 2017

CONFIDENTIAL

Contents

INVESTIGATOR AGREEMENT

I have read the VERITAS study protocol version 1.4 (March 2, 2017), including all appendices, and I agree that it contains all necessary details for my staff and me to conduct this protocol as described. I will personally oversee protocol conduct as outlined herein.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by DCRI or the sponsor. I will discuss this material with personnel to ensure that they are fully informed about the conduct of the protocol and the information being collected from patients enrolled in the VERITAS study. I am aware that, before commencement of this study at my clinical facility, the local (or central) institutional review board must approve this protocol. I agree to make all reasonable efforts to adhere to the VERITAS study protocol.

I, or my designee, agree to be present at all site visits and investigator meetings. In addition, I will ensure the presence of relevant study personnel under my supervision at these visits and meetings.

I agree to provide all subjects with a signed copy of the informed consent form, as required by government and International Conference on Harmonization regulations. I further agree to report to the DCRI any protocol deviations in accordance with the terms of this protocol, Good Clinical Practice Guidelines, and applicable regulatory requirements. All information pertaining to the protocol shall be treated in a confidential manner.

_____ _____

Principal Investigator Name (print) Signature

_____

Date

1. Background

1.1. 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. 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.

1.2. Integrating Technology into Post-surgical Joint Replacement Rehabilitation Care

A growing body of scientific literature exists with respect to leveraging technology in support of various approaches to tele-rehabilitation, which can be an innovative way to deliver PT after TKR to increase access to care without additional patient risks.[3-6] A Canadian study of tele-rehabilitation providing PT in real-time via video and audio interaction between therapist and patient demonstrated non-inferiority of outcomes compared with traditional in-person PT after TKR.[7] This was confirmed with a meta-analysis of tele-rehabilitation which also found patients were highly satisfied with the use of telerehabilitation.[8] Remote guidance and supervision address issues with geographic access due to lack of availability or transportation. However, the ratio of physical therapists to patients remains an issue, and total costs for care are likely similar once accounting for costs of technology and technological support.

1.3. Rationale for VERITAS Randomized Controlled Trial

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. 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.

2. Study Aims

The goals of this research study are the following:

1. To compare the effects of tele-rehab-supported PT versus traditional home and/or clinic-based PT for TKR on 90-day health service use costs.
   Hypothesis (Superiority): Patients who receive tele-rehab-supported PT will have lower total 90-day episode of care costs compared with patients in the traditional PT group.

2. To compare tele-rehab-supported PT and traditional PT on patient-centered outcomes
   a. Effectiveness hypothesis (Non-Inferiority): 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): The tele-rehab intervention will be non-inferior to traditional PT at 12 weeks (pain, self-reported number of re-hospitalizations and number of reported falls).

3. To explore whether individual patient characteristics are associated with differential improvement from 6 to 12 weeks assessed by patient-reported outcomes.

3. Study Design

3.1. General Overview

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

This study will be undertaken only after the site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of record has given full approval of the final protocol, informed consent form, and applicable patient recruitment materials. Site coordinators will also need to complete appropriate training on the protocol and data collection systems prior to being activated for enrollment. Participating sites may begin screening patients upon written authorization from DCRI Coordinating Center staff.

Once authorized to begin, sites will pre-screen patients scheduled for TKR for eligibility. Those appearing to meet the inclusion criteria will be approached by the site coordinator and invited to participate. Those who qualify and express interest will be scheduled to meet with the site coordinator when they come in for their pre-operative clinic visit. If the pre-operative visit timing is not conducive to enrollment, the site coordinator may schedule a separate visit for enrollment purposes. 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 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 capture will occur at the following time points, and is detailed in Table 1 below:

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

Table 1: Study Activities and Data Capture

Activity	Screening	Enrollment / Baseline	D/C	6 weeks post-op	12 weeks post-op
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

[1] Submitted monthly via email to DCRI Coordinating Center.
[2] Completed at either timepoint 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] BL 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.

3.2. Site Selection Criteria

Approximately 6 orthopedic surgical practice groups will be selected to enroll patients in the VERITAS clinical 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.

3.3. Patient Selection Criteria

3.3.1. Inclusion Criteria

Patients are eligible to be included in the trial if they meet the following criteria:

- ≥ 18 years of age
- Scheduled to have a non-traumatic TKR
- Can be enrolled a minimum of 10 days prior to surgery (in-person visit)
- Have a Risk Assessment and Prediction Tool (RAPT) score of ≥ 6 indicating expected discharge home after surgical hospitalization

3.3.2. Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

- Unable or unwilling to provide informed consent, including but not limited to cognitive or language barriers (comprehension)
- Scheduled for staged bilateral TKR
- Living in a nursing home prior to surgery

3.4 Study Arms

This study will enroll 150 patients into each of two groups, for a total enrollment of 300 patients.

3.4.1 Tele-rehab (Intervention) Group

The tele-rehab PT-supported system for this study is the Virtual Exercise Rehabilitation Assistant (VERA™) system developed by Reflexion Health. VERA™ is a cloud-based virtual tele-health system that functions using 3D motion tracking technology to measure motion, remotely monitor the effectiveness of a prescribed regimen, and provide detailed audible instructions and immediate feedback to patients on exercise quality. A therapist or other healthcare provider issues a therapy regimen through the clinician interface, and the VERA™ system installed in the patient's home delivers the therapy using interactive, motion-capturing technology and an avatar to demonstrate, track, and monitor the patient's exercise performance. Patients are able to view their own progress in the system and perform prescribed exercises and activities selected by the treating physical therapist. Performance is remotely monitored either in real-time or asynchronously, and as in traditional PT, the program of activities can be revised by the physical therapist to best match the progress of the patient. The therapist and patient can "meet" for virtual real-time appointments as needed. The VERA™ system received FDA 510(k) clearance in October, 2015, and is available on the public market for purchase by healthcare providers.

The coordinating center will organize VERA™ installation into patients' homes for those randomized to the intervention group. Participants will be contacted by staff of Reflexion Health to schedule installation after enrollment and prior to surgery. After installation, the intervention patients will virtually meet with the physical therapist to begin prehab. All patients in the intervention arm will have their PT regimen designed and monitored by a study PT based in the Duke Department of PT/OT, using the remote clinician interface that is incorporated into the VERA™ platform.

After the system is in the patient's home and the patient has spoken with the study therapist, s/he will be encouraged to access the system to begin pre-operative activities and become familiar with the system. Patients will be able to access the system as often as they like. Participants who do not interact with the system during the first 7 days after installation will be contacted by the study therapist encouraging them to begin.

Within 2 business days of hospital discharge, the study therapist will contact the patient to review the post-surgical PT program and recommend any changes to therapeutic activities or intensity. Participants will be encouraged to be as active with the program as their abilities, health conditions, and pain allow.

Patient progress will be monitored remotely by the study therapist. If at any time the study therapist feels that the patient requires additional support to ensure the success of their post-discharge therapy, s/he may escalate the patient back to the orthopedic surgeon's office for assessment. This assessment may include the prescription of supplemental PT with one or more local, in-person visits, at the orthopedic surgeon's discretion, to be completed in addition to continuing with in-home PT sessions via the tele-rehab platform. A VERA™ progress report from the study therapist will be provided to the site coordinator to deliver to the surgeon ahead of the 6-week follow-up visit. Discharge from VERA™ will be determined by the study physical therapist.

Patients will be given a telephone number to contact the Reflexion Health technical support team if they need technical support with VERA™. These telephone contacts will not involve any program participation guidance in order to ensure validity of the study results.

3.4.2 Traditional PT (Control) Group

Patients randomized to traditional PT will complete care as usual. This includes prehab as recommended by the participating site, in-hospital care, and home health or clinic-based PT as directed by the clinical team. There will be no restriction on the timing or number of PT encounters.

3.5 Patient-Reported Outcomes

Both standardized and de novo instruments will be utilized to collect patient-reported information regarding health. Domains of health data will include knee feeling and function, overall perception of his/her own health, activity level, pain, falls, and health service utilization. Assessments will be collected at multiple time points throughout the study, and include the following items:

- Knee Injury and Osteoarthritis Outcome Score (KOOS)[9] – pain, symptoms, activities of daily living, function in sports and recreation, and knee-related quality of life.
- Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health survey[10] – outcomes and health-related quality of life.
- Satisfaction with Physical Function questionnaire[11] – satisfaction with ability to complete basic functional tasks.
- Physical activity – frequency and duration of moderate activity/exercise.
- Pain – scale from 0 (no pain) to 10 (worst pain imaginable).
- Falls – number occurring since last contact.
- Return to work – resumption of pre-injury working status
- Health service utilization – healthcare encounters including office visits, phone calls and emails, and hospitalizations. Captured with the aid of a patient diary tool (see section 4.2.5).

3.6 Data Collection Methods

Three data collection methodologies will be used for this study: an Excel spreadsheet to track patient screening, a web-based data capture system for use by site coordinators in chart abstraction, and a Call Center to perform patient follow-up interviews.

3.6.1 Screening Log

Sites will be provided a screening log in Excel format, on which they will record de-identified information about all patients screened for potential inclusion in this study. The log will be maintained on an ongoing basis, and will be submitted to the DCRI Coordinating Center once per month, or ad hoc as requested by coordinating center staff. The log will serve to document how patients are included or excluded based on eligibility requirements, and whether eligible patients consent or decline to participate.

3.6.2 DCRI Registry System

The study will use 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. Data are expected to be present in the patient's medical record, either as standard of care or as documented for study purposes.

Access to the data capture system is role-based, with each authorized person receiving a unique user ID and password with appropriate permissions. Prior to being granted access to the system, site staff will be required to undergo appropriate training by the DCRI coordinating center.

3.6.3 DCRI Call Center

DCRI Call Center staff will contact all patients via telephone approximately 6 and 12 weeks after discharge to administer the follow-up assessments and collect details from the patient diary. The Call Center will attempt to contact patients using the information provided on the patient contact form at the time of consent. Additionally, the Call Center

provides a toll-free number for patients to use to either complete their follow-up interviews, or to schedule their interviews at a convenient time. The Call Center is staffed days, nights, and weekends to facilitate a high completion rate. Interviewers receive standardized training in data collection, and follow a prepared script to minimize variation and missing variables.

4. Study Procedures

4.1. Screening and Informed Consent

After obtaining written authorization from the DCRI Coordinating Center that study activities may begin, the site coordinator will review participating surgeons' schedules for adult patients (age ≥ 18) scheduled for TKR at least 10 days into the future. Whenever possible, potentially eligible patients will be introduced to the study with a letter mailed to their homes in advance of their pre-op visit. The study coordinator may then complete a follow-up phone call to those patients to assess interest, and complete the pre-screening assessment of RAPT score and living situation (not in a nursing home). If the patient qualifies and is interested, he or she will be asked to meet with study staff during his/her regular pre-op visit to further discuss the study, and be enrolled if he/she agrees.

It is expected that enrollment (consent, medical record release, and patient contact information) and baseline data collection (surveys) will be completed concurrently with the routine pre-op visit. If this is not possible, a separate study visit can be scheduled for this purpose. Additionally, patients who are unable to be contacted prior to their pre-op visit, but still able to meet the requirement for enrollment at least 10 days prior to surgery, may have their interest assessment, screening, and enrollment all completed at the pre-op visit, or at a separate study visit. Patients whose surgery dates have not been finalized at the time of the enrollment visit may be enrolled, but should not be randomized until the surgery date is scheduled. Sites should not submit baseline enrollment materials (signed consent, medical record release, contact form, and baseline survey) to the DCRI Coordinating Center until randomization occurs.

Regardless of timing for the interest assessment, screening procedures, and randomization, *all enrollment, baseline data collection, and randomization activities must be completed at least 10 days prior to the patient's surgery date.* Otherwise, the patient will be considered ineligible.

Information regarding <u>all</u> screened patients will be documented on a study screening log (spreadsheet) and submitted to the DCRI Coordinating Center on a monthly basis via email. The log will contain de-identified information regarding all patients who were screened, were excluded (RAPT < 6, nursing home resident, scheduled for bilateral TKR, unable to consent, unable to enroll at least 10 days prior to surgery), declined to participate, or were enrolled.

Each patient who agrees to participate must provide written consent in person, prior to completing any study activities. The informed consent explains to potential patients the study aims, procedures, and any potential risks. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without affecting their care in any way. They will be given sufficient time to review the informed consent document, discuss the consent with the investigator or an authorized member of the investigational staff, ask any additional questions, and record consent by means of their dated signature. The patient will

receive a copy of the signed consent form. Only the patient is authorized to provide written informed consent, unless an alternative consent method (e.g., a legally authorized representative) has been approved in advance by the DCRI Coordinating Center and the study site's IRB of record.

A copy of the signed informed consent will be faxed to the DCRI Call Center within 1 business day of randomization. The original signed paper document will be retained by the site and stored in a secure location, according to the site's IRB-approved procedures.

4.2. Baseline

The following procedures will be completed at the enrollment/baseline study visit, which will be performed during the routine pre-op visit whenever possible. All baseline activities must be completed *no less than 10 days* prior to the patient's surgery date.

4.2.1 Randomization

After providing written informed consent, patients will be randomized to either traditional PT or the tele-rehab platform for PT. Site coordinators will obtain the patient's assignment by completing a short randomization form in the DCRI Registry System. After saving the form with a Complete status, the system will return a randomization result. The coordinator will note this information in the patient's study record, as it will be required in order to manage the patient's discharge orders for traditional PT services versus the tele-rehab system. Randomization assignment will also be recorded on the baseline DCF.

If the patient's surgery date is known at the time of the enrollment/baseline visit, randomization may be completed during the visit, before or after collection of the patient contact form, medical record release, and patient-reported baseline assessments (see sections 4.2.2 and 4.2.3 below).

If a patient's surgery date is *not* known at the time of the enrollment/baseline visit, the patient contact form, medical record release, and patient-reported baseline assessments may still be completed, but randomization should be postponed. All documents should be held at the site until a surgery date is selected, at which time randomization may occur and documents may be submitted to the DCRI Call Center.

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.

4.2.2 Patient Contact Form and Medical Record Release

After signing the consent, patients will be asked to complete a contact form providing their address, phone number, and email address, as well as the best time to reach them. They will also be asked to provide this information for alternate contacts, at least one of which is not related to them. This information will be used to facilitate the 6- and 12-week follow-up phone calls by the DCRI Call Center. Additionally, a medical record release form will be collected for use in the event that the DCRI Coordinating Center needs to collect medical records or bills for the 12-weeks health service utilization assessment.

Copies of the completed patient contact form and medical record release form will be faxed to the DCRI Call Center within 1 business day of randomization. If a patient's surgery date is unknown at the time of consent, a patient contact form and medical record release may still be completed, but randomization should be postponed. All documents should be held at the site until a surgery date is selected, at which time randomization may occur and documents may be submitted to the DCRI Call Center. The original documents will be retained by the site and stored either on paper or electronically in a secure location, according to the site's IRB-approved procedures.

4.2.3 Patient-Reported Baseline Assessments

Each patient will complete following assessments at baseline, during the pre-op visit or study enrollment visit. These assessments must be completed at least 10 days prior to the patient's surgery date:

- Surveys regarding health (KOOS, PROMIS Global Health, Satisfaction with Physical Function Scale)
- Physical activity
- Falls and hospitalizations in the prior 3 months
- Comfort with using technology
- Self-selected personal goal for recovery

Copies of the completed patient-reported baseline assessments will be faxed to the DCRI Call Center within 1 business day of randomization. If a patient's surgery date is unknown at the time of consent, baseline assessments may still be completed, but randomization should be postponed. All documents should be held at the site until a surgery date is selected, at which time randomization may occur and documents may be submitted to the DCRI Call Center. The original documents will be retained by the site and stored either on paper or electronically in a secure location, according to the site's IRB-approved procedures.

4.2.4 Baseline Case Report Form

The following patient data will be collected:

- Socio-demographic information
- Medical history and comorbidities
- Vital signs (heart rate, blood pressure, 10m gait speed) including height and weight

4.2.5 Patient Diary

Sites will be provided copies of a diary form to 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. Patients will also be instructed to rate weekly (on Sunday) their level of achievement of their self-selected

personal recovery goal. Data recorded on the diary will be collected from the patient verbally by the DCRI Call Center during the planned follow-up interviews.

4.3 Surgical Hospitalization and Discharge

Within two days of the scheduled surgery date, site coordinators will confirm the dates of admission and surgery, and enter these in the DCRI Registry System on the discharge data collection form. This will enable the DCRI Coordinating Center to confirm follow-up by the study therapist for intervention patients, and timing of outcome assessments for all patients. When confirming admission and surgical dates, the site coordinator also should confirm the expected discharge plan for all study patients to be a discharge home, and coordinate with hospital discharge planners to ensure that intervention patients are not referred to home health or outpatient PT.

Prior to hospital discharge, patients will be assessed for gait speed, pain, and falls during the hospitalization. While these are standard physical assessments, site coordinators may need to coordinate collection of these in-hospital data with the hospital team and inpatient physical therapist, to ensure they are captured for all study patients. The study coordinator is expected to enter these data on the discharge data collection form in the DCRI Registry System within 3 calendar days of hospital discharge. DCRI may also send an email to study staff within 1 business day of the original surgery date to confirm whether or not the surgery occurred.

Study staff should also coordinate with hospital staff, or develop an alternate method, to remind patients to begin completing their diary of healthcare encounters after discharge.

4.4 6 Weeks Post-Op

Standard clinical follow-up for TKR patients occurs approximately 6 weeks after surgery. At this routine visit, patients will be administered standard assessments for gait speed and range of motion (ROM) in the operated knee. Study coordinators may need to coordinate with the clinic team to ensure these data are documented consistently in the medical record.

The study coordinator is expected to enter these data on the 6-week data collection form in the DCRI Registry System within 14 calendar days of the visit.

At approximately 6 weeks after surgery, the patient will also be contacted by the DCRI Call Center to collect the following data via telephone interview. The interview is expected to last 20-30 minutes:

- Survey regarding health (KOOS)
- Adherence to prescribed PT regimen
- Pain
- Physical activity
- Falls since hospital discharge
- Healthcare encounters since hospital discharge, and weekly status of personal recovery goal (patient diary entries)

4.5 12 Weeks Post-Op

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. The interview is expected to last approximately 20 minutes:

- Surveys regarding health (KOOS, PROMIS, Satisfaction with Physical Function)
- Adherence to prescribed PT regimen
- Physical activity
- Falls since last interview
- Healthcare encounters since last interview, and weekly status of personal recovery goal (patient diary entries)
- Thoughts about the tele-rehab platform (intervention patients only)

Also at 12 weeks after surgery, select sites may be asked to provide a summary of enrolled patients' outpatient clinic encounters (phone, email, in person) with orthopedic staff and physical therapists. This may be used to validate patient-reported encounters from the diary. Collection of the information, if requested, may be facilitated using the medical record release form signed by the patient at the time of enrollment.

5. Statistical Methods

The goal of this study is to assess the cost of the episode of care for total knee replacement, and whether the use of a tele-rehab platform is successful in mitigating some of those costs. The episode for analysis will be from surgery through 3 months post-discharge, in alignment with the new Comprehensive Care for Joint Replacement (CJR) bundled payment model being piloted by the Centers for Medicare and Medicaid Services (CMS). This will be a time-driven activity-based cost (TDABC) analysis. DCRI will be responsible for regular reporting of enrollment statistics, data quality, and data query status to the sponsor.

In addition to assessing the primary objective of cost, the study also will assess standard clinical measures of recovery (range of motion, gait speed) and qualitative measures of patient perceptions regarding their health and functional status (patient surveys) using both standardized and non-standardized tools. These assessments are intended to demonstrate the non-inferiority hypothesis that patients receiving PT via the tele-rehab platform did not have worse outcomes than patients receiving traditional in-person PT.

5.1. Sample Size

The primary aim of this study is to assess the difference in outpatient post-surgical costs between the control and intervention groups. 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, while the coefficient of variation (CV) is the ratio of the population mean over the SD. Lower variability would enable detection of a smaller cost difference, or the detection of a larger difference with fewer patients. The below table gives several mean ratios that could be detected with 80% power and 300 subjects where R1 is the ratio of the means (Control / Intervention) at which the power is calculated using a two-sample t-test with equal variance and a significance level of 0.05.

Power	N1	N2	N	R0	R1	Effect Size	CV	Alpha
0.8023	150	150	300	1.000	1.033	0.3255	0.1	0.050
0.8070	150	150	300	1.000	1.067	0.3275	0.2	0.050
0.8003	150	150	300	1.000	1.100	0.3247	0.3	0.050
0.8045	150	150	300	1.000	1.134	0.3264	0.4	0.050
0.8184	150	150	300	1.000	1.170	0.3324	0.5	0.050
0.8101	150	150	300	1.000	1.200	0.3288	0.6	0.050
0.8078	150	150	300	1.000	1.230	0.3278	0.7	0.050
0.8096	150	150	300	1.000	1.260	0.3286	0.8	0.050
0.8143	150	150	300	1.000	1.290	0.3306	0.9	0.050
0.8209	150	150	300	1.000	1.320	0.3335	1.0	0.050
0.8098	150	150	300	1.000	1.340	0.3287	1.1	0.050
0.8025	150	150	300	1.000	1.360	0.3256	1.2	0.050
0.8153	150	150	300	1.000	1.390	0.3310	1.3	0.050
0.8125	150	150	300	1.000	1.410	0.3298	1.4	0.050
0.8116	150	150	300	1.000	1.430	0.3295	1.5	0.050
0.8123	150	150	300	1.000	1.450	0.3297	1.6	0.050
0.8004	150	150	300	1.000	1.460	0.3247	1.7	0.050
0.8039	150	150	300	1.000	1.480	0.3262	1.8	0.050
0.8082	150	150	300	1.000	1.500	0.3280	1.9	0.050
0.8007	150	150	300	1.000	1.510	0.3248	2.0	0.050

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

If the mean cost difference expected is around $500, then the SD should be no more than $1500 in order to maintain at least 80% power. If the cost difference is around $200 then the SD would need to be no more than $600.

5.2. Data Analyses

Data will be analyzed as intent-to-treat, therefore all randomized patients will be included for analysis as randomized, regardless of whether or not they completed all protocol requirements. 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.

Baseline patient demographics, clinical characteristics, and outcomes assessed at each time point will be summarized overall and for each group. Continuous variables will be summarized using the mean, SD, median, inner-quartile range (IQR) and range, while categorical variables will be presented using counts and percentages. The primary cost comparisons will be done using a t-test if data are normally distributed or can be normalized using a transformation such as the logarithm or square root, otherwise, the nonparametric Wilcoxon Rank sum test will be used.

All analyses will be completed using SAS version 9.4 or higher, and a p-value < 0.05 will be considered statistically significant. A detailed statistical analysis plans will be prepared prior to analyses.

5.3. Data Quality Assurance

Missing data fields will be queried upon initial entry into the web-based data collection tool. In addition to instant queries, periodic data quality reports will be sent to each site via the web-based data collection tool to permit entry of missing or incomplete data fields. Sites may also be asked to respond to data clarification requests. In the event that missing data are not reclaimed on query, each variable will be evaluated separately before each analysis. This evaluation is necessary to explore the reason for the missing data and to check for other known variables in the dataset that may predict why the data are missing.

6. Ethical Considerations and Trial Oversight

6.1. Ethical Considerations

This trial will be submitted to an IEC or IRB (local or central) for approval. Minimum supporting documentation includes the final protocol, informed consent form, data collection forms, surveys and interview scripts, and applicable patient recruitment materials. Progress reports will be submitted to IRBs and regulatory authorities as required by local laws and regulations. This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with good clinical practices and applicable laws and regulations of the institution where the trial is being conducted, as appropriate.

As part of local IRB submission for the study, sites will be expected to outline their proposed methods and timeline for completing procedures to assess patient interest and pre-screen for eligibility. Sites also will be expected to obtain IRB approval for verbally consenting the patient before completing the RAPT score assessment in order to determine eligibility.

The patient will provide authorization for the uses and disclosure of their personal health information as described in the informed consent form. The confidential nature of the patient information will be maintained.

6.2. Trial Oversight

Trial operation management and scientific oversight for VERITAS will be performed by Duke Clinical Research Institute (DCRI). Sites will be provided with both telephone numbers and email addresses, as appropriate, to contact the DCRI study team for assistance, which generally will be available from 8 am – 5 pm Eastern Time Monday through Friday, excluding holidays.

Throughout the study, DCRI will maintain records of all issues and resolutions when a site is assisted.

6.3. Trial Leadership

Duke University and Duke Clinical Research Institute (DCRI), along with the sponsor, Reflexion Inc., will be responsible for VERITAS design, implementation, and leadership. Data analysis and publications will be managed according to a written plan designed to maintain appropriate scientific oversight and rigor.

7. Administrative Requirements

7.1. Study Completion

Study enrollment will continue until 300 patients have been enrolled. Enrollment is anticipated to last approximately 10 months. The study will be considered complete upon completion of all study-related procedures (data collection) for the last patient enrolled.

7.2 Adverse Experience Reporting

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

7.3. Source Documentation

At a minimum, source documentation must be available to substantiate patient identification, eligibility, participation, and proper informed consent procedures. Specific items required as source documents will be reviewed with the investigator before the study.

7.4 Patient Reimbursement

Patients will be reimbursed for their time in participating in this study, based on completion of study benchmarks. Funds for patient reimbursement will be provided to participating sites, who in turn will issue reimbursement directly to their enrolled patients, as appropriate. Details of the reimbursement schedule and requirements will be detailed in the site-specific informed consent document.

7.6. Record Retention

Because this study is comparing two approved methods for delivering standard post-surgical PT, sites will not receive on-site monitoring visit(s) for this study. However, the investigator/ institution will maintain all source documents that support the data collected regarding each patient, as well as all study documents as specified by the applicable regulatory requirement(s). If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. DCRI must be notified in writing of the name and address of the new custodian. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to all study documentation.

8. References

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