COVER PAGE

Official Study Title: Feasibility of Blood-flow Restriction Training Prehabilitation in Older Adults Awaiting Total Knee Replacement

NCT number: NCT06111690

IRB Approval Date: 09-05-2024

Unique Protocol ID: HSC20210590H

Protocol Template Form

Item 1 UTHSCSA Tracking Number	HSC20210590H

Item 2 Abstract / Project Summary	Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific. **DO NOT EXCEED THE SPACE PROVIDED**.

Purpose/Objectives: The overall aim of this research is to demonstrate that preoperative exercises (prehabilitation) using blood-flow restriction training (BFRT) is safe, well tolerated, improves muscle function, decreases functional limitation, and increases physical activity in older adults awaiting total knee replacement (TKR).

Research Design/Plan: This is a single group pre-post design study. Outcomes will be measured at baseline, after 6 weeks of prehabilitation, and 8 weeks after TKR.

Methods: Twenty individuals ≥60 years old awaiting TKR due to diagnosis of end-stage knee osteoarthritis who meet the inclusion/exclusion criteria will be invited to participate in a 6 weeks of low-intensity BFRT prehabilitation. We will assess muscle morphology (i.e., cross-sectional area and intramuscular fatty content) using dual x-ray absorptiometry (DEXA) scan, quadriceps muscle strength using an isokinetic dynamometer, a battery of performance-based physical function, self-reported physical function and quality of life, and biomarkers of inflammation using blood serum. Feasibility assessment will be done by looking at safety (i.e., adverse events), compliance, and attrition rate.

Clinical Relevance: The low intensity prehabilitation program using BFRT may lead to improvements in muscle morphology and strength, as well as physical function before TKR. Since muscle weakness and functional limitations experienced preoperatively affect the recovery after TKR, these individuals may experience a significant benefit from our program. Thus, our program may allow patients undergoing TKR to perform daily activities early on postoperatively. Moreover, by increasing physical activity and preventing exacerbation of joint inflammation, our program might impact the general health in older adults after TKR.

Item 3 Background	

Describe past experimental and/or clinical findings leading to the formulation of your study. *For research involving unapproved drugs, describe animal and human studies.* *For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.*	Preoperative exercises interventions (prehabilitation) have gained increasing attention from researchers in different areas of rehabilitation. Prehabilitation before total joint replacement has shown to reduce postoperative length of stay and increase the likelihood of discharge home instead of a rehabilitation facility. Knee osteoarthritis (KOA) is a debilitating musculoskeletal disorder that affects older adults and its incidence continues to grow. Total knee replacement (TKR) is known as the most successful intervention to improve pain and quality of life in individuals with end-stage KOA. However, the surgery fails to address quadriceps muscle weakness, functional limitations and decreased physical activity experienced by those individuals for years. Most of the functional limitations are due to quadriceps weakness that affects important daily tasks such as ascend-descend stairs, sit-to-stand from a chair, and walk long distances. Several studies have proposed a variety of exercise programs targeting muscle strength and physical function pre- or post-surgery, but their results are inconsistent. We believe that these inconsistencies are due to the exercise intensity prescribed. Older adults with end-stage KOA are at the verge of undergoing TKR, which preclude them from participating in traditional resistance exercises that require at least 70% of the maximal voluntary contraction to improve muscle strength. More recently, low-intensity blood flow restriction training (BFRT) has been introduced to the field of musculoskeletal rehabilitation. BFRT has the potential to improve muscle
	function (i.e., muscle volume, strength and fat content) comparable to traditional resistance exercises with less mechanical load to the knee joint. Therefore, a prehabilitation program using low-intensity BFRT might be well tolerated by individuals with end-stage KOA, leading to preoperative improvements in quadriceps strength and physical function, both of which are predictors of functional performance after TKR. Although a few studies have shown that BFRT is a viable intervention to treat muscle weakness with less mechanical load, this intervention has not been tested in the context of prehabilitation in individuals with KOA awaiting TKR. Thus, it is unknown whether these individuals can tolerate such interventions or not.
Item 4 Purpose and rationale *Insert purpose, objectives and research questions/hypotheses here.* *If you cut and paste from another document, make sure the excerpted material answers the question*	Primary outcome: feasibility of BFRT during prehabilitation in older adults awaiting TKR. Secondary outcomes: muscle strength and morphology (i.e., volume and quality), physical function, real-time physical activity and concentration of inflammatory biomarkers. Endpoint: Baseline (T0), after 6 weeks of prehabilitation (T1) and 8 weeks postoperative (T2) Justification for Endpoint: - T0 will provide overall idea on subjects' baseline characteristics of outcome-related data. - T1 will provide data on safety, compliance and attrition rate of the BFRT prehabilitation program, as well as its effect on muscle strength and morphology, physical function, real-time physical activity and concentration of inflammatory biomarkers. - T2 will provide data on the continuing effect of BFRT prehabilitation on muscle strength and morphology, physical function, real-time physical activity and concentration of inflammatory biomarkers postoperatively. Rationale: The low intensity prehabilitation program using BFRT may lead to improvements in muscle morphology and strength, as well as physical function before TKR. Since muscle weakness and functional limitations experienced preoperatively affect the recovery after TKR, this population may experience a significant benefit from our program. Thus, the results of our investigations may allow patients undergoing TKR to perform daily activities early on postoperatively. Moreover, by increasing physical activity and preventing exacerbation of joint inflammation, our program might impact the general health in individuals after TKR.

Item 5 Study Population(s) Being Recruited In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number: 1	Identify the criteria for **inclusion**:	

e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc. List each different population on a separate row and provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *To add rows use copy & paste*		Identify the criteria for **exclusion**:
Older adults with knee osteoarthritis awaiting total knee replacement	Individuals will be included if they: (a) are awaiting primary unilateral TKR due to diagnosis of end-stage KOA. Potential individuals must have at least 8 weeks waiting time in between study baseline assessment and surgery. This 8-week timeframe will allow for completion of baseline (T0) and follow-up assessments (T1: immediately after 6-week prehabilitation program); (b) are older than 60 years; (c) speak fluent English to reliably complete the study questionnaires and understand study instructions.	To ensure safety, Individuals will be excluded from the study if they: (a) have a history of cardiovascular disease, uncontrolled hypertension (blood pressure ≥140/90 mmHg), deep-vein thrombosis, varicose veins, or rhabdomyolysis; (b) have absolute contraindications to exercise, as established by the American College of Sports Medicine (uncontrolled arrhythmias, third degree heart block, recent EKG changes, unstable angina, acute myocardial infarction, and acute congestive heart failure); (c) report of 2 or more falls within the past year; (d) cannot walk a distance of 100 feet (30.5 meters) without an assistive device or need of a rest period; (e) have bilateral TKR or undergoing TKR revision or other total joint replacement in the lower extremities; or (f) have severe visual or hearing impairment. In addition to the affects that these impairments have on safety during participation in the intervention, they may also interfere with data collection (questionnaires and telephone checks); (g) have a lower extremity amputation; (h) are unable to comfortably bear weight on the affected knee; (i) have a BMI above 40. This exclusion is used because subjects with BMI ≥40 are more likely to develop patellar radiolucencies, have poorer muscle function and more pain. To minimize potential confounding effects, individuals will be excluded if they have: (j) history of muscular disease (e.g., muscular dystrophy) or neurological disorder that may affect lower extremity function (e.g., cerebrovascular accident, neuropathy, Parkinson's disease, multiple sclerosis); (k) had additional surgery to the lower extremities within the past 12 months.

		To promote reliability of self-reported data, individuals will be excluded if they have: (l) a Folstein Mini-Mental State Examination score of <24. To minimize attrition and maximize adherence, individuals will be excluded if they: (m) have acute or terminal illness; (n) are planning to have another TKR (primary on contralateral, or revision on same knee) within 4 months; (o) are planning to relocate to another city within 4 months. Subjects with Sickle cell disease Belt placement on a limb with lymphedema or vascular access Subjects who have any on-going medical emergency

Item 6
Research Plan / Description of the Research Methods *a.* *Provide a **comprehensive narrative** describing the **research methods**. Provide the **plan for data analysis** (include as applicable the **sample size calculation).***

Step-by-Step Methods:

Twenty subjects will be performing low-resistance exercise with (BFRT). Intervention will start at least seven days after initial evaluation, so it does not influence measures of real-time physical activity. We will use a log to register exercise completion and to record bilateral knee pain before, during and after each intervention session at the PT-Lab.
BFRT will be done using low-resistance (20-30% of 1-repetition maximum) leg extensions, leg curls, and sit-to-stand exercises. Performing exercises at this intensity with the blood flow restricted by a cuff, which maintains arterial inflow while obstructing venous outflow distal to the occlusion site, creating a metabolic environment that alters neuromuscular activity and improve quadriceps muscle volume and strength comparable to traditional high-resistance training (≥70% of 1-repetition maximum) in older adults. BFRT cuff will be placed around subject's thighs prior to exercise. Cuff pressure to be used for the BFRT will be established by placing the cuff on the proximal end of the thigh and inflated until full occlusion is achieved. A portable Doppler will be used to capture auscultatory signal of the posterior tibial artery for this assessment. Based on the pressure (mmHg) used to achieve full occlusion, the BFRT cuff ((B)StrongTM; Park City, UT) will be set up at 50% of that pressure to start the intervention and will progress up to 80% pressure according to subject's tolerance. This adjustment will be done once a week in a PT lab, when subjects will have the BFRT cuff pressure increased by 5-10% and will perform the intervention supervised by a trained researcher. Intervention will consist of 10-minute warm-up on a stationary bike, 4 sets (30, 15, 15, and 15 repetitions) of each proposed exercise bilaterally, and stretching exercises of the lower extremity as cool-down. Subjects will perform a 10-repetition submaximal testing for 1-repetition maximum to estimate the resistance to be used for each exercise. We will use adjustable ankle weights (1-20 pounds) for leg extensions and leg curls, and a weighted vest (3-120 pounds) for sit-to-stand exercise. Total time to complete intervention is ~40 minutes. Subjects will wear BFRT cuffs only during the low-resistance exercise (~15-20 minutes). The maximum time recommended to wear the BFRT cuffs is 20 minutes.

Study visit procedures:
Subjects will self-identify as referred by UT Dept. of Orthopaedics provider at least 8 weeks prior to routine total knee replacement surgery. Potential participants will be screened by phone at time of initial reach out to ensure eligibility criteria is met.
Screening. A trained designated tester will conduct a screen interview over the telephone using a structured questionnaire. Then, to validate the inclusion and exclusion criteria obtained by telephone, the tester will conduct an on-site interview using standardized history and physical exam forms. Also, to rule-out peripheral arterial disease, the evaluator will conduct an ankle-brachial index assessment. Only individuals within normal cut-off values for ABI (i.e., between 0.9 and 1.3) will be eligible to participate in the study.

Baseline Assessment (Visit 01). Baseline data will be collected by a trained research assistant. Estimated time to perform the baseline testing is ~2.5 hours. Individuals will be instructed to avoid strenuous physical activity 48hrs prior to testing. Baseline session will be performed in the following sequence: 1) DEXA scan at the Barshop Institute; 2) at the PT laboratory: 2a) blood drawing; 2b) questionnaires on demographics, physical function, quality of life and biomedical information; 2c) performance-based physical function; and 2d) quadriceps muscle strength.
Visit 01 (Baseline; all procedures completed for research)
Informed consent will be obtained by approved research team members and medical history and demographics collected. Falls, Cumulative Illness and Contraindications questionnaires and the mini-mental will be administered by trained staff to confirm inclusion/exclusion criteria. Once all criteria are met, subjects will be asked to complete the following:

Vital signs

- Blood sample will be collected (approx. 30ml) to assess inflammatory biomarkers. Blood samples to analyze concentration of inflammatory biomarkers (research). Blood samples will be stored in the freezers located at the Department of Medical Laboratory Sciences in the School of Health Professions at UTHSCSA. Freezers hold temperature stable at -80oC, which is necessary to maintain the quality of blood samples. A research assistant from the Department of Medical Laboratory Sciences will centrifuge the blood samples to separate serum from plasma. (research)
- Whole-body DXA scan to look at muscle composition of both thighs
- Physical Functional Assessment to include self-selected gait speed, timed 5 chair rise, single leg stance time, timed-up and go test, stair ascend/descend test, and 6-minute walk test
- Patient-Reported Outcomes Measurement (PROMIS)
- RAND-36-item Health Quality of Life Survey
- Subjects will be provided with an actigraph monitor device and asked to wear it for one-week to assess a baseline physical activity prior to BFRT sessions

Visit 02 – Visit 07 (Treatment Weeks 1 through Week 6; all procedures completed for research)
One week after baseline visit, subjects will complete 12-18 sessions of low-intensity blood flow restriction training (BFRT), two to three times a week, for six weeks, based on patient willingness/availability. A minimum of 12 sessions is required for study participation. BFRT sessions will be completed as described above at the UT Physical Therapy Research Lab. An exercise and pain log will be completed during and after each intervention session. All training sessions will be provided by qualified providers who are also IRB approved research team members.

Visit 08 (Pre-operative Follow up Week 7; all procedures completed for research)
A pre-operative follow-up visit will be scheduled one week after completion of BFRT intervention sessions. Subjects will be asked to complete the following:
Vital signs
Blood sample will be collected (approx. 30ml) to assess inflammatory biomarkers (research).
Whole-body DEXA scan (research)
Physical Functional Assessment to include self-selected gait speed, timed 5 chair rise, single leg stance time, timed-up and go test, stair ascend/descend test, and 6-minute walk test
Patient-Reported Outcomes Measurement (PROMIS)
RAND-36-item Health Quality of Life Survey
Actigraph monitor provided at the end of Treatment week 6 and collected at time of pre-op follow up Week 7

Visit 09 - Routine Total Knee Replacement Surgery (Routine Standard of Care)
Routine knee surgery will be performed per standard of care. Results will be requested for research purposes

Visit 10 (Post-operative Follow up 8-weeks after TKR surgery; all procedures completed for research)
Same procedures as V08 will be completed

Visit 11 – this is a virtual research visit only. Subjects will be asked to mail actigraph monitoring device by mail in a prepaid envelope provided by the study team. This will qualify as the end of study visit.

Adverse events will be monitored at each visit.

Primary Outcomes: 1) Quadriceps muscle function:
1a. Strength will be measured using an isokinetic dynamometer (Biodex System 4 Pro, Shirley, NY). We will record the quadriceps femoris maximum voluntary isometric contraction (MVIC) as torque output (Nm). Subjects will be seated in the dynamometer's chair with their knee at 60 degrees of flexion. Subject position, stabilization, and gravity correction will be performed according with the Biodex manufacturer's guidelines. Subjects will exert as much isometric force as possible while trying to extend the knee against the force arm of the dynamometer. The MVIC will be the highest torque (Nm) of four trials.33 Torque will be the variable used in data analysis. Strong verbal encouragement from the tester and visual feedback from the dynamometer screen will be provided during trials. Previous studies using this method in individuals with arthritis indicate that it was tolerated well and did not result in adverse effects.34,35

1b. Cross-sectional area and Quality will be measured using a whole-body DEXA scan to investigate muscle composition of the thigh region bilaterally.36,37 Serial axial plane DEXA scan will be used to quantify changes in thigh muscles cross sectional area (CSA) and quality (i.e., amount of intramuscular fat) bilaterally. Subjects will be imaged in supine with the legs extended flat on the table. The scanner measures the absorption of two different energy levels of X-rays as they pass through the body. This information is used to create an image of the body that shows the distribution of bone, fat, and muscle tissue that have different X-ray attenuation. Using these differences in X-ray attenuation, the DEXA software is able to distinguish and quantify the amount of muscle and fat in a specific region of interest, such as the thigh muscles.
Secondary Outcomes:
2) Performance-Based Physical Function. We are performing a battery of performance-based measures that are easily done in the clinical setting: self-selected gait speed, 40m fast-paced walk test, 30-sec chair stand test, and stair climb test. These tests cover important domains of lower extremity function such as walking ability, dynamic balance, muscle strength and power, endurance, and movement control. These tests have shown to be reliable, responsive to interventions, and discriminate from low to high functional ability in individuals at various ages and functional levels.42-47 Subjects with TKR tend to self-report their outcome as good even when they have difficulty performing daily tasks.48,49 Also, performance-based measures in subjects with TKR are more sensitive to change than self-reported measures.50

3) Patient-Reported Physical Function will be assessed using the PROMIS® (Patient-Reported Outcomes Measurement Information System), which is used to evaluate and monitor physical, mental, and social health in persons with several conditions.

4) Health Related Quality of Life will be measured using the RAND 36-Item Health Survey. The RAND 36 is a reliable and valid tool to measure eight concepts of health status: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.51,52

5) Real-time physical activity will be measured using the Actigraph (Pensacola, FL). The Actigraph is a triaxial accelerometer worn on the wrist that provides information on daily physical activity in minutes/day, kilocalories/day and steps/day. The software allows for converting the data into levels of physical activity intensity such as sedentary, light and moderate. Subjects will wear the device on their wrist for seven consecutive days. Subjects will also complete a paper log to inform when device was not worn.

6) Blood samples. A trained and experienced health care professional will collect two samples of blood from subject's arm, each about 30 ml (2 tablespoons). These samples will then be appropriately stored and frozen at -80C in the Department of Medical Laboratory Sciences at UT Health San Antonio. Then, at the time for analyzes, the samples will be transported to the Bioanalytics Research Core Laboratory at the School of Nursing to process the inflammatory

biomarkers. The laboratory will use the 'MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel' to assess a panel of 8 inflammatory biomarkers: Interleukin (IL)-1β, IL-2, IL-5, IL-6, IL-10, IL-12p70, IL-13 and Interferon-γ.32,53

Additional Measures

1) Demographic factors: age, gender, ethnicity, marital and educational status

2) Biomedical factors

a) Medication prescribed and over-the-counter used for pain will be recorded in the medication form. We will record the current and highest dosage of any pain medication used during the last month (when performing pre-intervention evaluation), or during the interval between evaluations.

b) Comorbidity data will be collected using the Cumulative Illness Rating Scale.54,

c) Body Mass Index will be calculated as the subject's body weight divided by the height squared.

d) Knee Range of Motion will be measured in the supine position utilizing a standard goniometer. The available range of knee flexion and extension will be measured. When measuring passive knee extension, the heel will be elevated on a bolster to ensure the end range of extension is achieved.

e) Knee Pain in both knees (surgical and non-surgical sides) will be measured using an 11-point (0 to 10) numeric scale. The scale will be anchored at one end with the phrase "no pain" (0) and at the other end with the phrase "worst imaginable pain". Subject will be instructed to report the greatest pain during last 24h.55,56

Research personnel will keep track of assessment procedures using a checklist. An exercise log will be used to track delivered exercise sessions. All questionnaires will be self-administered using Redcap.

Although subjects are asked to not participate in any exercise-related program during the study period, research personnel will track exercises performed by subjects on a log.

Study personnel reserve the rights to discontinue delivery of intervention if subject presents with muscle or joint pain that cannot be resolved by administering over-the-counter pain medication.

Research personnel will ensure to follow-up with subjects who have discontinued the study in regards to their recovery from muscle or joint flare-ups due to study intervention to monitor AE, SAE and/or UPIRSOs.

Statistical Considerations

Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

Our hypotheses are that:

- our exercise protocol will be safe, compliance with intervention will be >80% of completed exercise sessions, and retention will be >80% of subjects.
- Subjects will demonstrate improvement in muscle strength and morphology, physical function, quality of life, physical activity, and biomarkers of inflammation from T0-T1 (before TKR), which will hold true from T0-T2 (after TKR).

Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

Due to the exploratory (pilot) nature of the study, we aim to recruit 20 subjects to answer our question on the feasibility of our exercise protocol.

Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

This is a single group pre-post design. All participants recruited will be assessed regarding compliance, adherence, and safety of our exercise protocol. Data on demographics, biomedical factors, and outcomes measures (i.e., muscle

	strength and morphology, physical function, quality of life, physical activity, and biomarkers of inflammation) will be entered in the dataset for each timepoint. **Statistical Analyses** Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses Descriptive statistics on adverse events (i.e., joint and/or muscle pain) during exercise sessions and at each timepoint will be provided. Data on secondary outcomes (i.e., muscle strength and morphology, physical function, quality of life, physical activity, and biomarkers of inflammation) will be compared between T0-T1, T0-T2 and T1-T2. Due to the small sample size (N=20) we will conduct a non-parametric paired difference test (i.e., Wilcoxon signed-rank test) to identify whether those comparisons are statically significant. Data Analysis Plan: A flow chart will be prepared to identify and summarize issues in recruitment and retention, record total numbers screened, numbers excluded with reasons for non-participation, timing and frequency of dropout, etc. Retention will be assessed by frequency count of dropouts. Survival analysis of time to dropout may point to parts of the protocol that are difficult (e.g., very early dropout, loss to follow-up). We will perform a descriptive summarization of demographic and baseline (T1) values of biomedical factors, and outcomes measures (i.e., muscle strength, physical function, quality of life, physical activity, and biomarkers of inflammation), post 6-week prehabilitation values (T2), and 12 weeks (T3) after TKR values. Then, change values from T1 to T2, and change values from T1 to T3 will be described stratified by intervention group. This information will be important to perform formal sample size and power computations for a future larger trial. Due to the small sample size, more attention will be paid to a trend towards a relatively smaller p-value rather than statistical significance based on a strict criterion (e.g., α=0.05).

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures *example:* • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Risks** List the reasonably expected risks under the following categories as appropriate:
	○