Study Protocol and Analysis Plan

Title: Blood Flow Restriction after Meniscus Repair

Document Date: 10/25/2023

NCT04436523
Protocol ID: 19-29641

Study Application (Version 1.10)

1.0 General Information

***Enter the full title of your study:**

Comparison of outcomes utilizing blood flow restriction training as a rehabilitative protocol in post-operative meniscus repair patients

***Enter the study alias:**

Blood flow restriction training in orthopaedic knee conditions
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
○	**UCSF** - *777050* - PHYSICAL THERAPY
○	**UCSF** - *139404* - M_Ortho-Admin-Core-Rsdnt Admin
◆	**UCSF** - *139400* - M_Orthopaedic Surgery

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Lansdown, Drew MD, MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Arriaga-Martinez, Ivan
Co-Principal Investigator
Chiu, Jonathan V
Other Investigator
Cole, Elliott W
Other Investigator

Colyvas, Nicholas
Other Investigator
Edwards, Sara
Other Investigator
Feeley, Brian T MD, MD
Co-Principal Investigator
Freitas, Nina
Other Investigator
Laroque, Elly S
Other Investigator
Ma, C. Benjamin MD, MD
Other Investigator
Theismann, Jeffrey
Other Investigator
Wang, Kevin
Other Investigator
Wong, Stephanie E MD, MD
Other Investigator
Zhang, Alan L, MD
Other Investigator

B) Research Support Staff

Carpio, Jocelyn G
Study Coordinator
Sampson, Hayden
Study Coordinator

3.3 *Please add a Study Contact

Carpio, Jocelyn G
Lansdown, Drew MD, MD
Sampson, Hayden

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated January 2019 - Revised Common Rule (January 2018) Compliant - v92

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us

what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

It is important to study innovative ways to enhance the rehabilitation of orthopaedic patients to optimally restore patient function. Blood flow restriction (BFR) is a training tool that has been shown to be useful in the rehabilitative setting, but its effectiveness in treating patients with orthopaedic knee conditions requires further investigation. This study therefore seeks to understand whether BFR is a useful rehabilitation tool across various populations with musculoskeletal knee conditions. BFR is a unique and promising strategy for patients who cannot tolerate high-load resistance training, as it can be combined with with low-load exercises during rehabilitation to optimize muscle strength and hypertrophy. Patients that may benefit most from this are post-operative knee patients during early phases, including those that may have weightbearing restrictions, and patients with orthopaedic knee joint conditions with impaired load-tolerance. These patients must often limit physical activities due to post-operative surgical precautions or pain, which results in poorer patient outcomes, including muscular atrophy, increased risk of injury, and delayed return to activity/sports. This study will help clarify whether BFR can reduce these complications through improvements in strength, muscle size, and function in patients with orthopaedic knee conditions. If successful, this concept could be applied across other surgeries and disciplines within orthopaedics.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- (•) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

- (•) Minimal risk
- ( ) Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

Generally, only *Greater than Minimal Risk* studies require *Full Committee Review*. We suggest you check *Expedited Review* instead or change the risk level, if you checked the wrong box.

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

○ Yes ◉ No

4.10 * CLINICAL TRIAL: (REQUIRED)
Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

◉ Yes ○ No

Clinical Trial Registration - 'NCT' number for this trial:

Pending

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

☐ Phase 0
☐ Phase 1

- [ ] Phase 1/2
- [ ] Phase 2
- [ ] Phase 2/3
- [x] Phase 3
- [ ] Phase 4
- [ ] Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

- (•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

- ( ) Yes (•) No

4.14 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

- ( ) Yes (•) No

4.15 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [x] Departmental scientific review
- [ ] Other:

* Which Department(s) provided review: **(REQUIRED)**

UCSF Department of Orthopaedic Surgery

4.16 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

- (•) No
- ( ) Yes, and requires IRB and GESCR review
- ( ) Yes, and requires GESCR review, but NOT IRB review

4.17 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

- ( ) Yes (•) No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

○ Yes ◉ No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

○ Yes ◉ No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
No Sponsor has been added to this IRB Study						

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☑ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 UCSF AND AFFILIATED SITES (check all that apply):

- ☐ UCSF Benioff Children's Hospital Oakland (BCHO)
- ☐ UCSF China Basin clinics and facilities
- ☐ UCSF Helen Diller Family Comprehensive Cancer Center
- ☐ UCSF Langley Porter Psychiatric Institute (LPPI)
- ☑ UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)
- ☑ UCSF Mount Zion
- ☐ UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- ☑ UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals)
- ☐ Zuckerberg San Francisco General (ZSFG)
- ☐ SF VA Medical Center (SF VAMC)
- ☐ Fresno - UCSF Fresno OR Community Medical Center (CMC)
- ☐ Gladstone
- ☐ Institute on Aging (IOA)

- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)

6.2 LOCATIONS: At what locations will study visits and activities occur:

UCSF Orthopaedic Institute in Mission Bay - Outpatient clinics and ambulatory surgery center
UCSF Orthopaedic Institute in Mission Bay - Physical Therapy
UCSF Medical Center at Mount Zion - Physical Therapy

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- ( ) Yes
- (•) No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

- ( ) Yes
- (•) No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By '**multi-center trial**' we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

- ( ) Yes
- (•) No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAMC, Gladstone, ZSFG) are the coordinating center.

- [ ] Other UC Campus
- [ ] Other institution
- [ ] Other community-based site

☐ Foreign Country

☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.14 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus, commercial, or institutional):

○ Yes ◉ No

7.0 Research Plan and Procedures

7.1 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove:

Blood flow restriction (BFR) training has the potential to increase muscle size and strength, which can be valuable in combating atrophy and weakness in patients after acute injury or in the post-operative setting. BFR involves use of a tourniquet to occlude venous outflow while maintaining partial arterial inflow. As a result, this anaerobic environment stimulates muscular hypertrophy through a variety of local and systemic factors [1-3]. Exercise performed at lower loads, including at 20-50% loading of a 1-repetition maximum (1-RM), can promote similar hypertrophy to higher intensity training [4]. Studies are emerging on BFR, including a recent randomized controlled trial demonstrating benefits in muscular strength and size in both the ipsilateral limb undergoing BFR and the contralateral limb [5]. This method of training has also been shown to be safe and may even decrease risk of deep venous thrombosis [6, 7]. Several groups have applied **BFR post-operatively after anterior cruciate ligament reconstructions and patients with various orthopaedic knee conditions** and have shown the **potential to improve quadriceps atrophy and strength** [5-11].

Patients with orthopaedic knee conditions often undergo periods of restricted weightbearing, immobilization, and/or significant reductions in physical activities, which can lead to substantial amounts of quadricep atrophy [12,13]. Quadriceps force is important in maintaining appropriate loading mechanics, which impacts risk for further injury and osteoarthritis [14, 15]. Quadriceps weakness is well-documented in patients following knee surgery, including arthroscopic partial meniscectomy, and in patients with degenerative knee conditions. Those undergoing meniscal repair see even greater extents of thigh musculature atrophy compared to those undergoing meniscectomy only given the longer period of immobilization post-operatively used to allow for meniscal healing [12,13]. Studies, however, are limited in evaluating patients with orthopaedic knee conditions, including those following acute meniscus repair surgery, undergoing BFR. A BFR protocol could help offset thigh musculature atrophy and improve rehabilitation in patients with orthopaedic knee conditions.

We hypothesize that quadriceps extension force will be significantly higher in patients undergoing a rehabilitative protocol with BFR versus those undergoing standard rehabilitation.

7.2 AIMS: List the specific aims:

Aim 1: Evaluate the force production and strength of the affected extremity after BFR compared to those in the standard rehabilitation control group.

Hypothesis 1: Force production, as measured by peak force determined via hand-held dynamometer at 30 and 90 degrees of knee flexion for quadriceps and hamstrings, will be significantly higher after rehabilitation with incorporation of BFR relative to patients without BFR.

We will evaluate previously described primary measures including peak quadriceps/knee extension force and limb circumferences [8-11, 16, 17]. Rating of perceived exertion (RPE) will be measured during testing to ensure the patients are meeting appropriate standards of effort (RPE goal 7-8). Measurements would be taken weekly for up to 10 weeks post-operatively during assigned physical therapy sessions; these weekly measurements will be taken by trained physical therapists at UCSF who are blinded to the patient's treatment group.

Aim 2: Compare performance on functional outcome measures relative to those in standard-of-care rehabilitative protocols and secondarily evaluate patient-reported outcomes.

Hypothesis 2: Functional outcome scores, as measured via standard scoring for single leg squat and Ybalance tests, as well as patient-reported outcomes measured via the International Knee Documentation Committee (IKDC) score will be higher in those patients undergoing BFR training relative to those undergoing standard therapy.

We will compare functional and patient-reported outcome measures between the two groups to ascertain if there are clinical outcome differences after blood flow restriction training. Functional milestones evaluated include single leg squat test, 3-hop test, and Y-balance test. Patient-reported outcomes will be measured using the IKDC standard knee evaluation form at baseline and at the conclusion of the study period. By assessing the above aims, we seek to distinguish to see if BFR training helps mitigate quadriceps atrophy in patients with orthopaedic knee conditions. This readily available and non-invasive treatment may have the potential to greatly improve orthopaedic rehabilitation and limit the detrimental effects of post-operative atrophy and progressive muscular deconditioning.

7.3 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

This study will have two parallel arms. The first one will be a **double-blinded, single-institution, randomized controlled trial** of patients undergoing in-person rehabilitation following arthroscopic meniscus repair. The second will be a **single blinded, single institution, prospective clinical trial** of patients undergoing in-person or telehealth rehabilitation of orthopaedic knee conditions. In both arms, the study compare (1) a standard-of-care rehabilitation protocol versus (2) standard-of-care rehabilitation combined with BFR training with cuff occlusion applied to the affected extremity. All patients will be enrolled prospectively, prior to beginning rehabilitation. Patients with arthroscopic meniscus repair who are unable or choose not to participate in in-person rehabilitation will be allowed to undergo telehealth rehabilitation through the second arm of this study.

Rehabilitative exercises would be advanced per the physical therapists' discretion with similar exercises for patients in both groups for direct comparison. These exercises are part of an already-established rehabilitation protocols that are in place, with the only difference being the addition of the BFR cuff in the intervention group. Patients would undergo their supervised rehabilitation for 8-12 weeks.

7.4 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Muscular hypertrophy and strength are largely thought to be associated with recruitment of larger motor units associated with type II muscle fibers [3]. Because type II muscle fibers are recruited with higher intensities and contractile forces, it is thought that performing exercise at loading >65% of 1-RM has the largest effect on muscle mass and strength gains [18]. Blood flow restriction (BFR) training, however, may allow for similar hypertrophic and strength response while functioning at lower loading or mechanical tension [3, 4]. BFR training is increasing in popularity in commercial gyms, athletic training programs, rehabilitation, and research settings. This non-invasive treatment involves the use of a tourniquet system to restrict venous inflow while maintaining arterial outflow during exercise. A purported benefit is the relative increase in cross-sectional muscle area which corresponds to increased strength and power output [1-6, 8, 10-11, 16-17]. Mechanistically, the benefits of BFR appear to stem from both local and systemic factors [1-3]. Metabolic stress induced by a relatively hypoxic environment under the tourniquet

may increase systemic and localized hormones and increase cellular swelling [3]. Another benefit of BFR is that because the loading is less than that of higher-intensity training, which primarily affords its effect through high mechanical tension, there is less muscular damage and theorized quicker recovery from training [3].

Due to its benefits in improving size and strength at lower loading and with quick recovery, BFR is a potential avenue for patients with injuries or in the post-operative setting to counteract disuse atrophy without requiring high-load training. By applying BFR protocols to those undergoing meniscus repair surgery and recovering from other orthopaedic knee conditions, we can evaluate whether BFR training will improve size and strength of the thigh musculature and understand the impact of this treatment on functional and patient-reported outcomes. This would be beneficial to advising rehabilitation methods and clarifying the role BFR may have on accelerating recovery.

7.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

In healthy patients, there have been demonstrated benefits in knee extension torque and cross-sectional area, although inconsistencies in study protocols limit interpretation [5, 9, 10]. A randomized controlled trial has demonstrated that BFR can have benefits not just distal to the area of occlusion, but also proximally on the ipsilateral extremity and even on the contralateral extremity which may be attributable to the systemic benefits of the training [1-3, 5].

Orthopaedic studies to date have largely focused on BFR in patients undergoing anterior cruciate ligament reconstruction, as it is well-described that this group has significant quadriceps atrophy. Thus far these studies have proven to be safe and do demonstrate the possibility in reducing atrophy [5-11]. Studies, however, are limited in the population of patients undergoing arthroscopic meniscus repair and other orthopaedic knee conditions. Patients undergoing arthroscopic meniscal repair also have decreased quadriceps force production like those undergoing anterior cruciate ligament reconstructions which is exacerbated by a period of immobilization post-operatively [12,13]. Furthermore, patients with knee osteoarthritis have also been found to have increased quadriceps muscle atrophy [28]. This diminished strength contributes to poor loading mechanics, therefore increasing the risk of further injury and osteoarthritis [14, 15].

Therefore, it is of interest to pursue rehabilitative protocols aimed at improving strength in those with orthopaedic knee conditions, including arthroscopic meniscus repair, as it is important to discover if BFR can cause a clinical difference in those with perhaps less natural quadriceps atrophy than those undergoing anterior cruciate ligament surgery. One pilot study evaluated BFR after knee arthroscopy (including several heterogenous procedures) and demonstrated nearly two times increased extension strength compared to controls, hinting that benefits may not be just in those with as severe quadriceps atrophy as seen in anterior cruciate ligament injuries.

7.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

7.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

(•) Yes ( ) No

7.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Social media-based research activities
- [x] Observation

- [x] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [x] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [x] Randomization to one intervention versus another
- [ ] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

7.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Patient selection:

Patients will be recruited for participation prior to beginning rehabilitation. We will include male and female patients with an age range of 18 to 60 years old. Patients will be recruited from the Sports Medicine division of the UCSF Department of Orthopaedic Surgery. There are 5 fellowship-trained sports surgeons who will actively recruit patients for this study. Our group has had prior success in randomized controlled trials. Patients will be excluded if they have risk factors for venous thromboembolism, including cancer, currently on oral contraceptive medications, or prior history of thromboembolism. Additional exclusion diseases include sickle cell anemia, Diabetes Mellitus, and vascular disease for increased risk for vascular complications.

Post-operative physical therapy will be completed at one of two UCSF outpatient physical therapy locations or through telehealth with a UCSF physical therapist. There are at least four faculty physical therapists who will participate in this study, all of whom are board-certified orthopaedic clinical specialists and are familiar with BFR techniques.

Study design:

This study will have two parallel arms. The first one will be a **double-blinded, single-institution, randomized controlled trial** of patients undergoing in-person rehabilitation following arthroscopic meniscus repair. The second will be a **single blinded, single institution, prospective clinical trial** of patients undergoing in-person or telehealth rehabilitation of orthopaedic knee conditions. In both arms, the study compare (1) a standard-of-care

rehabilitation protocol versus (2) standard-of-care rehabilitation combined with BFR training with cuff occlusion applied to the affected extremity. All patients will be enrolled prospectively, prior to beginning rehabilitation. Patients with arthroscopic meniscus repair who are unable or choose not to participate in in-person rehabilitation will be allowed to undergo telehealth rehabilitation through the second arm of this study. Rehabilitative exercises would be advanced per the physical therapists' discretion with similar exercises for patients in both groups for direct comparison. For patients undergoing meniscus repairs, these standardized post-operative protocols will include a period of non-weightbearing followed by a period of weightbearing as guided by the surgeon. Intra-operatively, or prior to the initiation of the rehabilitation, the following will be noted to guide future analysis: Outerbridge Scale of Cartilage Injury, the type of meniscus tear, type of repair, and the percentage of meniscus resected. Clinical records would be reviewed for clinical, operative, and imaging data.

Aim 1: Evaluate the force production and strength of the affected extremity after BFR compared to those in the standard rehabilitation control group.

Hypothesis 1*: Force production, as measured by peak force determined via hand-held dynamometer at 30 and 90 degrees of knee flexion for quadriceps and hamstrings, will be significantly higher after rehabilitation with incorporation of BFR relative to patients without BFR.*

***Rationale*:** If it is shown that BFR can improve strength and limit atrophy in patients with orthopaedic knee conditions, it will provide an avenue of rehabilitation for quicker recovery.

***Approach*:**

The BFR protocol itself is guided by prior studies. While there has not been a consistent protocol used, several themes in the more recent studies remain constant and would be used. Tourniquet setting would be set to 80% of the extremity arterial limb occlusion pressure (LOP) recorded with the patient lying supine, which is similar to that of prior studies and therefore varies with a patient's personalized occlusion pressure [5, 11, 16].

Using the Delfi Personalized Tourniquet System during in-person, the exercises would be performed as guided by the physical therapist (Appendix 2). Subjects undergoing telehealth BFR rehabilitation will be given a SAGA BFR unit and various resistance bands to use through the duration of the study (Appendix 3). The telehealth subjects will be instructed on safe utilization of the SAGA BFR unit under direct supervision of a licensed physical therapist who is certified in BFR. Subject education will also emphasize that the SAGA BFR device should only be utilized with the parameters and exercises that are prescribed by the physical therapist. These specific exercises and parameters will be reviewed, modified when indicated, and written for the patient's reference during each physical therapy session. Participants will also receive written instructions on properly operating the SAGA device for
reference. Patients in the telehealth group would be expected to return the SAGA BFR device upon completion of their rehabilitation protocol.

The Delfi and SAGA BFR systems are readily available within the UCSF Physical Therapy department and both have the benefits of automatically calculating a patient's specific LOP, having a pressure application and interval timer, and a reps indicator. Varying sizes of tourniquet are available with limb protection sleeves. The devices will be calibrated upon start-up of each session to ensure accurate measurement and proper instrument operation and allows for auto-regulation of pressure. The devices come with both audio and visual safety alarms warning of under- or over-pressurization. There is no difference in risk profiles between the Delfi and SAGA BFR devices. Both devices are automatic pneumatic BFR systems that provide the greatest accuracy of personalized BFR pressures, constantly monitor for maintenance of pressure, allow for immediate pressure release, and are superior to manual and non-pneumatic BFR bands that are commonly utilized in both clinical practice and BFR research.

For participants in both the control and BFR training groups, exercises performed in the rehabilitation protocol would progress as guided by patient function from contractile to bodyweight exercises to additional low-load resistance [5, 11, 16]. Exercises included and the specific in-person and telehealth rehabilitation protocols are noted in Appendix 2 and Appendix 3, respectively.

The in-person rehabilitation control group will have a cuff applied but inflated to a value of 20-30 mmHg, which will not occlude blood flow to the affected extremity.

The rehabilitation protocol would be performed for a total of 8-12 weeks. Postoperative rehabilitation will be divided into a non-weightbearing and weightbearing/strength-building phase as guided by surgeon discretion after meniscus repair. Rehabilitation would begin within 3-7 days after meniscus repair. Of note, in the non- weightbearing phase, low-intensity neuromuscular

electrical stimulation (NMES) will be combined with BFR [20]. Non-postoperative patients will be progressed through standardized exercises according to patient strength and tolerance at the discretion of the physical therapist, as outlined in Appendix 3.

For both the in-person and telehealth rehabilitation groups, 4 sets of 30-15-15-15 repetitions would be performed per exercise with 15-30s rest between sets while the cuff is inflated. Exercises will be progressive loaded per physical therapist discretion with a goal of an exercise intensity of 20-30% 1-RM with 30-45s rest between sets. Occlusion will be maintained throughout the inter-set rest time, but patients will be given non-occlusive rest between exercises if desired by the patient or as guided by the physical therapist between exercise demonstrations and set-up. The reperfusion timer associated with the tourniquet system will ensure adequate reperfusion time between pressurization cycles. Postoperative patients will attend physical therapy sessions twice a week for the non-weightbearing period (typically up to six weeks) and once-to-twice a week during the weightbearing phase. Non-postoperative participants will meet with their physical therapist once-to-twice per week through the entire study period. RPE would be evaluated to strive for a goal RPE of 7-8 during the rehabilitation session.

Measurements taken by trained physical therapists at UCSF (who are blinded to the patient's assigned study group) would be taken between weekly or less frequent intervals for patients undergoing telehealth rehabilitation. These would include peak quadriceps/knee extension force and hamstring force production at 30 and 90 deg of knee flexion, measured as standard with a hand-held dynamometer which is readily available in the physical therapy center. Limb circumferences of the thigh and leg would be taken at two distances: 1/3 and ½ proximal along the length from the tibial tuberosity to the greater trochanter. The circumferences each would be assessed with tape measure three times for averaging.

The rehabilitation protocols themselves are standard-of-care rehabilitation, guided by the surgeon/physician and the physical therapist, and would be unchanged aside from the intervention of the BFR cuff in the intervention group. **These measurements are routinely taken by the physical therapists**.

Expected Outcomes*:* We expect to see increased strength measures and increased limb circumferences in the BFR rehabilitative protocol group relative to the standard-of-care group.

Aim 2: Compare performance on functional outcome measures relative to those in standard-of-care rehabilitative protocols and secondarily evaluate patient-reported outcomes.

Hypothesis 2*: Functional outcome scores, as measured via standard scoring for single leg squat and Y-balance tests, as well as patient-reported outcomes measured via the International Knee Documentation Committee (IKDC) score will be higher in those patients undergoing BFR training relative to those undergoing standard therapy*.

***Rationale*:** By having a rigid physical therapy protocol with possibly increased quadricep strength secondary to BFR, we would expect better knee control and ability to complete functional testing to appropriate safe standard. Performing adequately on functional testing is critical to advise return to activity and sport. Patient-reported outcome measures are representations of patient perception, and it is important to understand patient perception of pain and function after the different rehabilitative protocols.

Approach: Standard functional milestones to be evaluated are: single leg squat test, 3-hop test, and Y-balance test. These tests are used routinely in the clinic to evaluate control of knee mechanics, proprioception, and balance. All of these are important functions to return to activity safely. These tests will be evaluated post-operatively at 6 weeks, 3 months, and 6 months. Rating of these tests will be performed by the surgeon in the clinic at the post-operative visits as has been previously described and on both the operative and non-operative extremities [21-24] and compared between groups using the associated scoring scales. **These functional tests are a part of standard post-operative and orthopaedic evaluation**.

In addition to these functional measures, patient reported outcomes would be measured at each clinic follow-up visit via the International Knee Documentation Committee (IKDC) outcome score, which has been demonstrated to demonstrate higher performance on measurements in those with meniscal injuries compared to Knee Injury and Osteoarthritis Outcome Score (KOOS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) [25]. This evaluation is subdivided into sections for symptoms, sports activities, and function and would be available for sub-analysis. The IKDC survey will be administered at 6-week, 3-month, and 6-month after beginning rehabilitation. **These IKDC surveys would be administered for research purposes and are not routinely used in post-operative or orthopaedic clinic visits**.

Expected Outcomes: We expect to see higher scores on functional measures in the BFR rehabilitation group compared to the standard of care group. Secondarily, we anticipate better IKDC outcome score in those undergoing BFR training compared to standard therapy.

In summary,

(1) Patient-reported outcomes (PROs) will be taken prior to, during, and after rehabilitation

(2) Strength and thigh circumference measures will be taken and if the subject may not tolerate strength testing on the injured side, we will use the contralateral uninjured leg as a baseline for strength

(3) Functional testing will *not* be performed when the surgeon, physician, or physical therapist determine the patient would be at risk for further injury due to pain, weakness, instability, etc.

7.10 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ from the care that people would otherwise receive at this institution or the study site if not being done locally:

The research procedure and protocol involves minimal change to standard clinical practice. The primary difference is that the intervention group would be performing the same exercises as the standard-of-care rehabilitation control group with the addition of the blood pressure cuff for blood flow restriction training applied to an occlusive pressure. For the in-person rehabilitation control group will have the cuff applied, but inflated only to 20-30 mmHg to not occlude blood flow. The International Knee Documentation Committeee (IKDC) survey is not routinely administered in our orthopaedic or physical therapy clinic visits, but would be administered to both groups as a measure of patient-reported outcomes.

7.11 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

The International Knee Documentation Committee (IKDC) survey will be administered to patients in both study arms at 6-week, 3-month, and 6-month clinic visits or electronically.

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

7.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

○ Yes ◉ No

7.13 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

Power Analysis:

Aim 1 – *Knee Extension*

In a previously published study by Bowman et al., knee extension torque in this RCT's BFR group increased by 11% +/- 13 and the knee extension torque in the control group increased by 3% +/- 9 [5]. Using this data, the effect size expected is 0.72. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 50 patients (25 per group) for patients following meniscus repairs and 25 patients with additional orthopaedic knee conditions.

Aim 2 – *Y-balance testing & IKDC*

In Hughes et al. recent study comparing BFR to traditional heavy load resistance training in post-surgery ACL patients, Y-balance testing was most similar in the anterior direction, with scores normalized to leg length 32.9 +/- 9.7 for the BFR group and 17.5 +/- 6.7 in the traditional group [26]. Using this data, the effect size expected is 2.23. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 8 patients (4 per group) for Y-balance testing. For IKDC, overall mean difference in that paper was 35.63 +/- 7.06 for the BFR group and 23.33 +/- 8.76 for the traditional group [26]. The effect size with this data is 1.54. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 14 total patients for IKDC (7 per group). Of note, Irrgang et al. described the international knee documentation committee (IKDC) subjective knee form and determined the value for a true change in score of 9.0 points which was achieved in that study [27].

Overall, the power analysis is most limited by knee extension (75 total patients or 25 per group). To account for dropout, canceled surgeries, and patients who are unable to make all of their physical therapy visits, we aim to enroll 40% more, or a goal of **105 patients total (35 per group)**.

Statistical Analysis:

Statistical analysis will be performed comparing groups utilizing non-normative distribution analyses after obtainment of data. The alpha value for significance will be set to 0.05. Confidence intervals will be established on mean strength measures and thigh circumferences. For functional measures and IKDC survey, average scores and standard deviations will be utilized.

7.14 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

Please see a full separate bibliography attached. Most relevant references are below:

- Bowman EN, Elshaar R, Milligan H, Jue G, Mohr K, Brown P, Watanabe DM, Limpisvasti O. Proximal, distal, and contralateral effects of blood flow restriction training on the lower extremities: a randomized controlled trial. *Sports Health* (2019). 11(2):149-156. PMID: 30638439
- Erickson LN, Lucas KCH, Davis KA, Jacobs CA, Thompson KL, Hardy PA, Andersen AH, Fry CS, Noehren BW. Effect of blood flow restriction training on quadriceps muscle strength, morphology, physiology, and knee biomechanics before and after anterior cruciate ligament reconstruction: protocol for a randomized controlled trial. *Phys Ther* (2019). PMID: 30951598.
- Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood flow restriction training after knee arthroscopy: a randomized controlled pilot study. *Clin J Sports Med* (2017). 27(3):245-252. PMID: 27749358.
- O'Donnell K, Freedman KB, Tjoumakaris FP. Rehabilitation protocols after isolated meniscal repair: a systematic review. *Am J Sports Med*. 2017;45(7):1687-1697. PMID: 28256906.
- DePhillipo NN, Kennedy MI, LaPrade RF. Blood flow restriction therapy after knee surgery: indications, safety, considerations, and postoperative protocol. *Arthrosc Tech* (2018). 7 (10):e1037-e1043. PMID: 30377584.
- Lipker LA, Persinger CR, Michalko BS, Durall CJ. Blood flow restriction therapy versus standard care for reducing quadriceps atrophy after anterior cruciate ligament reconstruction. *J of Sport Rehabilitation* (2018). doi: 10.1123/jsr.2018-0062.
- Natsume T, Ozaki H, Saito AI, Abe T, Naito H. Effects of electrostimulation with blood flow restriction on muscle size and strength. *Med Sci Sports Exerc*. 2015;47(12):2621-7. PMID: 26110693.
- Hughes L, Rosenblatt B, Haddad F, Gissane C, McCarthy D. Comparing the effectiveness of blood flow restriction and traditional heavy load resistance training in the post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: a UK National Health Service randomised controlled trial. *Sports Medicine*. 2019:1-19.

8.0 Drugs and Devices

8.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

○ Yes ◉ No

Note: This question is frequently answered incorrectly. If any drugs or biologics, approved or unapproved, are being administered under this protocol, you should check 'Yes' unless you are *absolutely* sure that NONE of the drugs are part of the research protocol. Tip: Ask the PI or the sponsor if you are not sure how to answer this question.

8.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

◉ Yes ○ No

8.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED) Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

○ Yes ◉ No

8.5 LIST THE DEVICES: List the medical devices or in vitro diagnostics to be studied or used. In the device details screen you will be asked questions such as:

- **Whether the device is FDA approved or investigational**
- **Medicare device category**
- **If the device will be provided at no cost**
- **If an IDE is necessary, the IDE number, and who holds the IDE**
- **Risk category of the device**
- **FDA status of the device**

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	Delfi Personalized Tourniquet System	Yes	No	

Manufacturer/Supplier of Device	Delfi Medical Innovations Inc.
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	UCSF Physical Therapy Centers
Will Devices be supplied at no Cost	Yes

Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

⊟	SAGA Blood Flow Restriction Bands	No	Yes	

Manufacturer/Supplier of Device	SAGA Fitness
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	UCSF Physical Therapy Clinics
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	No
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

8.6 * EXPANDED ACCESS: Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

9.0 Sample Size and Eligibility Criteria

9.1 ENROLLMENT TARGET: How many people will you enroll:

105

If there are multiple participant groups, indicate how many people will be in each group:

Our goal enrollment is **105 patients total (35 per group in the randomized control trial and an additional 35 for the non-randomized group)**.

9.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Power Analysis:
Aim 1 – *Knee Extension*
In a previously published study by Bowman et al., knee extension torque in this RCT's BFR group increased by 11% +/- 13 and the knee extension torque in the control group increased by 3% +/- 9 [5]. Using this data, the effect size expected is 0.72. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 50 patients (25 per group) for patients following meniscus repairs and 25 patients with additional orthopaedic knee conditions.

Aim 2 – *Y-balance testing & IKDC*
In Hughes et al. recent study comparing BFR to traditional heavy load resistance training in post-surgery ACL patients, Y-balance testing was most similar in the anterior direction, with scores normalized to leg length 32.9 +/- 9.7 for the BFR group and 17.5 +/- 6.7 in the traditional group [26]. Using this data, the effect size expected is 2.23. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 8 patients (4 per group) for Y-balance testing. For IKDC, overall mean difference in that paper was 35.63 +/- 7.06 for the BFR group and 23.33 +/- 8.76 for the traditional group [26]. The effect size with this data is 1.54. Utilizing a goal of 0.8 power, alpha 0.05, and equal enrollment between groups, power analysis reveals a sample size goal of 14 total patients for IKDC (7 per group). Of note, Irrgang et al. described the international knee documentation committee (IKDC) subjective knee form and determined the value for a true change in score of 9.0 points which was achieved in that study [27].
Overall, the power analysis is most limited by knee extension (75 total patients or 25 per group). To account for dropout, canceled surgeries, and patients who are unable to make all of their physical therapy visits, we aim to enroll 40% more, or a goal of **105 patients total (35 per group)**.

9.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 13-17 years
- [x] 18-64 years
- [ ] 65+

9.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [ ] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [ ] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

9.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [ ] Children / Minors
- [ ] Adult subjects unable to consent for themselves
- [ ] Adult subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [ ] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners
- [ ] Economically or educationally disadvantaged persons
- [x] None of the above

9.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

Male and female patients, ages 18 to 60 years old, who are either: 1) undergoing arthroscopic meniscus repair of either the medial or lateral meniscus, or both. We will include all meniscus repair types (all-inside, inside-out, outside-in). 2) have an orthopedic knee condition, including but not limited to knee osteoarthritis, patellofemoral pain, and status post knee arthroscopy

9.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

- Patients will be excluded if they have risk factors for venous thromboembolism, including cancer, currently on oral contraceptive medications, or prior history of thromboembolism.
- Additional exclusion diseases include sickle cell anemia, Diabetes Mellitus, and vascular disease for increased risk for vascular complications.

Increased risk for vascular complications will be listed as those with hereditary coagulopathies; or evidence of peripheral vascular disease on physical examination, including diminished pulses, skin changes, or history of lower extremity cramping pain with walking. History of venous thromboembolism will exclude a patient from the study.

9.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

(•) Yes ( ) No

9.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

( ) Yes (•) No

10.0 Recruitment and Consent

10.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

○ Yes ◉ No

10.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- [x] Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- [ ] Already approved recruitment registry
- [ ] Re-contact of participants from the investigators' previous studies
- [ ] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool (describe below)
- [ ] CTSI Recruitment Services unit
- [ ] Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- [ ] Other method (describe below)

* Provide details about the subject identification methods: **(REQUIRED)**

Subjects will be identified in the outpatient clinic setting at the UCSF Orthopaedic Institute by one of the staff surgeons/physicians. For the randomized cohort, patients will be identified after having an MRI-confirmed meniscus injury for which surgical management via repair is recommended. Participants would be identified pre-operatively at their pre-operative clinic visit via the inclusion criteria previously described. For the non-randomized cohort, surgeons /physicians will identify patients with orthopedic knee conditions being referred to UCSF physical therapy. Screening of participants for exclusion criteria would be performed by both the treating surgeon and clinical research coordinator.

10.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [x] Investigators' own patients or patients seen within the same practice
- [ ] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [x] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [ ] Other method (describe below)

10.4 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

Eligibility for recruitment will be determined at surgeon/physician clinic visit after an MRI-confirmed meniscus injury for which an arthroscopic meniscus repair surgery is recommended or prior to beginning orthopaedic physical therapy rehabilitation. Both the treating surgeon/physician and the research coordinator will confirm eligibility and that the patients meet the inclusion criteria and do not have any exclusion criteria.

10.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [ ] Potential participant
- [ ] Other (explain below)

10.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [ ] Phone
- [ ] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

10.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

Fellowship-trained sports medicine physicians or orthopaedic surgeons working at the UCSF Orthopaedic Institute will be conducting the initial search for potential participants. These surgeons will identify patients as potential candidates who will require physical therapy rehabilitation after a planned meniscus repair surgery or patients who may benefit from physical therapy for their orthopaedic knee condition. Subjects will be approached in the clinic setting after explaining the diagnosis and offering the standard-of-care treatment. The trial will be explained by the treating physician or surgeon, including randomization into study arms when applicable. If the patient expresses interest in the trial, a research coordinator will visit with the patient during the clinic visit prior to surgery or rehabilitation to discuss the details of study enrollment.

A Participant Information Sheet will be provided to participants by surgeons.

10.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a consent form at the end of the consent discussion (signed consent)
- [x] Provide online 'eConsent' using an E-Signature system
- [ ] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

10.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

The trial will be explained by the treating surgeon including randomization into study arms when applicable. If the patient expresses interest in the trial, a research coordinator will visit with the patient prior to starting physical therapy rehabilitation to discuss the details of study enrollment and consent patients into the study. This would occur in the privacy of the clinic room with the patient. Emphasis will be on voluntary enrollment and consent documents will be provided to the patient. The patient will be offered time to ask questions and will also be given time to consider options if they have not decided by the end of the clinic visit; however, to be enrolled in the study, the patient will need to decide prior to starting physical therapy rehabilitation. Prior to signing the consent form, teach-back will be used to ensure patient comprehension of the study and its goals, and alternative options.

If the research coordinator and patient are not able to meet in person to discuss the study details and consent documents, they can do this remotely via phone or Zoom. The consent form, HIPAA form and California Bill of Rights will be sent through DocuSign and can be signed electronically by the patient.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

CITI Human Subjects Protection training is completed by all study staff conducting consent conversations. All investigators have performed clinical studies both inside and outside of UCSF and all clinical research coordinators have experience with multiple consent processes and the UCSF IRB.

10.10 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [ ] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [ ] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

10.14 TIME: What is the estimated time commitment for participants (per visit and in total):

As is standard, there would be two physical therapy visits per week for minimum six weeks and up to twelve weeks as guided by the therapist. Each physical therapy visit is anticipated to take 30 min. In total, physical therapy visits would therefore take 12 to 15 hours.

Post-operative visits would be as are standard and would occur at two weeks, six weeks, three months, and six months and would be expected to take 30 min per visit, for a total of 2 hours for post-operative visits with the surgeon.

Of note, this time would be comparable with a standard-of-care physical therapy program.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

10.15 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

(•) Yes ( ) No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Patients would ordinarily receive the same surgery and/or physical therapy rehabilitation whether or not they are involved in the study. If not in the study, they would also undergo a similar set of exercises as guided by physical therapists and would have the same routine surgeon/physician clinic visits. Physical therapy visits would likely taper earlier if not involved in the study (Patients may decrease to once weekly visits earlier if progressing well with physical therapy). They would not have as many post-operative measures of strength, thigh circumference, or patient-reported outcomes if not a participant. The study adds the use of the blood flow restriction device in the intervention group in a formalized and randomized process for direct comparison; however, the use of this device is already occurring with our physical therapists in routine post-operative visits as well so patients not in the study may be exposed to the intervention in a less standardized fashion.

10.16 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

(•) Yes
( ) No
( ) Not applicable

11.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

11.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

(•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

11.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

(•) Yes

If **no**, a waiver of authorization can NOT be granted.

11.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

11.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [ ] Postal addresses
- [ ] Phone numbers
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

11.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Past medical history and x-ray findings will need to be collected to ensure patients do not meet any exclusion criteria. Patients will be excluded if they have risk factors for venous thromboembolism, including cancer, currently on oral contraceptive medications, or prior history of thromboembolism. Additional exclusion diseases include sickle cell anemia, Diabetes Mellitus, and vascular disease for increased risk for vascular complications.

Note: HIPAA requires that you collect the minimum necessary.

11.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

Identifiable data collected to determine eligibility for recruitment will be destroyed after participant enrollment has closed.

12.0 Risks and Benefits

12.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [ ] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [x] Risk of pain or physical discomfort caused by the research intervention
- [ ] Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

12.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

Patients may have difficulty tolerating the BFR training. Although prior studies do not report much patient discomfort, we aim for an RPE of 7-8. This may not be tolerable for all patients, and if it is not, it is important to note this when planning for a future rehabilitation protocol. We have accounted for potential patient dropout if patients later decide to decline the BFR protocol.

With meniscus injuries and with post-operative immobilization to protect surgical repair, patients may experience quadriceps atrophy. This is a normal result of immobilization and not related to the study intervention. The goal of the study intervention is to seek a way to minimize this risk using the BFR training.

Risks and side effects related to the blood flow restriction training include those which are:

Likely

- Soreness during or after activity
- Muscle fatigue

Less Likely

- Pain at the site of the blood pressure tourniquet/cuff

Rare but serious

- Blood clots

Venous thromboembolism was an initial theoretical concern with blood flow restriction training. However, this method of training has also been shown to be safe and may even decrease risk of deep venous thrombosis [6, 7]. A recent systematic review evaluating adverse events after blood flow restriction training noted just one instance out of 322 patients included of upper extremity deep venous thrombosis in a patient for whom BFR was used to manage thoracic outlet syndrome; it is unclear if in this patient the thrombosis pre-existed or was a result of the BFR [28].

12.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

Patients will be notified of their right to remove themselves from the study at any timepoint. The physical therapists administering the BFR protocol to the intervention arm will review with the patients prior to their physical therapy session that if they feel undue discomfort that they can notify the therapist who will cease the intervention. This is already a part of the routine practice of our physical therapists utilizing BFR.

With regards to the quadriceps atrophy that patients experience in the setting of meniscus injury and immobilization after meniscus repair surgery, physical therapy in general can help counter this risk. However, patients still will expect some atrophy and therefore the goal of the study is to evaluate a way to counteract this atrophy with BFR training.

The BFR devices themselves have both audio and visual alarms warning of under- or over-pressurization of the blood pressure cuff that will be monitored by the physical therapist for safety of use.

Risk minimization plans for risks associated with BFR training:

Likely

- Soreness during or after activity
- Muscle fatigue

For each of these risks, the patient will be informed of muscular soreness and muscle fatigue as may occur with exercise activity. The patient will be monitored and involved in a discussion with the physical therapist throughout the training to ensure the patient is able to tolerate muscle soreness. Patients will be advised on adequate hydration and fueling as would be important for recovery after routine exercise.

Less Likely

- Pain at the site of the blood pressure tourniquet/cuff

For this risk, the patient will be asked about their rate of perceived exertion and their pain level throughout the physical therapy session. If the patient's pain level is high and they would like to cease activity, they will be informed to let the therapist know immediately and the regimen will be stopped. The therapist will be routinely asking the patient about their pain level while training.

Rare but serious

- Blood clots

For this risk, the patient will be advised on the signs and symptoms of blood clots, for which patients are at increased risk in the post-surgical setting or in instances of immobilization. In arthroscopic procedures, no post-operative venous thromboembolism prophylaxis is recommended. The use of the blood pressure tourniquet system does not appear to significantly increase risk of blood clots, but the patient will be advised on signs and symptoms and evaluate for these at their post-operative clinical visits.

12.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

All of the methods described are feasible with the current research group, orthopaedic practice, and physical therapy center. The surgeries and rehabilitative protocols are as standard for appropriate patient care and will be part of the insurance-covered physical therapy program.

Clinical

All surgeries would be performed at the UCSF Orthopaedic Institute. This is a high-volume orthopaedic outpatient center with currently up to four operating rooms running four days a week. The practice includes seven fellowship-trained orthopaedic sports surgeons. A review of

case logs for the month of April 2019 demonstrated 11 meniscus repair surgeries over the four-week course. Technical equipment to perform these surgeries is readily available and the surgeries are a routine part of the practice.

Two physical therapy centers are associated with the UCSF Orthopaedic Institute that would be available for patient use.

For any unanticipated events, the Orthopaedic Institute is approximately 0.7 miles from the UCSF Benioff Children's Hospital Emergency Room at Mission Bay and 1.8 miles from the Zuckerberg San Francisco General Hospital Emergency Room. On-site at the Orthopaedic Institute, there are highly trained surgeons and operative and perioperative nurses available.

Major Equipment

The physical therapy centers include numerous trained physical therapists with training in the use of hand-held dynamometers to be used in torque measurements, and those devices are already on site. Currently the two Delfi Personalized Tourniquet Systems and four SAGA BFR Band Systems are available. At minimum there are currently four physical therapists available for the project who are trained in the use of the BFR systems. Standard physical therapy equipment including balls, bands, and foam rollers are available for use. The physical therapy department has NMES that is already being used on patients post-operatively that can be utilized during the non-weightbearing phase of training as previously mentioned.

12.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [x] Health and lifestyle changes may occur as a result of participation
- [ ] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

12.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

Blood flow restriction training has been shown to carry few risks. This method of training has been shown to be safe and may even decrease risk of deep venous thrombosis [6, 7], which was previously thought to be a potential risk. The most recent protocols show the potential to decrease quadriceps atrophy [5-11], which could enhance patients' functional and satisfaction measures post-operatively after a period of non-weightbearing. If there is no benefit seen with the intervention, participants would expect to see a similar result to those without the intervention. However, in the intervention arm we anticipate positive results with improved quadriceps strength which may lend to better functional measures, patient-reported outcomes, and return to activity.

13.0 Data and Safety Monitoring Plan

13.1 * DATA AND SAFETY MONITORING PLAN (DSMP): (REQUIRED) Provide a summary of the DSMP:

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

Data collection will be monitored by the clinical research coordinator. Data will be collected via a UCSF REDCap database which is HIPAA-compliant and secure. The research coordinator will be in charge of the database and blinded data will be presented to the researchers for data analysis and review. Study progress will be monitored by the research coordinator and the PI, including the total number of enrollees, surgical dates, and completion of physical therapy sessions and post-operative follow-up. Study progress will be monitored monthly at the UCSF Sports Medicine monthly research meeting.

In addition to data for the purposes of analysis (such as functional outcomes and measures taken in the physical therapy sessions), adverse events, unanticipated problems, and complications will be reviewed by the physical therapists, the PI, and the research coordinator. All of these complications will be reviewed immediately by the study group with immediate notification to the PI and clinical research coordinator.

Interim data analysis will be conducted once over 50% of the patients have been enrolled and completed their post-operative follow-up appointments including functional outcome scores.

Patients reserve the right to withdraw from the study at any time. Patients will be removed from the study intervention if they are unable to tolerate the discomfort or are unable to attend the appropriate number of physical therapy sessions. The study protocol will be re-evaluated at any time of adverse events or complications from the intervention and the study will be stopped if there are concerns for unanticipated risks.

13.2 * DATA AND SAFETY MONITORING BOARD (DSMB): (REQUIRED) Will a Data and Safety Monitoring Board (DSMB) be established:

- ○ Yes
- ◉ No

Guidelines

A Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a formal, independent committee that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety, efficacy,

appropriateness, relevance, and integrity of the study.

The UCSF IRB reserves the right to request a DSMB/DMC for any study. However, the following are factors that the IRB will consider when making this determination:

- There is a significant likelihood of a serious adverse event to subjects
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions
- A study for which the performance of an interim analysis is crucial for the protection of the subjects
- First use in humans
- First use in children
- The study involves gene therapy, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

14.0 Confidentiality, Privacy, and Data Security

14.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [ ] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

14.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

○ Yes ◉ No

14.3 SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

○ Yes ◉ No

14.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

14.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

○ Yes ◉ No

14.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obain a Certificate of Confidentiality:

○ Yes ◉ No

14.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

○ Yes ◉ No

14.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- ☑ Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- ☐ Added to the hospital or clinical medical record
- ☑ Created or collected as part of health care
- ☑ Used to make health care decisions
- ☑ Obtained from the subject, including interviews, questionnaires
- ☐ Obtained ONLY from a foreign country or countries
- ☐ Obtained ONLY from records open to the public
- ☐ Obtained from existing research records
- ☐ None of the above
- ☐ Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH

In addition to signing a consent form, each subject will have to sign the UCSF Research Subject Authorization Form (HIPAA Form). Upload the HIPAA Authorization Form in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits. Please call the IRB office at 415-476-1814 if you have questions about HIPAA research requirements.

If derived from a medical record, identify source:

Epic Apex

14.10 * IDENTIFIERS: Check all identifiers that will be collected and included in the research records, even temporarily: (REQUIRED)

- ☑ Names
- ☑ Dates
- ☐ Postal addresses
- ☑ Phone numbers
- ☐ Fax numbers
- ☑ Email addresses
- ☐ Social Security Numbers*
- ☑ Medical record numbers
- ☐ Health plan numbers
- ☐ Account numbers
- ☐ License or certificate numbers
- ☐ Vehicle ID numbers
- ☐ Device identifiers or serial numbers
- ☐ Web URLs
- ☐ IP address numbers

- [ ] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

- (•) Yes
- ( ) No

14.11 * PATIENT RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

- (•) Yes
- ( ) No

14.14 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [ ] Drug or alcohol abuse, diagnosis or treatment
- [ ] HIV/AIDS testing information
- [ ] Genetic testing information
- [ ] Mental health diagnosis or treatment
- [x] None of the above

14.18 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- [ ] Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial management portal
- [x] UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- [ ] Other web-based online surveys or computer-assisted interview tool
- [ ] Mobile applications (mobile or tablet-based)
- [ ] Text Messaging
- [ ] Wearable devices
- [ ] Audio/video recordings
- [ ] Photographs
- [ ] Paper-based (surveys, logs, diaries, etc.)
- [ ] Other:

* What online survey or computer assisted interview tool will you use: **(REQUIRED)**

- [ ] Qualtrics (Recommended)
- [x] RedCAP (Recommended)
- [ ] Survey Monkey (NOT recommended and may require UCSF ITS Security review)
- [ ] Other

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- [ ] Study sponsor
- [x] UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
- [x] UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
- [ ] Personal devices, such as laptops or tablets that are not owned or managed by UCSF
- [ ] SF VAMC

- [ ] Zuckerberg San Francisco General Hospital
- [ ] Benioff Children's Hospital Oakland
- [ ] Langley Porter Psychiatric Institution
- [ ] Other UCSF affiliate clinic or location (specify below)
- [ ] Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
- [ ] Other academic institution
- [ ] 3rd party vendor (business entity)
- [ ] Other (explain below)

14.19 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

- ○ Yes
- ◉ No

14.20 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

- ○ Yes
- ◉ No

15.0 Financial Considerations

15.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

- ○ Yes
- ◉ No

15.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

- ◉ Yes
- ○ No

Describe the costs that may be incurred by subjects or 3rd party payers as a result of participation:

- Explain why it is appropriate to charge those costs to the subjects
- If this is a therapeutic study, compare subjects' costs to the charges that would typically be associated with receiving care off-study (e.g. is it more expensive to participate in this study than to receive care off-study?)

Subjects or their insurance will be charged for their outpatient clinic visits, surgery, and physical therapy visits. As these are patients already undergoing surgery or rehabilitation, all costs are standard-of-care and would be incurred whether patients were part of the study or not.

There are no additional costs associated with the use of the BFR device.

16.0 Other Approvals and Registrations

16.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

- ○ Yes
- ◉ No

16.2 * HUMAN GENE THERAPY: Does this study involve human gene therapy: (REQUIRED)

○ Yes ◉ No

16.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

17.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

17.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, SFGH, VAMC, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a

modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Dr. Lansdown, Drew MD, MD	Principal Investigator - oversee study, study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Assistant Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Dr. Feeley, Brian T MD, MD	Co-Principal Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Professor in Residence; MD. Chief of Sports Medicine and Shoulder Service, UCSF Dept of Orthopaedic Surgery; MD.
Arriaga-Martinez, Ivan	Co-Principal Investigator - study design, data analysis, physical therapy data obtainment, manuscript preparation	Doctor of Physical Therapy; DPT.
Sampson, Hayden	Clinical Research Coordinator - review of protocols, consenting patients, administering of surveys, conducting patient follow-up, data management	Clinical Research Coordinator, UCSF Dept of Orthopaedic Surgery - Sports Medicine.
Dr. Ma, C. Benjamin MD, MD	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Professor in Residence; MD. Vice Chair of Adult Orthopaedic Clinical Operations, UCSF Dept of Orthopaedic Surgery; MD.
	Other Investigator -	

Zhang, Alan L, MD	study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Associate Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Carpio, Jocelyn G	Clinical Research Coordinator - review of protocols, consenting patients, administering of surveys, conducting patient follow-up, data management	Clinical Research Coordinator in the UCSF Dept of Orthopaedic Surgery - Sports Medicine.
Freitas, Nina	Other Investigator - study design, data analysis, physical therapy data obtainment, manuscript preparation	Doctor of Physical Therapy; DPT.
Laroque, Elly S	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Chiu, Jonathan V	Other Investigator - study design, data analysis, physical therapy data obtainment, manuscript preparation	Doctor of Physical Therapy; DPT and Orthopaedic Clinical Specialist (OCS).
Colyvas, Nicholas	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; Director of the UCSF Meniscus Preservation Center; MD.
Dr. Wong, Stephanie E MD, MD	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Assistant Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Edwards, Sara	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Orthopaedic Surgeon, Associate Professor, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
	Other Investigator -	

Cole, Elliott W	study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Clinical Fellow, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Theismann, Jeffrey	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Clinical Fellow, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.
Wang, Kevin	Other Investigator - study design, data analysis, clinic data obtainment, manuscript preparation; will be obtaining informed consent	Clinical Fellow, UCSF Dept of Orthopaedic Surgery - Sports Medicine; MD.

17.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., VAMC, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role

No External Personnel has been added to this IRB Study

Please describe the study responsibilities and qualifications of each affiliated person listed above:

18.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**, where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.