Reduction of Risk Factors for ACL Re-injuries using an Innovative Biofeedback Approach
"ACL Biofeedback Pilot"

Protocol Number: IRB# 17-007

NIAMS# R21AR069865-01A1

National Clinical Trial (NCT) Identified Number: NCT03273673

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Sponsor: Virginia Tech: Biomedical Engineering and Mechanics

Funded by: NIAMS

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Summary of Changes from Previous Version:

Date & Version	Affected Section(s)	Summary of Revisions Made	Rationale
07/31/2017 V1.1	6.1 & 8.2	Added description of the adjustable stool and the specific height for the stool so that it will be placed within 0.5 inches of the popliteal fold during both the assessment and the biofeedback session.	This change was made in order to standardize the location of the adjustable stool during testing and training for those participants who are able to complete a squat with their heels on the ground and their thighs parallel to the floor.
09/05/2017 V1.2	Title Page	Added the clinical trial identification number	Clinical trial approved through clinicaltrials.gov with the following identification number NCT03273673
11/06/2017 V1.3	1.3	Corrected the tracking time points for the biofeedback interventions	Needed to update the schedule of events to include tracking of Adverse Events as well as the no shows for the biofeedback interventions to indicate that these would be completed at each of the visits, which will occur two times per week for the 6 weeks of the intervention period.
01/02/2018 V1.4	1.3	Updated Table 1.3 Schedule of Activities (SoA)	This table was updated to clarify when various outcome measures were being collected for the various treatment groups.
01/02/2018 V1.4	5.2	Updated the exclusion criteria	Updated the exclusion criteria to include exclusion from the study if a potential participant was still attending formal physical therapy more than two times per week at the time of study enrollment
01/02/2018 V1.4	6.1.1	Updated Biofeedback intervention information including information on the warm-up and the foot position during the squat assessments.	To improve clarity and provide details regarding both foot position during the squat testing and training as well as providing details on standardization of pre-intervention warm-up this portion of 6.1.1 has been updated.
01/02/2018	8.2	Additional information provided regarding the set-up of the bicycle for	In order to standardize the assessments being completed as part of this study, additional

V1.4		**warm-up as well as the plyobox used during testing.**	**information was provided regarding the setting of seat height for the bicycle for warm-up as well as the height of the plyobox to be used during both the biomechanical assessments as well as the intervention sessions.**

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STATEMENT OF COMPLIANCE

This clinical trial, which will be referred to as ACL Biofeedback Pilot throughout the rest of the document, will be conducted in compliance with this protocol, the International Conference on Harmonisation Good Clinical Practice (ICH GCP) as well as applicable state, local and federal regulatory requirements. Each engaged institution will have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and will provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) registered with OHRP. Any amendments to the protocol or consent materials will be approved by the appropriate IRB prior to implementation. Select one of the two statements below:

(1) The ACL Biofeedback Pilot trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made by the IRB of record regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Reduction of Risk Factors for ACL Re-injuries using an Innovative Biofeedback Approach
Study Description:	ACL injuries are common among athletes and due to residual muscle weakness, limited knee motion and asymmetrical movement patterns after surgery many of these athletes will sustain secondary ACL injuries following return to sports. This project seeks to determine if a novel biofeedback-based rehabilitation approach can decrease a known risk factor for secondary injuries to the ACL. The project specifically focuses on correcting asymmetric movement patterns, a known risk factor for secondary injury that is not directly addressed by existing interventions through a 6 week therapy based biofeedback intervention.

Objectives:	*Primary Objective*: Determine the impact of a biofeedback training program on decreasing asymmetrical vertical ground reaction forces, frontal plane knee range of motion and the peak knee extension moment, known risk factors for secondary ACL injuries. *Secondary Objectives*: To demonstrate our ability to recruit, retain and determine patient compliance in completing a biofeedback retraining program.
Endpoints:	*Primary Endpoint for Objective 1:* Peak Knee Extension Moment Symmetry *Secondary Endpoints for Objective 1*: Peak Vertical Ground Reaction Force Symmetry Vertical Ground Reaction Force Impulse Symmetry Frontal Plane Knee Range of Motion Peak Knee Flexion Angle Symmetry Peak Knee Flexion Angle Peak Knee Valgus *Primary Endpoints for Objective 2*: Number of intervention sessions attended (compliance) Number of missed biomechanical assessment time points (retention)
Study Population:	The target sample for this study will include patients between the ages of 14 and 21, who had a primary ACL reconstruction by one of the referring physicians (Southwest Virginia) and plan to return to sport participation. We will be recruiting both men and women for this study with no specific gender breakdown.
Phase:	Pilot Study
Description of Sites/Facilities Enrolling Participants:	This is a single site study for the intervention and testing of enrolled subjects. Four referring physicians will be referring potential participants from a 60-mile radius around Blacksburg, Virginia.
Description of Study Intervention:	This will be a randomized controlled Phase 1, pilot clinical trial. Patients will be assigned to one of two study arms: 1) Biofeedback Intervention, 2) Attention Control. All participants in the study will continue with any other usual medical care they receive for their ACL reconstruction. BIOFEEDBACK INTERVENTION The 6-week biofeedback training program is focused on altering loading and movement asymmetry during biweekly sessions on non-consecutive days (12 sessions). The biofeedback training program will provide sensory (visual and tactile) feedback to the subject to heighten awareness of asymmetrical movement strategies (e.g. load shift, movement asymmetry) during a squat. The two exercises that will be completed during the biofeedback training program will be a visual feedback squat and a resisted squat (tactile feedback). Each of these tasks will be completed 30 (3 sets of 10 repetitions) times per session. We will provide a 20 second rest between trials, and a 10 minute break between the

visual and tactile feedback exercises to decrease the effect of fatigue.

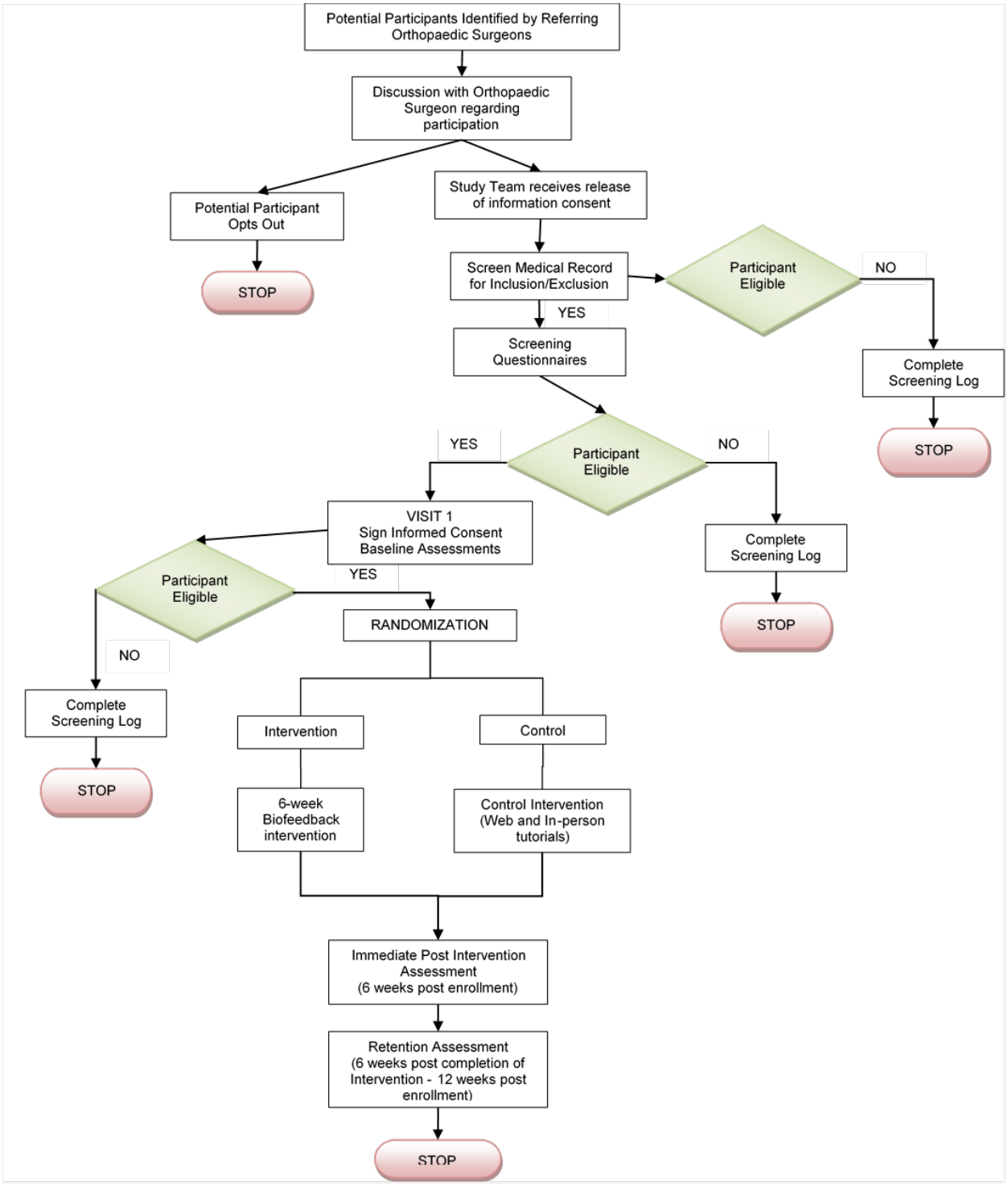
ATTENTION CONTROL

The 6-week attention control group program will focus on providing educational information to the participants related to the clinical and sports expectations as they are released to return to sport. These participants will be asked to meet 6 times during the 6-week intervention time period. Three of these visits will be completed in person and three will be completed using an online educational module (6 sessions). The online sessions will be completed in week 1, week 3, and week 5 while the in person sessions will be completed during week 2, week 4, and week 6. The content of these sessions will focus on providing information on ACL reconstruction, athlete expectation as they return to sport, incidence and risk factors for secondary ACL injuries, as well as some suggestions on the gradual progression back into sport.

Study Duration: The estimated study duration is 2 years from the enrollment of the first patient until the completion of data analysis.

Participant Duration: All participant visits will be completed in approximately 3 months (12 weeks) from the date of enrollment until all study visits are completed.

1.2 SCHEMA


Potential Participants Identified by Referring Orthopaedic Surgeons
Discussion with Orthopaedic Surgeon regarding participation
Potential Participant Opts Out
STOP
Study Team receives release of information consent
Screen Medical Record for Inclusion/Exclusion
Participant Eligible
NO
YES
Screening Questionnaires
Complete Screening Log
STOP
YES
Participant Eligible
NO
VISIT 1
Sign Informed Consent
Baseline Assessments
Complete Screening Log
STOP
Participant Eligible
YES
RANDOMIZATION
NO
Complete Screening Log
STOP
Intervention
Control
6-week Biofeedback intervention
Control Intervention (Web and In-person tutorials)
Immediate Post Intervention Assessment (6 weeks post enrollment)
Retention Assessment (6 weeks post completion of Intervention - 12 weeks post enrollment)
STOP

1.3 SCHEDULE OF ACTIVITIES (SoA)

Description	Baseline	6 Week Study Intervention Period						Follow-Up	
	Initial Biomechanical Assessment	Weeks						Biomechanical Assessment 2	Biomechanical Assessment 3
		W1	W2	W3	W4	W5	W6	W6	W12
Informed Consent	X								
Participant Demographics	X								
Participant Surgical Characteristics	X							X	X
Primary Outcome: Peak Knee Extension Moment Asymmetry	X							X	X
Secondary Outcomes	X							X	X
Exploratory Outcome Measures	X							X	X
Control in-person Interventions (No Show)			X		X		X		
Control Online Interventions (No Show)		X		X		X			
Biofeedback Interventions (No Show)		X X	X X	X X	X X	X X	X X		
Activity Level (All Participants) (1 time/week)		X	X	X	X	X	X		
Control Online Interventions (VAS Pain) One time per week		X	X	X	X	X	X		
Biofeedback Interventions (VAS Pain) 3 times per biofeedback session		X X	X X	X X	X X	X X	X X		
Adverse Events	X	X X	X X	X X	X X	X X	X X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Nearly 1 in 60 adolescent athletes will suffer an Anterior Cruciate Ligament (ACL) injury[1,27], at an estimated annual cost of $3 billion, and most will undergo an ACL reconstruction. [23,27,33] Following reconstruction and rehabilitation, adolescent athletes have a 15 fold increased risk of secondary ACL injuries when compared to an uninjured athlete. [31] The high risk of re-injury demonstrates that in many cases current post-operative interventions fail to restore adequate knee motion and neuromuscular control that are needed to decrease injury risk. Indeed, many patients cleared to return to sport by their doctors following ACL reconstruction demonstrate residual muscle weakness and imbalances, as well as asymmetrical movement patterns. [25,31,32,38,39] Based on this knowledge, we contend that one problem with current interventions is their focus on improving strength and joint range of motion while excluding the assessment of lower extremity movement patterns. The current return to sport criteria have been ineffective at returning athletes to sport while decreasing re-tear rates. This is confirmed in the American Academy of Orthopaedic Surgeons' ACL return to sport guidelines, which state a need for restoration of movement, but do not provide objective measures of assessment. [5,16,30] Our preliminary data indicate that following ACL reconstruction and clinical release to return to sports most patients have residual limb asymmetries during jumping and landing.[12,14,25] An article by Paterno et al reports that the primary risk factors for secondary ACL injury risk include asymmetrical frontal plane knee range of motion, and knee extension moment assessed during bilateral landing.[32] These movement deficits are the only factors that have been associated with an increase in secondary ACL injury risk following return to sport. Thus, to decrease the risk for secondary ACL injuries, there is a pressing need to evaluate novel interventions that improve lower extremity movement patterns and restore movement and loading symmetry prior to release to return to full sport participation.

Our preliminary data indicate that through the use of a biofeedback intervention we can 1) reduce risk factors for secondary ACL injury (reduce asymmetrical ground reaction forces, joint angles, and joint moments) one week after the completion of the intervention and 2) subjects are willing to attend biofeedback training sessions. This intervention provides simultaneous visual and tactile biofeedback as patients complete a single body weight task (squat) to alter landing mechanics. Retraining the single body-weight task allows for training in a less ballistic, more controlled environment to restore neuromuscular function. We will complete a randomized trial (control versus biofeedback) using adolescent ACL patients and three-dimensional motion capture (1) to determine the impact of a novel biofeedback training program on decreasing secondary ACL injury risk factors (movement and loading asymmetry[32]), and (2) to establish our ability to recruit and retain patients while assessing intervention compliance and the psychometric characteristics of the outcome measures.

2.2 BACKGROUND

ACL Injury and Re-injury: As many as 200,000 anterior cruciate ligament (ACL) injuries are diagnosed annually in the United States[1,27], and almost all affected patients (94%) seek to restore joint stability by undergoing ACL reconstruction surgery at an estimated annual cost

of $3 billion.[21,22,24] Because most patients receiving ACL reconstruction are adolescents between the ages of 15 and 30[33], many seek to return fully to sports after rehabilitation. Unfortunately, doctors' return-to-play decisions do not usually rely on objective measures of function[5,6]; instead, the decision is most often based on time, typically six to twelve months after surgery[4-6,16,30]. We and others have shown that athletes who are returned to sport based on current guidelines have residual muscle imbalances, muscle weakness, and altered lower extremity mechanics, and these deficiencies can be detected up to two years post-surgery[14,16,30].

Athletes returned to sport prior to appropriate restoration of function are at a greater risk for secondary ACL tears, defined as tears of the ACL graft or contralateral intact ACL. Secondary tears of the ACL are surprisingly common: despite the fact that not all patients return to pre-injury sport participation, up to 29% of all ACL reconstruction patients suffer a secondary tear. In slightly different terms, one study has shown a 15 times greater likelihood of ACL tear in an ACL reconstructed patient compared to a non-injured group.[31] Major risk factors for secondary ACL injury include movement and loading asymmetry between the surgical and non-surgical limbs.[31,32] We recently showed that asymmetrical loading and movement patterns remain after patients have been returned to full sport participation. Thus, secondary ACL injuries are a significant problem that is largely influenced by the failure of current approaches to restore movement and loading symmetry and use objective measures to assess readiness to resume participation in sports.

The Biofeedback Approach to Recovery: Our proposed biofeedback approach has its foundation in retraining programs that were developed and implemented for primary ACL injury prevention. These retraining programs are designed to alter lower extremity mechanics through retraining landing mechanics, a very dynamic and complex task.[28] Such programs have proven effective for primary ACL tears: they decrease the risk factors for injury,[20,28,29,40] however they have not decrease the incidence of ACL tears since implementation[11,20,29,37,40] Our novel biofeedback approach combines successful aspects of these existing programs with visual and tactile biofeedback. This strategy is further informed by recent work that examined the use of visual biofeedback to reduce loading asymmetry.[26] This work demonstrated that loading asymmetry could be attenuated using squatting tasks and visual biofeedback.[26] Current therapy interventions focus on muscle strength and range of motion and are ineffective in decreasing the incidence and risk factors for secondary ACL injuries. This proposal will be the first to implement a biofeedback training program in an ACL reconstruction population. If successful, this work will have a significant impact: it will provide the first retraining program that directly targets and effectively decreases known risk factors for secondary ACL injury risk factors.

Significance of our Approach: With the large proportion and increased incidence of ACL tears in adolescent athletes, it is imperative that we develop interventions to decrease the risk of secondary injuries and improve outcomes. Therefore, the **goals of the proposed study** are to determine the immediate impact of a biofeedback training program on decreasing risk factors for secondary ACL tears and determine if the impact is retained 6 weeks post-intervention. This study will also demonstrate our ability to recruit and retain post-operative ACL reconstruction patients until the completion of the novel biofeedback intervention and to assess their compliance with completing all of the exercises at each training session. In addition, we will determine the psychometric properties of the primary outcome measures, which have been previously identified as risk factors for a secondary ACL injury. This study will provide the foundation for the design and development of future studies that could shift the post-operative rehabilitation paradigm to include the assessment and normalization of

movement and loading asymmetries before patients are returned to sport participation. By changing the post-operative rehabilitation process to include biofeedback, this work will ultimately decrease both health care costs associated with ACL injuries and the number of patients suffering secondary ACL tears.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is a potential risk that participants could injure his/her foot, ankle, or knee or feel off balance while completing these tasks; however, the study team will ensure that the testing area is clean and free of debris. The risk again will be no greater than if the participant were performing these tasks on his/her own and are no more difficult than the sporting tasks that the participant's physician has allowed you to start doing during sport participation or what the participant would be doing at this point during physical therapy. There is a potential risk to the participant's confidentiality. Every effort will be made to maintain his/her confidentiality, however this cannot be guaranteed.

2.3.2 KNOWN POTENTIAL BENEFITS

There will not be any direct benefits to the participant if he/she decides to participate in this research project. The participant will receive additional one-on-one exercise training as well as an explanation of his/her movement mechanics at the completion of the last day of testing if the participant is interested. Research conducted on these data may help researchers to better understand how visual and tactile biofeedback change the way that ACL reconstruction patients move and if these exercises are able to decrease the risk factors for secondary ACL injuries after patients return to sport participation.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks to the participants in this pilot clinical research project are minimal compared to the potential benefits to both these patients as well as future ACL reconstruction patients. The risks of participating in this study are not any greater than the risks in participating in athletics. In order to minimize these risks, we will not ask the participants to complete any activities that have not been approved by his/her treating orthopaedic surgeon and that are not appropriate for the participant's current stage in rehabilitation. The results from this study could alter post-operative rehabilitation following ACL reconstruction leading to a decrease in the number of secondary ACL injuries following return to sports.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the impact of a biofeedback training program on decreasing asymmetrical peak knee extension moment.	Peak Knee Extension Moment Symmetry	Peak knees extension moment asymmetry between the operative and non-operative side is a known risk factors for secondary ACL injuries and is therefore being used as the primary outcome to determine the ability of the biofeedback intervention to decrease a risk factor for secondary ACL injury risk.
Secondary		
To demonstrate our ability to recruit, retain and determine patient compliance in completing a biofeedback retraining program.	• Number of intervention sessions attended (compliance) • Number of missed biomechanical assessment time points (retention)	This is a pilot clinical trial in which we need to determine both compliance with the biofeedback intervention as well as subject retention through the end of the study in order to appropriately plan for a future multi-center clinical trial.
Tertiary/Exploratory		
Determine the impact of a biofeedback training program on decreasing asymmetrical vertical ground reaction forces, frontal plane knee range of motion and the association between each of these measures and the change in the peak knee extension moment symmetry.	*Exploratory Endpoints*: • Peak Vertical Ground Reaction Force Symmetry • Vertical Ground Reaction Force Impulse Symmetry • Frontal Plane Knee Range of Motion • Peak Knee Flexion Angle Symmetry • Peak Knee Flexion Angle • Peak Knee Valgus	The peak knee extension moment is a known risk factor for secondary ACL injury risk, however, it is challenging to collect this measure in a clinical setting as it requires the collection of synchronized three-dimensional kinematic and kinetic data. Therefore, these exploratory endpoints will be assessed to determine their association with the change in symmetry in the peak knee extension moment. Through this analysis we hope to be able to identify additional measures to use in assessing this biofeedback intervention that will be more easily implemented in the clinical setting.

4 STUDY DESIGN

4.1 OVERALL DESIGN

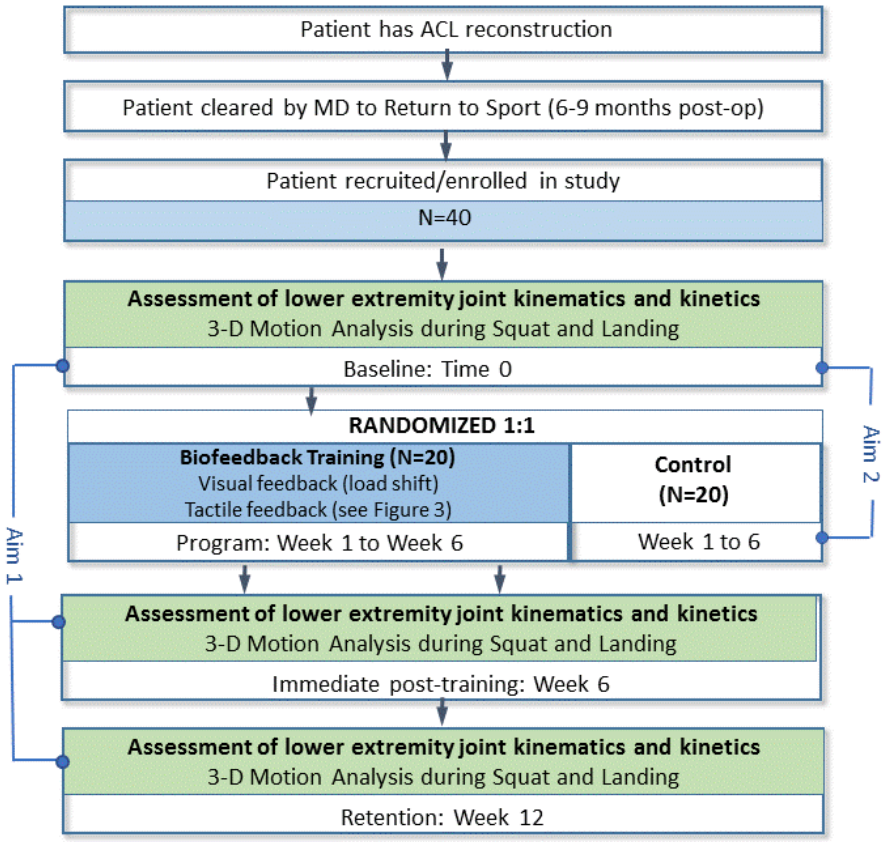
Aim 1: Determine the impact of a biofeedback training program on decreasing asymmetrical vertical ground reaction forces, frontal plane knee range of motion and the peak knee extension moment, known risk factors for secondary ACL injuries.
We will test the hypothesis that our biofeedback program will decrease the risk of secondary ACL injury by improving loading and movement symmetry during the dynamic task of landing from a jump 6 weeks post intervention.

Aim 2: To demonstrate our ability to recruit, retain and determine patient compliance in completing a biofeedback retraining program.
We will demonstrate our ability to recruit 40 ACL reconstructed patients and assess study retention and compliance.

Overview: The goal of this single site, pilot randomized clinical trial is to determine the impact of an innovative biofeedback training program on decreasing surrogate measures of secondary ACL injury risk in adolescent athletes. Movement and loading symmetry will be assessed using the limb symmetry index ($\boldsymbol{LSI} = (\boldsymbol{ABS}\,[\boldsymbol{Surgical} - \boldsymbol{Nonsurgical}])/\boldsymbol{0.5}(\boldsymbol{ABS}[\boldsymbol{Surgical}] + \boldsymbol{ABS}[\boldsymbol{Nonsurgical}]) * \boldsymbol{100}$)[2,3,7,34] prior to (baseline) and at two time points following (immediately following training (efficacy), and 6 weeks after (durability)) the biofeedback training program (**Aim 1**; **Figure 1**).

40 adolescent ACL patients (20 control, 20 intervention) will be recruited. Subjects will be block randomized into either the control arm or the intervention arm at baseline. All intervention subjects will complete an in-person (no home exercises) biofeedback retraining program for 6 weeks (2 times per week) with a focus on improving both load and movement symmetry through the use of tactile and visual feedback (**Figure 1**), which has been reported to be an effective biofeedback intervention[26]. Finally, this study will demonstrate our ability to recruit subjects, engage them in the novel biofeedback program, and retain them until study completion. The outcomes from **Aim 2** will inform future study designs.

Figure 1: Study Flow



Aim 1: Determine short- and long-term effect of biofeedback program on secondary risk factors for ACL re-injury
Aim 2: Demonstrate ability to recruit, retain and determine patient compliance in biofeedback program

Reducing measurement bias: To reduce the possibility of bias, the biofeedback intervention will be completed by a single individual (clinician – Athletic trainer) and the biomechanical assessments will be completed by a second individual who will be blinded to the subject's group assignment (research technician). The research technician will be trained by Dr. Queen to complete the biomechanical assessment using a standard set of directions, while Dr. Williams will train the clinician to complete the intervention using a standard set of instructions in order to decrease between subject variability and provide consistent feedback to the subjects. The intervention instructor will be directly trained by the clinical rehabilitation expert in proper technique and instruction. The clinical expert and the intervention instructor will have a phone call every 3 weeks and the clinical expert will visit the testing site once every 4 months to review procedures and ensure proper instruction throughout the course of the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The control group for this pilot clinical trial is an attention control group that will be completing 6 educational training sessions of the 6 week intervention period. This control group will consist of ACL reconstruction patients who are at the same stage as those that are randomized into the intervention arm, but will receive no additional biofeedback or exercise interventions. The attention control group was selected in order to decrease the chances of finding a group difference based on the additional time that the subjects were in contact with the study team.

4.3 JUSTIFICATION FOR DOSE

Based on previous physical therapy based interventions as well as current clinical practice we have designed this study to be a 6 week intervention in which subjects will attend a biofeedback training session 2 times per week throughout the intervention period. Two times a week was selected so that participants could space out these visits during the week to ensure that they were not attending sessions on subsequent days in order to decrease the risk of muscle soreness during the biofeedback training.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form

2. ACL Reconstruction: primary, unilateral ACL reconstruction with no pain in the contralateral leg
3. Rehabilitation: need to have completed at least 4.5 months of post-operative physical therapy and be within approximately 6 weeks of being ready to be released by his/her treating orthopaedic surgeon to return to full sport participation
4. Stated willingness to comply with all study procedures and availability for the duration of the study
5. Male or female, aged 14-21
6. Willing to adhere to the ACL Biofeedback intervention regimen

5.2 EXCLUSION CRITERIA

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

1. For females: currently pregnant or planning to become pregnant
2. History of more than one ACL reconstruction
3. Post-operative complications that required additional surgical intervention
4. Hospitalization for any reason other than the ACL reconstruction in the last 3 months
5. Plans for additional surgical procedures in the next 12 months
6. Live greater than 60 miles from the research lab
7. Have limitations that would prevent them from attending the biofeedback training sessions
8. Motor neuron diseases, Parkinson's disease, multiple sclerosis
9. Severely impaired hearing or speech (patients must be able to respond to phone calls)
10. No access to a telephone
11. Participating in another ACL intervention outside of standard post-operative physical therapy
12. Attending post-operative physical therapy more than 2 times per week at the time of study enrollment.
13. Inability to understand or speak English (since this will be required for the patient-based intervention)
14. Other self-reported medical problem that would prohibit participation in the study
15. Other health condition or personal issue judged by a study team member or primary care physician to make the patient inappropriate for study participation
16. Knee extension moment limb symmetry index (LSI) greater than or equal to 90% at the time of the initial study assessment

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal

set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment:
The target sample for this study will include patients between the ages of 14 and 21, who had a primary ACL reconstruction by one of the referring physicians. Participants will be excluded if they have a history of more than one ACL reconstruction, post-operative complications that required additional surgical intervention, hospitalization for any reason other than the ACL reconstruction in the last 3 months, plans for additional surgical procedures in the next 12 months, or any other health conditions determined by the study team to be contraindications to participating in the biofeedback program. Patients will also be excluded if they live greater than 60 miles from the research lab or have limitations that would prevent them from attending the biofeedback training sessions. In order to meet inclusion criteria and be enrolled in the study, participants need to have undergone a primary ACL reconstruction, completed post-operative physical therapy and be released by his/her treating orthopaedic surgeon to return to full sport participation.

Based on our prior and ongoing studies, we are confident that 40 participants can be enrolled within the 24 month recruitment period. We will use the electronic medical record to identify all patients who had an ACL reconstruction within the last 4 months or who are scheduled to have an ACL reconstruction with any of the referring orthopaedic surgeons. The medical records will be used to determine eligibility based on study inclusion and exclusion criteria. The parents, if the patient is a minor, of all potentially eligible patients will be approached by the treating orthopaedic surgeon or member of the surgeon's clinical staff. If the patient is over the age of 18, he/she will be approached directly by the treating orthopaedic surgeon. The three referring physicians have been working with the research study team on the recruitment and enrollment of ACL reconstruction patients for the last 4 months on an industry sponsored knee brace study. During this time the study team has been able to implement a successful recruitment procedure in which the patients are identified by the physician extenders in each clinic. These individuals then discuss the research study with the potential subject to determine the subject's interest in participation.

Retention:
All participants will be treated with respect, and we will be considerate of the time and energy that is involved with participation in this study. Participant retention will begin with the recruitment process. Based on medical records and release of information consent forms from the treating physician, only those patients who do not actively opt out will be contacted by phone to receive follow-up information about the study and assess their interest in participating. Once enrolled in the study, all participants will have contact with the study team at each measurement time point (baseline, 6 weeks and 12 weeks). In addition, based on group randomization the participants will also have contact with the study team either two times a week for six weeks or once a week for six weeks. Based on our prior experience, this level of contact helps to keep participants engaged. Calls to participants will also be scheduled at times that are preferred and convenient for each participant. We will also use telephone calls to remind participants about all in-person study visits. Participants not assigned to patient intervention arm will be

asked to complete 3 in-person educational sessions as well as three online training modules over the 6 week intervention period. This will encourage continued participation form patients assigned to this arm. Also, the importance of compliance will be emphasized throughout the study. Participants who do decide to withdraw from study participation however, will be encouraged to complete the study assessments. The reason for any missed intervention sessions as well as assessment sessions will be recorded for future analysis in order to improve planning for subsequent clinical trials.

All successful and unsuccessful attempts to contact participants will be documented within the subjects study record. Additionally, alternate contact numbers will be requested from participants to aide in locating the subject.

Participant recruitment and retention statistics will be collected and monitored on a regular basis such that any problems or negative trends can be identified early and appropriate measures taken and/or procedures modified.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

This will be a randomized controlled Phase 1, pilot clinical trial. Patients will be assigned to one of two study arms: 1) Biofeedback Intervention, 2) Attention Control. All participants in the study will continue with any other usual medical care they receive for their ACL reconstruction.

BIOFEEDBACK INTERVENTION
The 6-week biofeedback training program is focused on altering loading and movement asymmetry during biweekly sessions on non-consecutive days (12 sessions). The biofeedback training program will provide sensory (visual and tactile) feedback to the subject to heighten awareness of asymmetrical movement strategies (e.g. load shift, movement asymmetry) during a squat. The two exercises that will be completed during the biofeedback training program will be a visual feedback squat and a resisted squat (tactile feedback). Each of these tasks will be completed 30 (3 sets of 10 repetitions) times per session. We will provide a 20 second rest between trials, and a 10 minute break between the visual and tactile feedback exercises to decrease the effect of fatigue. Prior to the biofeedback intervention session, each participant will complete a 5-minute warmup on a stationary bike as was described during the biomechanical assessments.

Visual feedback: The simplest way to provide biofeedback during a squat is through visual feedback of load. Under this approach, subjects are asked to stand on force plates, which measure the ground reaction forces (load) beneath each foot. Shoulder width for each participant will be measured as the distance between acromioclavicular joints. This distance will then be measured on the force plates and 2 pieces of tape will be placed this distance apart (one on each force plate) and participants will be asked to stand with one heel on each piece of take. Stance width will be recorded on the data collection sheet and then entered into REDCap so that this distance can be used during each subsequent training and testing session and foot position can be measured and marked prior to participant arrival. Participants face a projection screen that displays two bar graphs of the vertical ground reaction force, depicting each foot's

load. Subjects will be asked to stand with their feet shoulder width apart (one foot on each force plate) with their hands in front on them with the shoulder flexed to 90 degrees for counter weight. The foot width will be standardized to ensure that foot placement is consistent for both the squatting trials as well as during the biofeedback training. The subject will be asked to squat down until their thighs are parallel with the ground or until their heels begin to come off from the ground, whichever occurs first. A stool will be placed behind the subject and will be set to the height where the subject's thigh will be parallel to the ground if they sat down (stool will be placed at the height of the popliteal fold), so that the subject will know the deepest position they have to achieve. If the subject is able to achieve a squat position where the thigh is parallel to the floor they will be instructed to squat until they barely touch down on the bench and then slowly stand back up without transferring any weight to the bench. Subjects are asked to squat down and watch the change in load beneath each foot. After completing the first squat, subjects will be asked to complete all subsequent squats with the goal of keeping the bars level on the graph or maintaining equal within a LSI ≥ 90% (symmetric) load on both feet. This process will be completed a total of 30 times (3 sets of 10 repetitions each) during each of the training sessions with the same goal each time of maintaining the bars at an equal level. This is a simple measure that subject can easily understand and that can be altered through biofeedback.24

Tactile feedback: The second set of exercises at each biofeedback session will be resisted squats. A subject will be asked to squat while an external force is applied to the side of the knee (Figure 3) requiring the subject to work against this resistance to maintain balance and complete the squat. The band will be placed on the surgical limb of each patient and will be pulled at approximately a 45 degree angle toward the contralateral side. Pulling the subject toward the non-operative limb (one that is typically displaying higher loads) will require the subject to pull toward the surgical limb and maintain good frontal plane position by resisting frontal plane valgus. This is a typical exercise utilized in the clinic to aid in equal weight bearing and active hip abduction. The squat position that will be used during these exercises will be the same as the squat position used in both the visual biofeedback task as well as during the biomechanical testing. The subjects will be asked to stand with their feet at the standardized width and again squat until they make contact with the stool that will be positioned behind them during the biofeedback session. Subjects will be asked to complete 30 tactile feedback squats (3 sets of 10 squats) during each of the biofeedback sessions.

ATTENTION CONTROL

The 6-week attention control group program will focus on providing educational information to the participants related to the clinical and sports expectations as they are released to return to sport. These participants will be asked to meet 6 times during the 6-week intervention time period. Three of these visits will be completed in person and three will be completed using an online educational module (6 sessions). The online sessions will be completed in week 1, week 3, and week 5 while the in person sessions will be completed during week 2, week 4, and week 6. The content of these sessions will focus on providing information on ACL reconstruction, athlete expectation as they return to sport, incidence and risk factors for secondary ACL injuries, as well as some suggestions on the gradual progression back into sport.

6.1.2 DOSING AND ADMINISTRATION

The dose for each participant will be dependent on the group to which he/she is randomized. However, the dose will be the same for all participants in the Biofeedback Intervention as well as being the same between all participants in the Attention Control arm of the study.

BIOFEEDBACK INTERVENTION
The 6-week biofeedback training program is focused on altering loading and movement asymmetry during biweekly sessions on non-consecutive days (12 sessions). The biofeedback training program will provide sensory (visual and tactile) feedback to the subject to heighten awareness of asymmetrical movement strategies (e.g. load shift, movement asymmetry) during a squat. The two exercises that will be completed during the biofeedback training program will be a visual feedback squat and a resisted squat (tactile feedback). Each of these tasks will be completed 30 (3 sets of 10 repetitions) times per session. We will provide a 20 second rest between trials, and a 10 minute break between the visual and tactile feedback exercises to decrease the effect of fatigue.

ATTENTION CONTROL
The 6-week attention control group program will focus on providing educational information to the participants related to the clinical and sports expectations as they are released to return to sport. These participants will be asked to meet 6 times during the 6-week intervention time period. Three of these visits will be completed in person and three will be completed using an online educational module (6 sessions). The online sessions will be completed in week 1, week 3, and week 5 while the in person sessions will be completed during week 2, week 4, and week 6. The content of these sessions will focus on providing information on ACL reconstruction, athlete expectation as they return to sport, incidence and risk factors for secondary ACL injuries, as well as some suggestions on the gradual progression back into sport.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable

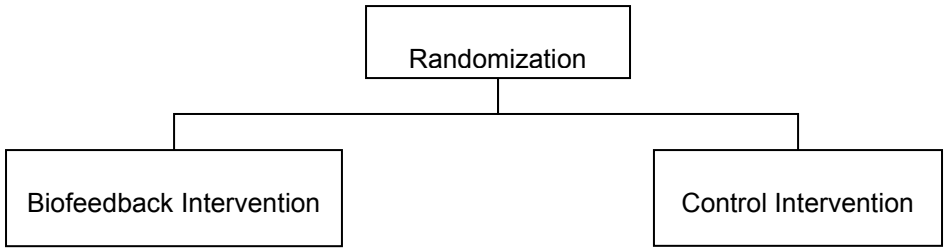
6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This will be a randomized controlled trial (see figure below).

Participating patients will be randomized using a 1:1 between the Intervention vs. Control arms.



Participants will be equally allocated between the two groups, with randomization stratified according to gender, age and activity level to ensure that the groups are balanced in these respects. All participants in the study will continue with any other usual medical care they receive for their ACL reconstruction.

Eligible participants will be randomized following the first biomechanical assessment (during which informed consent is obtained). After this baseline biomechanical assessment, participants will be scheduled for his/her first study visit (biofeedback intervention or control in-person education session) at this time each participant will be informed about the research arm to which they have been assigned. The Research Assistant will call participants within 24-48 hours of each appointment to remind them of their appointment day and time as well as answer any questions.

Randomization will be based on a computer generated sequence maintained by the project statistician. The Research Assistant or Principle Investigator will obtain the randomization status from the statistician.

Participant randomization assignments will be entered and stored in a password protected, study specific database maintained by the research assistant and verified by the study statistician.

As this is an open trial, therefore, participant unblinding procedures are not necessary.

6.4 STUDY INTERVENTION COMPLIANCE

All members of the study staff will endeavor to maximize adherence to the study's protocol and minimize non-compliance. However, it is the responsibility of the Principal Investigator to report all protocol deviations/violations to the Virginia Tech IRB within 10 business days of the time the PI becomes aware to the event. In addition, the PI will include a summary of any protocol deviations/violations in the biannual report to the study's Safety Officer. Protocol deviations will be collected, analyzed, and monitored in the study's protocol deviation log, which is kept in the Investigator's regulatory files within a locked file cabinet. A sample protocol deviation form can be found in the MOOP (Appendix J).

Protocol deviations include, but are not limited to, the following examples:

- Enrollment or randomization of an ineligible participant
- Follow-up visit at a time point different from that specified in the protocol
- Failure to obtain Informed Consent
- Entering a participant into another clinical study

- Failure to keep IRB approval up-to-date
- Wrong treatment administered to participant

6.5 CONCOMITANT THERAPY

Not applicable

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the ACL Biofeedback intervention does not mean discontinuation from the ACL Biofeedback Pilot study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- At the time of discontinuation an AE or SAE report will be completed and submitted to the IRB as well as to KAI per the information included in the MOOP (Section 10.0 Safety Reporting).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Study participant sustains an ACL tear of either limb
- Participant unable to attend the ACL Biofeedback intervention session for 2 days/weeks

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) (MOOP Appendix K). Subjects who sign the informed consent form

and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study staff.

The following actions must be taken if a participant fails to return to the lab for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week of the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls will be made to the participant). These contact attempts will be maintained in the study database.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

All patients will be cleared by their treating orthopaedic surgeon to complete the tasks in this study prior to enrollment. The orthopaedic surgeon will provide the study team with signed confirmation that the patient has been released to complete the study activates based on their current post-operative recovery (physician release letter) as well as providing the patient's confirmation that they approval the release of their information (patient release of information) so that they are able to be contacted by the study team to determine the patient’s interest in participating in the study.

Based on our prior and ongoing studies, we are confident that 40 participants can be enrolled within the 24 month recruitment period. Patients will be identified by his/her treating orthopaedic surgeon as being appropriate for study enrollment at approximately 4.5 months post-ACL reconstruction and safe to complete the study tasks. Once the surgeon and patient have agreed to an interest in study participation and the patient has provided signed consent for release of information, the medical records will be reviewed by a member of the study team to determine enrollment eligibility based on study inclusion and exclusion criteria. All potentially eligible patients (parents if the patient is a minor) will be approached by the treating orthopaedic surgeon or member of the surgeon’s clinical staff. If the patient is over the age of 18, he/she will be approached directly by the treating orthopaedic surgeon. During this discussion, the treating surgeon will explain the activities to be completed during the study and will provide the patient with documentation that the surgeon believes the patient is medically appropriate for study enrollment. The referring physicians have been working with the research study team on the recruitment and enrollment of ACL reconstruction patients for the last year on an industry

sponsored knee brace study. During this time the study team has been able to implement a successful recruitment procedure in which the patients are identified by the physician extenders or the surgeon and the above described procedure has been completed in each clinic. If a patient is interested in participating, the signed consent to release information is sent to the research study team and the secondary medical record screening is completed. Informed consent and assent will be approved by the institutional review board.

Prior to the start of the study, all participants (and parents will complete parental permission and patient will complete ascent if participant is <18 years old) will complete informed consent in person in the lab. The consent form will be sent to the potential participant by email or mail based on the patient's preference prior to study enrollment. Potential participants (parents if the potential participant is a minor) will be allowed to review the consent form prior to his/her first visit to the lab. Each participant will be allowed ample time to review the consent form and determine if he/she is interested in participating in the study. All questions will be answered prior to the consent form being signed and the study being initiated. If a consented subject becomes 18 during the course of the study he/she will be consented as an adult at the next study visit.

Following administration of the consent and HIPAA authorization, we will measure height and weight and determine BMI. If female participants become pregnant, their active involvement in the study will end because later stage pregnancy will alter movement mechanics due to increased joint laxity. In addition, weight gain would also likely confound study results. As part of the telephone screening process, women will be excluded if they self-report being pregnant or planning to become pregnant.

We will aim to ensure that subject selection is equitable and all relevant demographic groups have access to study participation by contacting all patients who meet inclusion / exclusion criteria, regardless of demographic characteristics. We have also aimed to produce recruitment and intervention materials that are appropriate for individuals with low literacy or education levels. We will continue to recruit patients until we reach our sample size goal of n=40.

Screening questionnaire data will be entered directly into the study database. We will have paper copies of screening questionnaires that may be used in cases of computer network failure. We anticipate this will be rare. However, if paper forms are needed, data will then be entered as soon as possible. Any paper copies that are used will be stored in the subject's individual study folders which are kept in a locked file cabinet in a locked office of a study team member.

Subject data for all subjects enrolled in the study will be entered into a secure computerized enrollment log. This data will be accessible only to study personnel needing access to fulfill their study related duties.

8.2 SAFETY AND OTHER ASSESSMENTS

Following recruitment and the completion of informed consent, each subject will be asked to complete an initial biomechanical assessment in the Kevin P. Granata Biomechanics Lab at Virginia Tech. All subjects will be asked to wear form fitting shorts and a shirt, plus a pair of athletic shoes (Nike Pegasus, Nike Inc, Beaverton, CO) all of which will be provided for them to use during testing (Figure 2). Previous literature has shown that differences in footwear can alter the ground reaction forces.35,38 Therefore in a between-subject design comparing two

groups (Aim 1) it is important to alleviate any potential differences due to footwear. Patients will warm up by cycling on a stationary bike at a comfortable pace for 5 minutes. The seat height for the bike will be standardized for all subjects so that when the leg is fully extended at the bottom of the pedal stroke there will be between 5 and 10 degrees of knee flexion. The seat settings will then be recorded on the data collection sheet and entered into REDCap in order to ensure that the same seat settings are used at each visit. After the warm-up, patients will have retro-reflective markers attached at specific locations on both lower extremities to track segmental motion during both squatting and landing. Three-dimensional coordinate data will be collected using a 10-camera motion capture system at a sampling rate of 120 Hz (Qualysis, Sweden). Ground reaction forces will be collected using 2 embedded force plates at a sampling rate of 2400 Hz (AMTI, Watertown, Massachusetts). Each subject will be asked to complete a standing trial followed by a series of squatting and landing trials as described below:

Squatting trial: Subjects will be asked to complete 15 bilateral squats. Subjects will be asked to stand with their feet shoulder width apart (one foot on each force plate) with their hands in front on them with the shoulder flexed to 90 degrees for counter weight. The foot width will be standardized to ensure that foot placement is consistent for both the squatting trials as well as during the biofeedback training. The subject will be asked to squat down until their thighs are parallel with the ground or until their heels begin to come off of the ground. A stool will be placed behind the subject and will be set to the height where the subject's thigh will be parallel to the ground if they sat down (the stool will be placed at the height of the popliteal fold), so that the subject will know the deepest position they have to achieve. The stool will be placed within 0.5 inches of the desired location using a height adjustable plyobox and dense foam padding. The height setting of the plyobox will be recorded for each subject on the data collection form and will subsequently be entered into REDCap to ensure that the same plyobox position is used during each assessment and each biofeedback session. If the subject is able to achieve a squat position where the thigh is parallel to the floor they will be instructed to squat until they barely touch down on the bench and then slowly stand back up without transferring any weight to the bench. The squat assessment will be completed so that the exact same setup and protocol will be used for the biofeedback training program and obtain a baseline measure of skill during a squat. Upon completion of the squatting trials, subjects will be asked to complete 10 vertical stop-jump tasks. The stop-jump task was selected based on its game-like nature. The stop-jump task is a good simulation of a basketball jump-shot or heading a soccer ball and therefore could produce loads and movements that are closely related to those seen during game play.

Landing trial: Subjects will be asked to complete 10 trials of a vertical stop-jump task. During the vertical stop-jump task, subjects will run straight forward for up to 5 steps taking off on 1 foot, landing on 2 feet (one foot on each force plate), and taking off again on 2 feet.[16,18,20,21] Prior to testing maximum jump height will be determine using a vertec. During testing, a ball will be hung above the force plates at 75% of the subject's maxmum jump height to provide a target during jumping. Subjects will be instructed to jump up and grab the ball and then come down bilaterally on the two force plates. No instructions will be provided on how to land or what to do with their arms to initiate the jump. The stop-jump task will be used to determine if the biofeedback intervention is effective at decreasing secondary ACL risk factors as these risk factors were determined during landing. Subjects will be allowed to practice the task between 3 and 5 times until they are comfortable with the movement. A minimum of 5 minutes' rest will be given between conditions to minimize the effects of fatigue. If the results of the baseline jumping assessment indicates that the subject has a limb symmetry index (LSI) of greater than or equal to 90%, which is indicative of limb symmetry during hopping in healthy subjects, he/she will be excluded from the intervention.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her

clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent diagnosis.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The study clinician and the principle investigator in consultation will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed by the study clinician), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study principle investigator and either of the research assistants will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All AEs are collected, analyzed, and monitored by using an Adverse Event Form (MOOP Appendix G). AEs and/or laboratory abnormalities identified in the protocol as critical to participant safety will be reported to the NIAMS and the safety officer. All AEs experienced by a participant during the time frame specified in the protocol (from the initial day of testing as well as the initiation of the biofeedback program through the end of the study) will be reported, as outlined in the protocol (Section 1a of the MOOP).

The procedure for collecting and reporting AEs will be detailed in the following sections. This information will include the role of the Principal Investigator and the Medical Monitor (Dr. Thomas K. Miller) in assigning severity and defining the relationship between the AE and the study intervention. A sample AE form can be found in Appendix G. Requirements for reporting AEs to the NIAMS and the study's independent Safety Officer (SO)) is described below.

The Principal Investigator (PI) and study staff members will be responsible for the safety of study participants. It is not anticipated that there will be any significant physical or psychological risks associated with this study. However, federal regulations require prompt reporting to the Virginia Tech Institutional Review Board (IRB), all injuries, adverse events, or other unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in this research study.

Study team members who become aware of any adverse event related to the study will notify the principal investigator, Dr. Queen, immediately. Study team members will have contact information for Dr. Queen for daytime, evening and weekend hours. If Dr. Queen is not available for contact when a study team member becomes aware of a study-related adverse event, Dr. Savla or Dr. Ollendick, co-investigators on the study, will be contacted. Once Dr. Queen (or a co-investigator) is contacted about the adverse event, she / he will make a determination about the reporting requirements in accordance with the Virginia Tech IRB guidelines. This will include notification of the Virginia Tech IRB within 24-hours if a study-related death, within 5 business days if another serious adverse event, and within 10 business days if a protocol deviation/violation, or other unanticipated problem.

The Principal Investigator will report all adverse events and protocol deviations to the study's NAIMS safety officer on a biannual basis, or as requested. The PI or co-investigator will report all serious adverse events to the study's safety officer within 48 hours of the event being made known to the investigator. This immediate report will be followed by a detailed written report as soon as possible.

All adverse events will be collected, analyzed, and monitored in the study's adverse event log, which is kept in the Investigator's regulatory files within a locked file cabinet.

The following definitions from the US Office of Human Research Protections will be used:

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event. In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

All serious adverse events (SAEs), unless otherwise specified in the protocol and approved by the IRB and the NIAMS, require expedited reporting by the Principal Investigator to the study's Safety Officer. SAEs will be reported to the Safety Officer and the NIAMS, through the NIAMS contractor within 48 hours of being reported to the Investigator. The immediate reports will be followed by detailed, written reports as soon as possible as follow up information may be required before a written report can be provided. The Principal Investigator will report all serious adverse events to the study's NAIMS safety officer on a biannual basis.

Study team members who become aware of any serious adverse event related to the study will notify the principal investigator, Dr. Queen, immediately. Study team members will have contact information for Dr. Queen for daytime, evening and weekend hours. If Dr. Queen is not available for contact when a study team member becomes aware of a study-related adverse event, Dr. Savla or Dr. Ollendick, co-investigators on the study, will be contacted. Once Dr. Queen (or a co-investigator) is contacted about the serious adverse event, she / he will make a determination about the reporting requirements in accordance with the Virginia Tech IRB guidelines. This will include notification of the Virginia Tech IRB within 24-hours if a study-related death, within 5 business days if another serious adverse event.

All serious adverse events will be collected, analyzed, and monitored in the study's serious adverse event log (MOOP Appendix H), which is kept in the Investigator's regulatory files within a locked file cabinet.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The Principal Investigator and study staff will send an IRB approved letter to each study participant in the event of an AE or SAE that is determined by the IRB to change the study risks to the participant. In addition, at the completion of the study an IRB approved letter will be sent to each participant to inform them that the study is completed and provide them with information related to the study outcomes and provide a link to any research articles that are published related to this study.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB, the Safety Officer and the NIAMS, through the NIAMS contractor within 48 hours of being reported to the Investigator. The immediate reports will be followed by detailed, written reports as soon as possible as follow up information may be required before a written report can be provided. The Principal Investigator will report all serious adverse events to the study's NAIMS safety officer on a biannual basis.
- Any other UP will be reported to the IRB and the Safety Officer and the NIAMS, through the NIAMS contractor within 10 business days if a protocol deviation/violation, or other unanticipated problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures),the Safety Officer and the NIAMS, through the

NIAMS contractor, and the Office for Human Research Protections (OHRP) within 10 business days of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

All statistical analysis will be completed under the direction of Dr. Salva. Depending on the outcome, change (completion-baseline), or the value at completion will be assessed, and the statistical significance of the group differences can be assessed by a t-test or the non-parametric equivalent (2-sample Wilcoxon). Standardized differences will be calculated for the purposes of powering the subsequent clinical trial.

- Primary Efficacy Endpoint(s):
  We will test the hypothesis that our biofeedback program will decrease the risk of secondary ACL injury by improving loading and movement symmetry (knee extension moment asymmetry) during the dynamic task of landing from a jump 6 weeks post intervention.

  Movement and loading symmetry will be assessed using the limb symmetry index ($\boldsymbol{LSI} = (\boldsymbol{ABS}\,[\boldsymbol{Surgical} - \boldsymbol{Nonsurgical}])/\mathbf{0.5}(\boldsymbol{ABS}[\boldsymbol{Surgical}] + \boldsymbol{ABS}[\boldsymbol{Nonsurgical}]) * \mathbf{100}$)[2,3,7,34] prior to (baseline) and at two time points following (immediately following training (efficacy), and 6 weeks after (durability)) the biofeedback training program.

- Secondary Efficacy Endpoint(s):
  No hypothesis testing will be completed for the secondary endpoint as this is a pilot clinical trial and will be used to determine the best procedures to following when planning a subsequent multi-center clinical trial. Therefore, we will demonstrate our ability to recruit 40 ACL reconstructed patients and assess study retention and compliance.

9.2 SAMPLE SIZE DETERMINATION

This is a pilot study, with the purpose of discerning parameter estimates for use in powering a subsequent multi-center clinical trial. To estimate statistical power for this pilot design, we consider a comparison of outcomes by group across time. Previous studies have not examined the knee extension moment limb symmetry index, therefore the difference in knee joint position and the knee extension moment will be employed as proxy variables in order to estimate statistical power for this pilot design. We considered a comparison of outcomes between pre- and post-intervention[17,18] and side-to-side differences in ACL-R patients. (Table 4).[15]

Using 2-sided testing between groups based on previous results, we will need 14 patients overall randomized at 1:1 ratio assuming 80% power to detect a significant difference in the knee extension moment between the groups with α=0.05.[13] Therefore, with recruitment of 40 subjects (goal of retaining 30 subjects through study completion), we are adequately powered to declare significance. Thus, while not the primary purpose of this experiment, we are adequately powered to declare significance between groups.

Table 4: Sample Size Calculations (N=sample size per group)

	Pre-intervention	Post-intervention	Sample Size
Peak Knee Extension Moment[10]	3.7 ± 0.9	2.4 ± 0.5	N=7
Peak Knee Flexion[18]	88.8 ± 8.0	105.0 ±5.6	N=5
	Control	**Intervention**	**Sample**
Knee Flexion Angle [18]	83.5 ± 20.5	103.8 ± 16.3	N=15
Vertical ground reaction force[18]	2.0 ± 0.4	1.6 ± 0.3	N=14

9.3 POPULATIONS FOR ANALYSES

The following populations will be included in the statistical analysis:

- Modified Intention-to-Treat Analysis Dataset (participants who completed at least 50% of the intervention visits in the Biofeedback Arm of the study and who attended at least one of the post-intervention assessment visits)
- Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (participants who completed at least intervention visit)
- Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (participants who completed at least 80% of the study intervention visits)
- Other Datasets that may be used for sensitivity analyses

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

- For descriptive statistics the results will be reported as percentages as well as means and standard deviations as appropriate for the measure. Categorical data will be reported as percentages while continuous data will be reported as means with standard deviations as well as data ranges.
- For inferential tests, indicate the p-value and confidence intervals for statistical significance (Type I error) and whether one or two-tailed.
- Checks for the assumption of normality will be performed prior to additional statistical procedures. If this assumption is not met then corrective procedures will be applied such as transformation or nonparametric tests as appropriate.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The goal of the proposed study is to determine the impact of an innovative biofeedback training program on decreasing risk factors for secondary ACL injuries in adolescent athletes. Based on

previous work, the primary variable of interest and a surrogate for secondary ACL injury risk will be the knee extension moment limb symmetry index (LSI). The previously established movement asymmetry risk factors[32] and therefore the primary measures of interest are the knee extension moment, vertical ground reaction force, and frontal plane knee range of motion. Symmetry between the operative and non-operative limbs in this study will be determined by calculating the limb symmetry index (LSI). Asymmetry in the peak knee extension moment has been identified as significant predictors of secondary ACL injuries (therefore reduction in this asymmetry will decrease the risk for secondary ACL injuries).[32]

For **Aim 1** of this pilot study a within subject repeated measures assessment (ANOVA), as implemented under mixed models**,** will be used to determine if a clinical (LSI>90%) and/or statistical difference exists between the pre- and the two post-intervention time points (efficacy and durability) for the primary outcome of interest (knee extension moment asymmetry). Post-hoc testing will be completed for any variable that is determined to be statistically different.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For **Aim 2**, we will calculate rates of recruitment, retention and compliance. No hypothesis tests will be performed. However, correlates to these metrics will be assessed. For each of the outcome measures the between session analysis will allow us to calculate test-retest reliability. The use of correlations will allow us to compute criterion and predictive validity.

Study retention will be defined as a subject who attends each of the biomechanical testing session (baseline, immediately following intervention (intervention)/6 weeks after baseline (control), and then 6 weeks after training (intervention) or 12 week after the baseline (control). Proportion retention will be computed by dividing the number of retained subjects at the end of the intervention by the total number of patients randomized into the study. Compliance with the intervention will be defined as a subject who attends at least 80% of the biofeedback training sessions during the six weeks of the intervention. Proportion adherence will be computed by dividing the number of sessions attended by the total number training sessions (number of training sessions n=12).

9.4.4 SAFETY ANALYSES

Monthly reports will describe target and actual enrollment by site and in aggregate, individuals screened with reasons for screen failure, and enrollment status (enrolled, active, completed, discontinued treatment, and lost to follow-up). Monthly reports will also list or summarize AEs and SAEs. Administrative reports will list the forms completed, entered, and missing, and/or erroneous data and forms. The NIAMS has requested a monthly study update to be provided on the fifth of every month by the study PI. Reports to the Safety Officer (SO) will be completed biannually throughout the study and will be submitted by the study PI to KAI based on a schedule that will be on when the first subject is enrolled into the study.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not applicable – study will be block randomized in order to decrease the potential for differences in baseline characteristics between the two study groups (Intervention and Control).

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

Due to the pilot nature of this clinical trial we will not be performing any subgroup analyses. However, in order to better understand the outcomes and in an attempt to plan for a future multi-center trial, we will explore possible confounders such as age, time from surgery, time in rehabilitation, concomitant meniscal pathology, sex, and the initial injury mechanism. This information could allow for program modifications and/or determine if certain baseline characteristics need to be achieved prior to starting the biofeedback program.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be recorded in the study database, however, study results that will be reported will be based on the group aggregate data for each of the study groups.

9.4.9 EXPLORATORY ANALYSES

Over the course of the study secondary outcomes will be examined to determine any mediating effects these variables may have, which could explain differences across time (**Table 3**). Secondary outcomes will be evaluated using exploratory analyses in order to generate hypotheses for future studies. These exploratory analyses will be conducted using linear mixed models.[23,35,36] We will test both primary and secondary outcomes at an alpha level of 0.05 and will not control for potential Type-I errors due to multiple testing, using Bonferroni or Hochberg criteria,[8,9,19] due to the pilot nature of this study. If an effect is declared 'significant' we will provide a cautionary note in resulting publication, as to the exploratory nature of the findings.

Table 3: Outcome Measurements

Primary Outcomes
Peak Knee Extension Moment Symmetry
Secondary Outcomes
Peak Vertical Ground Reaction Force Symmetry
Vertical Ground Reaction Force Impulse Symmetry
Frontal Plane Knee Range of Motion
Peak Knee Flexion Angle Symmetry
Peak Knee Flexion Angle
Peak Knee Valgus

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All patients will be approached by their treating orthopaedic surgeon to inquire about their interest in hearing more about this clinical trial. At that time the clinician will provide the potential participant with a release letter (MOOP Appendix C) that indicates that the patient is clinically ready to participant in this clinical trial. At that time, the potential participant will also be asked to sign the release of information consent (MOOP Appendix B). This signed form will be sent to the study team to indicate the potential participant's interest in learning more about the research project.

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol; (1) adult informed consent, (2) Minor ascent, and (3) parental permission.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principle investigator (PI will then contact all study participants to provide information on the status of the study), the NIAMS, as well as regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIAMS, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the NIAMS.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the NIAMS, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Virginia Tech. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Virginia Tech research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Virginia Tech.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Virginia Tech. After the study is completed, the de-identified, archived data will be stored at in the ACL Biofeedback REDCap database that was designed for this clinical trial. The use of this data by other researchers including those outside of the study will be approved by the Institutional Review Board as a retrospective review of existing data with the permission of the study principle investigator.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Robin Queen, PhD, FACSM Associate Professor Biomedical Engineering and Mechanics Orthopaedic Surgery	Thomas Miller, MD Chief of Sports Medicine Carilion Clinic Associate Professor Orthopaedic Surgery
Virginia Tech Virginia Tech Carilion School of Medicine	Carilion Clinic Virginia Tech Carilion School of Medicine
445 Old Turner Street 230 Norris Hall – Virginia Tech Blacksburg, VA	Institute – Orthopaedics & Neurosciences 2331 Franklin Rd. Roanoke, VA
(540) 231-3134	(540) 776-0221
rmqueen@vt.edu	tkmiller@carilionclinic.org

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Safety Officer (SO) who has expertise as an orthopaedic surgeon and is familiar with the ACL reconstruction and rehabilitation. The SO was appointed by the NIAMS and is independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The SO will operate under the rules stated by the NIAMS and this information was reviewed at the study's organizational meeting. At this time, each data element that the SO needs to assess will be clearly defined. The SO will provide input to the NIAMS through the NIAMS contractor.

10.1.7 CLINICAL MONITORING

With this study being a single site study there will not be site visits. However, these assurances will be made by the study PI at the site as well as being verified by the clinical health psychologist who is a member of the study team, but not involved in the day to day testing of these participants.

The purpose of these reviews is to:

- Ensure the rights and safety of participants
- Confirm that the study's conduct follows GCP guidelines
- Ensure maintenance of required documents
- Verify adherence to the protocol
- Monitor the quality of data collected
- Ensure accurate reporting and documentation of all AEs

During monitoring visits, the data recorded on CRFs are reviewed and verified against source documents to ensure:

- Informed consent has been obtained and documented in accordance with IRB/ FDA regulations
- The information recorded on the forms is complete and accurate
- There are no omissions in the reports of specific data elements
- Missing examinations are indicated on the forms
- Participant disposition when exiting the study is accurately recorded

The Study PI will ensure that the clinical monitor has access to all study documents, including informed consent forms, drug accountability records, and source documents, including pertinent hospital or medical records.

Once the review is complete, a monitoring report is drafted to provide feed-back regarding the activities that were accomplished and any problems or issues that may have been uncovered during the visit. The report should be straightforward, stating any problems uncovered and describing recommendations to address them. A timeline should be agreed upon and included in the report to ensure that follow-up of any issues is completed and implemented into the study's procedures. The review as described above will be completed once every quarter throughout the study by the clinical health psychologist along with the study PI.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Audits of source-to-database documents will occur regularly, with complete audits of critical variables, and random sample audits of non-critical variables. In addition, there will be complete audits of selected subjects. The data management binder, developed and maintained by RMT, will be regularly updated to reflect the current status of the study, and the databases will be subject to planned quality control audits. In addition, data management will produce regular quarterly reports of data quality, recruitment metrics, and outstanding queries.

While this is a pilot study and data will be easily tracked, we intend to set up systems that will mimic the larger proposed trial. A critical component is the development of a data management plan that documents key processes and procedures. The plan will be incorporated into a project specific data management binder that includes the protocol, scope of work, annotated data forms, database structure, query rules, data flow scheme, specific work instructions for all data management processes, copies of supporting forms and data clarification forms, and audit plans. Upon screening and enrollment, research data entry will occur in the web-based REDCap software program which will have undergone extensive validation and testing to meet HIPAA compliance rules. New data will be inspected for completeness, and queried for programmed logic checks and out-of-range values. Only consented subjects will have their data stored and entered in REDCap. The person responsible for data will work with the project manager to set up tracking participant enrollment, CRF completion and prompts for email and telephone reminders and appointment scheduling.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principle investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Most of the source data for this clinical trial will be collected directly in an electronic REDCap database to avoid issues with data entry and improve speed of data collection for the participants.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study if the participant is unable to complete the outcome forms within the electronic system. Data recorded in the

electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by Virginia Tech. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the NIAMS, if applicable. It is the responsibility of the NIAMS to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Operations and Procedures (MOOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the principle investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NIAMS Program Official and the Safety Officer. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The study team will seek to publish study findings as soon as they are available. We will aim to write papers describing the study design, baseline sample characteristics, and other analyses of interest regarding baseline measures, as these become available. We will perform regular data cleaning throughout the study so that analyses of main study outcomes may begin very shortly after these assessments are completed. The study team will follow guidelines for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). We expect

that manuscripts describing main study outcomes will involve authorship of all study co-investigators (as long as ICMJE criteria are met). Other manuscripts must be reviewed and approved by the Principal Investigator and Senior Statistician on the project, at minimum, before submission.

In compliance with the current NIH policy to ensure public access to NIH funded research all publications will be submitted in an electronic format upon acceptance for any publications that result from research supported, in whole or in part by the funding for this project. The final manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

In compliance with the NIH policy, electronic submission will be made directly to the NIH National Library of Medicine's (NLM) PubMed Central (PMC): http://www.pubmedcentral.nih.gov. PMC is the NIH digital repository of full-text, peer-reviewed biomedical, behavioral, and clinical research journals. It is a publicly-accessible, stable, permanent, and searchable electronic archive.
At the time of submission, the author will specify the timing of the posting of her final manuscript for public accessibility through PMC. Posting for public accessibility through PMC is requested and strongly encouraged as soon as possible (and within twelve months of the publisher's official date of final publication).

The publisher may choose to furnish PMC with the publisher's final version, which will supersede the author's final version. Also, if the publisher agrees, public access to the publisher's final version in PMC can occur sooner than the timing originally specified by the author for the author's final version.

Additional details for submitting authors pertaining to the implementation of the NIH policy can be found at the following website: *http://www.nih.gov/about/publicaccess/index.htm*.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIAMS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not Applicable

10.3 ABBREVIATIONS

ABS	Absolute Value
ACL	Anterior Cruciate Ligament
AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intention-To-Treat
LSI	Limb Symmetry Index
MOOP	Manual of Operations and Procedures
NCT	National Clinical Trial
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
NLM	National Library of Medicine
OHRP	Office for Human Research Protections
PI	Principal Investigator
PMC	PubMed Central
SAE	Serious Adverse Event
SO	Safety Officer
SoA	Schedule of Activities
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
V1.1	**07/31/2017**	**Section 6.1 & 8.2** **Added description of the adjustable stool and the specific height for the stool so that it will be placed within 0.5 inches of the popliteal fold during both the assessment and the biofeedback session.**	**This change was made in order to standardize the location of the adjustable stool during testing and training for those participants who are able to complete a squat with their heels on the ground and their thighs parallel to the floor.**
V1.2	**09/05/2017**	**Title Page** **Added the clinical trial identification number**	**Clinical trial approved through clinicaltrials.gov with the following identification number NCT03273673**
V1.3	**11/06/2017**	**Section 1.3** **Corrected the tracking time points for the biofeedback interventions**	**Needed to update the schedule of events to include tracking of Adverse Events as well as the no shows for the biofeedback interventions to indicate that these would be completed at each of the visits, which will occur two times per week for the 6 weeks of the intervention period.**
V1.4	**01/02/2018**	**Section 1.3** **Updated Table 1.3 Schedule of Activities (SoA)**	**This table was updated to clarify when various outcome measures were being collected for the various treatment groups.**
V1.4	**01/02/2018**	**Section 5.2** **Updated the exclusion criteria**	**Updated the exclusion criteria to include exclusion from the study if a potential participant was still attending formal physical therapy more than two times per week at the time of study enrollment**
V1.4	**01/02/2018**	**Section 6.1.1** **Updated Biofeedback intervention information including information on the warm-up and the foot position during the squat assessments.**	**In order to improve clarity and provide details regarding both foot position during the squat testing and training as well as providing details on standardization of pre-intervention warm-up this portion of 6.1.1 has been updated.**
V1.4	**01/02/2018**	**Section 8.2** **Additional information provided regarding the set-up of the bicycle for warm-up as well as the plyobox used during testing.**	**In order to standardize the assessments being completed as part of this study, additional information was provided regarding the setting of seat height for the bicycle for warm-up as well as the height of the**

			plyobox to be used during both the biomechanical assessments as well as the intervention sessions.

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