IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training , experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.

19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Dr. Mark D. Miller is the S. Ward Casscells Professor of Orthopaedic Surgery and the Head of the Division of Sports Medicine at the University of Virginia. He is also the team doctor at James Madison University in Harrisonburg, Virginia. He is nationally and internationally known for his expertise in sports medicine, shoulder surgery and knee surgery. Dr. Miller has published over 100 peer-reviewed articles and 20 textbooks. He takes care of athletes of all ages at all levels, from recreational sports to Olympic athletes. He has research interests in cruciate ligament injuries and specializes in complex ligament reconstruction (including ACL, PCL, Collateral Ligament injuries and Knee Dislocations.) The investigative team including Dr. Hart and Dr. Werner has extensive experience in clinical research and sports medicine studies.

Signatures

Principal Investigator

_____	Mark D. Miller, MD_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

The Principal Investigator signature is ONLY required if this is a new protocol, a 5 year update or a modification changing the Principal Investigator.

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator.

Brief Summary/Abstract

This study is designed as a prospective, double arm, study. Patients with a diagnosed rupture of the anterior cruciate ligament (ACL) who are scheduled for surgical reconstruction will be considered for enrollment. Eligible subjects will be allocated to one of two groups based on the location of the tibial tunnel (anterior vs. posterior) during the surgical procedure. The study population will consist of patients 16-50 years of age, with ACL rupture, who are seeking surgical reconstruction. Patients with active infection, previous ACL surgery, multiple ligament knee injury, previous joint modifying surgery in target knee within 12 months of planned procedure, flexion contracture, valgus alignment, pathologic ligament instability, knee osteoarthritis, inflammatory joint disease, metabolic bone disease (marked bone loss or moderate to severe osteoporosis), comorbidities such as type 1 diabetes, connective tissue disorder, or morbid obesity (BMI ≥35) will be excluded.

Subjects will return for follow-up visits at 6, 12, and 24 months post-surgery. If a subject is unable to come to UVA for a follow up visit, a home visit can be arranged with a member of the study team. Note that all data cannot be collected through a home visit, but instead only the subjective outcomes and some aspects of the knee exam can be collected. Follow up will be completed at 24 months for all enrolled subjects. Additionally, subjects with a prior ACL reconstruction who meet all study criteria, may enter the study at any post-operative time point (retrospective aspect of the study).

The primary objective of this study is to collect data on subjective and objective measures of knee related function in subjects with an anterior vs. posterior placed tibial tunnel through 24 months postoperative follow-up.

The primary analysis will compare groups at 24-months post-op with regard to:

1. Clinically significant difference of at least 8 points on IKDC score
2. Clinically significant difference of at least 2.4 mm knee joint laxity (KT-1000)

Background

1. Provide the scientific background, rationale and relevance of this project.

Although extensive research has been carried out on ACL Femoral Tunnel placement, very little attention has been given to the tibial tunnel. Staubli et al. suggest that the tibial tunnel be placed in the center of the ACL footprint, which they described as being approximately 43% of the way (anterior to posterior) across the proximal tibia at its widest extent.[1] However, others have suggested that a more anterior placement may yield improved biomechanical[2] and clinical[3] results. The center of the ACL footprint and the posterior aspect of the anterior horn of the lateral meniscus does not yield tibial tunnel placement a consistent percentage of the way across the tibial plateau[4], therefore, guidelines should be based on intraoperative fluoroscopic measurements. However, the question remaining is what percentage of the A-P distance across the tibia is the ideal location for the tibial tunnel in ACL reconstruction. This study will help answer that question.

Hypothesis to be Tested

Objective:
Compare anterior versus posterior tibial tunnel placement for ACL reconstruction in a prospective randomized clinical trial.

Hypotheses:
A more anterior placed tibial tunnel will yield improved outcomes with regard to:

1. Improved knee-specific self-reported function (IKDC)
2. Decreased knee joint laxity (KT-1000)

Study Design: Biomedical

1. Will controls be used? No

2. What is the study design?
Single-blind, randomized controlled clinical trial

3. Does the study involve a placebo? No

Human Participants

Ages: 16-50
Sex: Male and Female
Race: All

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.75(prospective aspect) 45 for retrospectice (UVA only)

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.
We expect up to a 20% rate of attrition due to loss of follow up.

3. How many subjects will be enrolled at all sites? 90- prospective, 45-retrospective (UVA only)

4. How many subjects will sign a consent form under this UVa protocol? Between Jordan-Young Institute and UVA up to 90 subjects will sign consent for the prospective portion of the study—N=55 at UVA. 45

subjects will sign a consent form for the retrospective portion of the study at UVA only. Total of 100 subjects will sign a consent form under this UVA protocol.

5. Provide an estimated time line for the study.

Enrolled subjects will be followed for 2 years post-surgery, or up until 2 years post-operatively for those who enter the study after surgery. We expect 50% enrollment to be achieved within one year, and 100% in two years. We would anticipate completion of follow up to occur in four years.

Inclusion/Exclusion Criteria

INSTRUCTIONS:
The inclusion and exclusion criteria should be written in bullet format.
If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
The stop date must be prior to the version date of this protocol.
*Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

- Age at time of randomization or initial surgery: 16 – 50 years (skeletally mature)
- Primary, uncomplicated ACL reconstruction
- Autograft (STG or BPTB)

2. List the criteria for exclusion

- Multiple ligament knee injury (full thickness)
- Revision ACL reconstruction
- ACL reconstruction with allograft
- Meniscectomy > 75%
- Treatable articular cartilage lesions (debridement acceptable)
- Diagnosis of tibiofemoral or patellofemoral osteoarthritis (Kellgren Lawrence grade > II)
- Valgus knee alignment (weight bearing line outside of joint center)
- Prior ligament reconstruction of cartilage repair surgery in either ankle, knee, or hip
- Prior arthroscopic debridement surgery in either ankle, knee, or hip within 12 months
- Clinical evidence of hip disease
- Patellofemoral joint instability
- Significant patellar or tibiofemoral mal-alignment
- BMI > 35
- Type 1 Diabetes Mellitus
- Known connective tissue disorder (e.g. Ehlers-Danlos)
- Peripheral neuropathy
- Neurovascular/ circulatory disorder
- Any form of inflammatory arthritis (e.g. RA, gout, pseudogout, lupus, etc.)

- Significant co-morbid conditions as determined by the investigator (e.g. malignancy, renal, hepatic disease, etc.)
- Known or suspected psychological disorder

3. List any restrictions on use of other drugs or treatments. N/A

Statistical Considerations

1. **Is stratification/randomization involved?** Yes.

►IF YES, describe the stratification/ randomization scheme.

Block randomization will be completed *a priori* via a random number generator. 20 subjects will be allocated to group within each block (10 per group). Group assignments will be sealed in an opaque envelope each containing a number from 001-090. Each subject will be randomly assigned in a 1:1 ratio to receive one of the treatments (group) described below. Randomization envelope #001 will be used for the first subject, #002 for the second and so on. Group assignment for enrolled subjects will be determined intra-operatively. Prior to the determination of group assignment, the treating surgeon will drill two tibial tunnel guide pins, assessing pin placement via fluoroscopy, to ensure that one tunnel is anterior and the other is posterior to the 35% line. The sealed envelope will then be opened following confirmation of guide pin placement, and the procedure will be performed in accordance with the randomized group assignment.

Patients with a prior history of ACL reconstruction who enter the study post-operatively will be assigned to the appropriate group based on graft placement (anterior or posterior) that was performed for clinical care.

►IF YES, who will generate the randomization scheme?

__X__ Other*:* Study coordinator

2. What are the statistical considerations for the protocol?

We have designed the study in a way that will make it easy to match an appropriate statistical procedure to test our primary hypotheses. Subjective and objective measures of knee function will be evaluated at 6, 12 and 24 months post-surgery.

3. Provide a justification for the sample size used in this protocol.

Sample size for IKDC and KT-1000 side-side differences are calculated based on the expected between-group differences observed at the final time point of this study – 24 months post reconstruction. In order to observe a 2.4 mm between group differences in joint laxity symmetry, we need 40 patients per group. This estimate accounts for up to 3.5 mm in variability in KT-1000 side-side measurement change from pre-post-surgery.[5] Further, we need 55 patients per group to detect a 8-point difference in IKDC score between groups assuming variability of 12 points in IKDC score.[6] These estimates account for 20% attrition. Estimates are calculated to find statistically significant differences allowing for 5% type I error rate and power exceeding 80%.

4. What is your plan for primary variable analysis?

We will use independent t tests to determine group differences at each time point.

5. What is your plan for secondary variable analysis?
We do not plan to use a secondary variable analysis.

6. Have you been working with a statistician in designing this protocol? Yes
IF YES, what is their name? Wendy Novicoff

7. Will data from multiple sites be combined during analysis? Yes

7(a). Does the study involve randomization? Yes

IF YES, will randomization be done at each site or among sites?
Randomization will be done at each site.

7(b). Has the sample size calculation considered the variation among sites? Yes

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Yes. The effect of the treatment (placement of tibial tunnel) will be assessed using standard measures of joint laxity and patient-reported function. We have no evidence to believe that these outcomes differ between sites under standard protocols.

7(d). Is there a common protocol used in all sites? NO

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Potential subjects will be identified, screened, and eligibility criteria reviewed in a similar manner at each institution. Each practice will follow the same criteria for enrollment. Statistical considerations will be employed following the completion of data collection to account for differences in patient characteristics/ demographics.

Biomedical Research

1. What will be done in this protocol?

Study Procedures:
All procedures apply to subjects who enter the study prior to surgery.

<u>Screening visit</u> (Visit 1)
After written informed consent is obtained, initial screening will consist of a thorough medical history and physical examination. Special attention will be given to inclusion and exclusion criteria as listed above. Only patients who meet all inclusion and exclusion criteria will be allowed to continue to baseline outcomes data collection. The following subjective outcomes and clinical examination data will be collected at each session.

<u>Subjective Outcomes</u> (10 minutes)

- International Knee Documentation Committee (IKDC) Subjective Knee Evaluation
- Marx Activity Rating Scale

X-ray (15 minutes)

- Standing 2-view (posterior-anterior, lateral)

Clinical Evaluation (10 minutes)

- Knee joint laxity with KT-1000
- Knee joint range of motion
- Thigh circumference (15 cm above knee cap)

Surgery (Visit 2)

- Record surgical details: procedure(s) performed, time of procedure, tunnel diameter, tunnel placement details, other arthroscopic findings pertinent to case

Follow Up Visits (Visits 3-5)

Subjects who enter the study after surgery will complete the visits below based upon when they enter the study from their surgery date. If subjects are unable to come to UVA for the follow up visits, it is possible to arrange a home visit with a member of the study team to collect outcomes. Please note that we can only collect questionnaires and the KT-1000 ligament laxity measurement of the knee exam through a home visit.

- 6 months (approximately 182 ± 14 days following surgery)
    - Review of criteria for enrollment
    - Record adverse events
    - Clinical evaluation
    - KT-1000 Ligament Laxity Assessment Questionnaires
        - Marx Activity Scale
        - IKDC Subjective Questionnaire

- 12 months (approximately 364 ± 21 days following surgery)
    - Record adverse events
    - Standing 2-view (posterior-anterior, lateral) x-ray
    - Clinical evaluation
        - KT-1000 Ligament Laxity Assessment
    - Questionnaires
        - Marx Activity Scale
        - IKDC Subjective Questionnaire

- 24 months (approximately 728 ± 28 days following surgery)
    - Record adverse events
    - Standing 2-view (posterior-anterior, lateral) x-ray
    - Clinical evaluation
        - KT-1000 Ligament Laxity Assessment

- Questionnaires
  - Marx Activity Scale
  - IKDC Subjective Questionnaire
- Quadriceps strength testing (15 minutes) (optional)
  - Maximal, normalized isometric knee extension force (Nm/kg)
  - Quadriceps central activation ratio (%)
- Gait Analysis (60 minutes) (optional)
  - Kinematic and kinetic analysis during walking and jogging

2. List the procedures, in bullet form, that will be done for research as stipulated in this protocol.

- Screening
- Subjective Outcomes
  - Marx Activity Scale
  - IKDC Subjective Questionnaire
- Clinical Examination
  - KT-1000 Ligament Laxity Measurement
- Quadriceps Strength Assessment
- Gait Analysis
- Surgical procedure (surgery is clinical care – placement of tibial tunnel is study related)
- Standing 2-view (posterior-anterior, lateral) x-ray s-3 total

Patients who enter the study post-operatively will be screened in the same manner as those who enter pre-operatively, and all study procedures will be completed accordingly.

3. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study? No

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding?
Yes, x-ray

__X__The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures? Yes
IF YES, list procedures: X-ray

►IF YES, *check one of the following two options:*

__X__This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record? Yes

6. Will you be using viable embryos? No

7. **Will you be using embryonic stem cells?** No

8. **Are any aspects of the study kept secret from the participants?** Yes

►**IF YES, describe:**
Group assignment will remain confidential until the end of the study

9. **Is any deception used in the study?** No

10. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.
All subjects will be prescribed the same rehabilitation program and guidelines in accordance with the standard of care post ACL reconstruction procedure. Participating in this study will not affect the care given or prescribed in any way.

Data and Safety Monitoring Plan

INSTRUCTIONS:
If you have any questions completing this section call 243-9847 for assistance.
A Sponsor is defined as entity that will receive data prior to publication.

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

__X__An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of

research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

1.2 How will you define serious adverse events?

__X__A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an unanticipated problem?

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What are the definitions of a protocol violation and/or noncompliance?

Do not change this answer

A **protocol violation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol violations may be major or minor violations.

Noncompliance can be a protocol violation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulation**s**. Noncompliance may be serious or continuing.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

__X__ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

1.6 What is the definition of a Protocol Enrollment Exception?

__X__NA- No outside sponsor

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol
Risk of infection from surgical procedure	Occurs rarely
Slight discomfort due to knee examination procedures	Occurs rarely
Risks from radiography (x-ray)	Occurs rarely
Risk that patients may be sore following the strength or gait protocols	Occurs rarely
Risk of discomfort from electrical stimulation during superimposed burst testing	Occurs rarely

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- **Review of medical history**
- **Review of eligibility criteria**
- **Adverse event monitoring at each visit**
- **Review of self-reported function at each visit**
- **Post-surgical care/ education (before and after surgery)**

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__X__At subject, PI or sponsor's request

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

INSTRUCTIONS;

- These are called stopping rules for early termination of the entire study.
- List criteria regardless of whether the study is sponsored or not.
- Be sure to include any criteria for which the UVa PI would halt the study at UVa.
- Check all that apply.

__X__Per IRB, PI, DSMB, or sponsor discretion

2.5 What are the criteria for breaking the blind/mask?

__X__Other: If deemed to impact clinical care

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__X__IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No

►IF NO, what criteria will be used?

__x___Only adverse events that are deemed related AND serious

3.2 How will adverse event data be collected/recorded?

__X__Paper AE forms/source documents

__X__Spreadsheet: paper or electronic

3.3. How will AEs be classified/graded?

_X_ Serious/Not serious Required for all protocols

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__X__The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__x___After subject begins study intervention

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__X__ Subject completes intervention and follow up period of protocol

This must be checked if protocol involves administration of Gadolinium for research purposes

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, related, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
For Device Studies: Unanticipated adverse device effects (internal)	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*

Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Enrollment Exceptions** *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the enrollment exception.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

4. How will the endpoint data be collected/recorded.

__X__Protocol specific case report forms

__X__Source documents

__X__Database: University server, password encrypted

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study?

__X__No additional oversight body other than PI at UVa Skip question 5.2

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor? *N/A*

5.3. What items will be included in the aggregate review conducted by the PI?

__X__All adverse events

__X__Unanticipated Problems

__X__Protocol violations/Issues of noncompliance

__X__Audit results

_____Application of dose finding escalation/de-escalation rules

These should be outlined under 2.4.

_____Application of study designed stopping/decision rules

__X__Early withdrawals

__X__Whether the study accrual pattern warrants continuation/action

__X__Endpoint data

5.4 **How often will aggregate review occur?**

For additional information on aggregate review see: www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

_____Per Enrollment/Events

__X__Annually

_____Semi-Annually

_____Quarterly

_____Monthly

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI? N/A

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__X__Part of IRB-HSR continuation status form

Collaborative Site Analysis Studies

1. **List the sites that will be sharing data/specimens**.

Jordan-Young Institute Orthopedic Surgery and Sports Medicine

2. **Will any data/specimens be sent to UVa for analysis from the sites outside of UVa?** Yes

   ►**IF YES, do you confirm you will have received a copy of the IRB approval from the outside site before receiving data/specimens from them?** Yes

3. **Do you confirm you will have a Material Transfer Agreement (MTA) through the Grants and Contracts office prior to sending or receiving data/specimens?** Yes

4. **Describe the process for sharing safety concerns.**

Frequent communication will occur between sites in the form of monthly emails and quarterly conference calls. The PI, study coordinators, and any appropriate sub-investigators will be involved in this communication.

Collaborative Site Analysis Studies DSMP			
Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
***Serious, unexpected and related or possibly related adverse events**	All Research Sites	Within 15 days after the site PI receives knowledge of the event.	IND/IDE Safety Report (Cover letter, copy of MedWatch/narrative)
For Device Studies: *Unanticipated adverse device effects (internal or external)	All Research Sites	Within 15 calendar days from the time the Site PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative
***Unanticipated Problem**	All Research Sites	Within 15 calendar days from the time the Site PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative
Protocol Violations/Noncompliance *The IRB-HSR only requires that MAJOR violations be reported, unless otherwise required by the sponsor.*	All Research Sites	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*

**as defined in each sites protocol*

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits, which may accrue to society in general, as a result of this study?

The risks include knee soreness from the physical exam and radiation exposure from x-ray. Benefits from a clinical perspective include providing evidence to improve clinical care through surgical intervention.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

The risks to the subject are low and the potential benefit to society, through knowledge gained about ACL outcomes, is great, therefore the risk-benefit ratio is optimal.

Bibliography

1. Staubli HU, et al. Knee Surg Sports Traumatol 1994; 2(3):138-146
2. Bedi A, et al. Am J Sports Med 2011 39(2):366-372
3. Hatayama et al. Arthroscopy 2013; 29(6):1072-1078
4. Werner BC, Gwathmey FW, Miller MD. Anterior Horn of the Lateral Meniscus as a Landmark for the Tibial Tunnel in ACL Reconstruction: A Prospective Study. Poster Presentation. AAOS 2015 Annual Meeting, Las Vegas, NV, March 24-28, 2015.
5. Berry J, et al. Error Estimates in Novice and Expert Raters for the KT-1000 Arthrometer. *J Ortho Sport Phys Ther.* 1999;29(1):49-55
6. Grindem H, et al. Nonsurgical or Surgical Treatment of ACL Injuries: Knee Function, Sports Participation, and Knee Reinjury: The Delaware-Oslo ACL Cohort Study. *J Bone J Surg*. 2014;96:1233-41

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

*The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrisons), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.

1. **How do you plan to <u>identify</u> potential subjects?**

- To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
- If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.
- Check the methods you plan to utilize:

a.__X__ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or an Improvement Project (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).
<u>If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) please see option b below.</u>

<u>DHHS:</u> Study team requests Waiver of Consent to identify potential subjects.

<u>HIPAA:</u> Allowed under Preparatory to Research if PHI to be accessed.

<u>IMPORTANT</u>
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b__X__ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.
If you plan to obtain data from the UVa Enterprise Data Warehouse (EDW) you are required to submit your request to the CDR. The CDR staff will work with the EDW to obtain the data you need.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*

--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

The information from which you are obtaining potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

IRB# _10797_____

If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797

c. _X__ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients' knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
--a UVa student working in the UVa HIPAA Covered Entity*
--a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

d. __X__ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

DHHS: NA

HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. _X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.

IRB# of registry/ database: _____

DHHS & HIPAA: NA

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Yes

2. How will potential subjects be contacted?

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a._X__Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- a UVa student working in the UVa HIPAA Covered Entity*
- a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

b. _X__ Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
a UVa student working in the UVa HIPAA Covered Entity*
a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:

- Your name
- Who you are: physician, nurse etc. at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information use one of the following as an option for response.
    - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
    - We obtained your information from your medical records at UVa.
    - Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.
- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c._X__Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: Allowed under Health Care Operations.

d._X__ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

3. **Will any additional information be obtained from a potential subject during "prescreening"?** No

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**

HIPPA:

If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.

If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Once a potential subject is identified, they will be interviewed in a quiet and private place and may have family or friends with them if they choose. If there is concern that the potential subject may not be able to read the potential subject will be asked to read the first sentence of the consent form to determine if they are capable of reading. Depending on the response they will either be offered the opportunity to read the consent form or have the consent form read to them. Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe will be done to you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form. The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form. Study procedures will then begin. The informed consent process for each individual subject will be documented in the subject's medical record.

6. Will subjects sign a consent form for any part of the study? Yes

7. Will the study procedures be started the same day the subject is recruited for the study? No

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees? Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?
All potential subjects will be provided the same study description and list of eligibility criteria. All subjects will be compensated equally. Additional benefits beyond those described will not be offered to any participants.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol? No

APPENDIX: Participation of Children

In the state of Virginia a person under the age of 18 is considered a child.

1. Explain why this research topic is relevant to children.

this topic is extremely relevant to children given the continued high prevalence of ACL injury in youth populations. Sporting activity through adolescents is advocated from a global health perspective, thereby exposing these individuals to greater risk for injury.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study? No

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.

Surgical reconstruction is standard of care for a complete rupture of the ACL. It is unknown whether directing the placement of the tibial tunnel to a more anterior or posterior position during this procedure will yield better patient outcomes. Therefore, these is no data to support one technique (placement) over the other, which is the purpose of this study. ACL reconstruction poses no additional risk in children beyond that in adults.

4. **Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state? YES**

INSTRUCTIONS:

- There are provisions in the research regulations that pertain to the participation of children who are considered wards of the state. A "ward," in this context signifies any child who has been adjudged dependent by a court and who is under the care or custody of a public official or agency, which may include foster children, or any child under the control of the Department of Social Services in the state of Virginia. An incarcerated youth is a child who is in penal custody or otherwise detained within the criminal justice system. These children are often under the care of the Department of Youth Services and some may also be wards of the state. Recruiting a ward of the state for research may be a very infrequent or unlikely event. It is important that these children not be discriminated against with regards to enrollment in research especially if the research offers a potential for benefit. However, their enrollment requires additional IRB determinations including the IRB appointing an advocate. Therefore, you are asked to consider the possibility of enrolling a ward of the state based upon eligibility criteria and the population of your study.
- If the study will enroll subjects from patients at UVa, this question MUST be answered YES

►IF YES: If the caregiver is someone other than the person providing permission for the child to participate, the study team may wish to consider the use of an additional form for them. (example:a child is in foster care however the biological parent has not lost legal custody and provides their permission for the child to participate, but the foster parent will be the person involved in driving the child to their study visits. This form might address things such as who will receive the compensation for driving the child to the visits- the foster parent or the biological parent).

►IF YES and if neither of the items 4a or 4b listed below is answered YES, children who are wards of the state must be excluded from this protocol. Add "wards of state" as an additional exclusion criteria.

4a. Is the research is this protocol related to the childs' status as a ward of the state? No

4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards? Yes

4c. Are you aware of the following requirement?
If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state.
Yes

5. **Does this study involve a placebo arm?**No

6. **Will UVa researchers conduct the study outside the state of Virginia?**No

Payment

INSTRUCTIONS:

What is the difference between compensation and reimbursement?

A reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Receipts or mileage must be submitted for a reimbursement.

Compensation is "payment" for things such as time, discomfort, inconvenience.
Total possible compensation should reflect the true value of the total possible dollar amount per participant for one year involvement in the study whether it be cash, check, gift card, goods, etc. or a combination of these items.

Retention "Gifts"- gifts may be given to a subject periodically during the study to remind them they are in the study. Sponsors may provide such items as water bottles, birthday cards etc. to the subject. NOTE: Cash or gift cards are NOT allowed as retention items.

1. **Are subjects being reimbursed for travel expenses** (receipts /mileage required)**?**No

2. **Are subjects compensated for being in this study?**Yes

►IF YES, answer the following questions (2a-2d).

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$100.00

2b. Explain compensation to be given.
Subjects will be compensated $50.00 for the successful completion of study visit 4 and 5 (12 and 24 months), with a maximum of $100.00 allowable. Subjects will not be compensated following the initial visit, or surgery-related visit, or 6-month visit because these are performed as a standard of care.

Subjects will not be compensated if the 12 and 24 month visits are home visits. Compensation is given only for in clinic visits at 12 and 24 months due to travel expenses, as well as the additional time for completion of the strength and gait analyses on the 24 month visit. Subjects will only receive compensation for the 12 month visit if they come in for a clinic visit and for the 24 month visit if they come in for a clinic visit and the gait and strength analyses are done.

2c. Is payment pro-rated?
Yes. Subjects will be compensated $50.00 for completion of study visits 4 and 5 only (12 and 24 months), even if they do not complete the entire study.

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa? Yes

2d(i). How will the researcher compensate the subjects?

__X__ Check issued to participant via UVA Oracle or State system

2d(ii). Which category/ categories best describes the process of compensation?

Choose one of the following 3 options

__X__ All compensation will be made via check issued to participant via UVA Oracle or State system
The preferred method

APPENDIX: Clinical Data Repository

1. Will you be obtaining data from the UVa Clinical Data Repository (CDR)? Yes

INSTRUCTIONS:
►If YES, check the categories of data elements below that you plan to obtain from the CDR.
You are advised to talk to CDR personnel prior to completing this section.

CATEGORY	DATA ELEMENTS	CHECK ALL THAT APPLY
Demographics	e.g. Gender, race, age	X
Administrative	e.g. Includes payor, payscale, length of stay, fact of visits (inpatient or outpatient), locations of service (inpatient or outpatient), providers	

Financial	e.g. Charges or costs associated with care	
Clinical Data	e.g. Diagnoses	X
	e.g. Procedures	X
	e.g. Mortality	
	e.g. Laboratory / Microbiology Results	
	e.g. Medications	
	e.g. Vitals, Height / Weight, Other Clinical Parameters	X
	e.g. Other (specify)	
Narrative Reports	e.g. Includes discharge summaries, pathology reports, operative notes, etc.	X

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1A-1F) to describe the plan to protect the data from improper use and disclosure.

1A. How will data be collected?

Data may first be collected using one of our desktop computers in our lab spaces. These data are collected and either saved to an excel spreadsheet or software template. Once the data are saved to a specific template, spreadsheet, etc., they can be moved to a secured server. In most cases, the data would be first moved onto the secured ES3 drive using an iKey token. We will not have a web-based system for this. All exported data will be encrypted and not have identifiable information.

1A(1).__X___ Collection of data onto an individual-use device (e.g. smart phone app, tablet, laptop)

If checked answer the following questions:

- What kind of device is it (e.g. laptop, tablet, desktop computer)? __X__
- Who manages / supports the device (e.g., Health Systems Computing Services (HS/CS), Information Technology Services (ITS), self)? _Self_
- How long with the data remain on the device before it is downloaded to a server managed by HS/CS, ITS or SON SECUREnet? __NA___
- Will anyone other than study team members have access to the data on the device? __No___
- Will data be downloaded to UVa in an encrypted secure manner such as the use of SFTP or HTTPS? __Yes___
- Are any backups made of the information on the device? __No___
- After information is downloaded will you delete all UVa subject data from the device? __Yes___
- Does the owner of the device (e.g. phone service provider/ app developer) have any rights to use or access the data either individually or in aggregate? No

1A(2.)_____ Collection of data via web-based format (e.g. online consent, online surveys) via a Non- UVa Secure Server (e.g. HS/CS, ITS or SON SECUREnet)
See 1A(6) below for an exception.

If checked answer the following questions:

- Provide the web address (URL): _____
- How long with the data remain on the Non- UVa Secure Server before it is downloaded to a server managed by HS/CS, ITS or SON SECUREnet? _____
- Will anyone other than study team members have access to the data on the Non UVa Secure Server? _____
- Will data be downloaded to a UVa Secure Server in an encrypted secure manner such as the use of SFTP or HTTPS? _____
- Are any backups made of the information on the Non- UVa Secure Server? _____
- After information is downloaded will you delete all UVa subject data from the Non- UVa Secure Server? _____
- Do the owners of the Non- UVa Secure Server have any rights to use or access the data either individually or in aggregate? _____
- If the data are regulated by HIPAA, is there a Business Associates Agreement (BAA) with the provider? _____

1A(3).__X___ Directly to a server managed by the principal investigator's department or school that is configured to store data regulated by HIPAA or highly sensitive data. If checked, please provide the name of the server: __ITS ES3___

1A(4)._X__ Directly to a Health Systems Computing Services (HS/CS), or School of Nursing SECUREnet with I Key managed server that is configured to store data regulated by HIPAA.If checked, please provide the name of the server: __HSCS O drive___
NOTE: for HS/CS must have HSCS in the URL of the server name .

1A(5)._____ Directly to an Information Technology Services (ITS) managed server that is configured to store data regulated by HIPAA.
If checked, please provide the name of the server: _____
NOTE: must have ITS in the URL of the server name.

1A(6)._____ Directly to a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP)

1.A(7).__X__ Paper

YES	NO	HIPAA Identifier

	X	1. Name
	X	2.Postal address information, other than town or city, state, and zip code
	X	3. Age or Date of Birth if over the age of 89
	X	4. Telephone numbers
	X	5. Fax numbers
	X	6. Electronic mail addresses
	X	7. Social Security number
	X	8. Medical Record number
	X	9. Health plan beneficiary numbers
	X	10. Account numbers
	X	11. Certificate/license numbers
	X	12. Vehicle identifiers and serial numbers, including license plate numbers
	X	13. Device identifiers and serial numbers
	X	14 Web Universal Resource Locators (URLs)
	X	15. Internet Protocol (IP) address numbers
	X	16. Biometric identifiers, including finger and voice prints
	X	17. Full face photographic images and any comparable images
	X	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	X	19. Any other information that could be used alone or in combination with other information to identify an individual.

►If you checked any of the items 1A(1) through 1A(3) will the data include any of the HIPAA identifiers listed below? ANWER QUESTION IN TABLE BELOW

INSTRUCTIONS: If any item above is checked, the study team must verify with the UVa Office of Information Security, Policy & Records Office (ISPRO) that adequate security is in place to collect highly sensitive data. www.virginia.edu/ispro Email: IT-Security@Virginia.edu
Submit ISPRO approval with new protocol submission.-CONFIRMED AND ON FILE

1B. How will data be stored?
INSTRUCTIONS: Choose only one of the following options:

__X__ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.

1C. Will specimens be stored by the UVa study team? No

1D. Will any of the data be stored electronically? Yes

►IF YES, will it include storage of any health information or other sensitive data? Yes
►IF YES, will the data include any of the HIPAA identifiers listed below?
ANWER QUESTION IN TABLE BELOW

YES	NO	HIPAA Identifier
X		1. Name
X		2.Postal address information, other than town or city, state, and zip code
X		3.Age or Date of Birth if over the age of 89
X		4. Telephone numbers
		5. Fax numbers
X		6. Electronic mail addresses
		7. Social Security number
X		8. Medical Record number
		9. Health plan beneficiary numbers
		10. Account numbers
		11. Certificate/license numbers
		112. Vehicle identifiers and serial numbers, including license plate numbers
		13. Device identifiers and serial numbers
		14 Web Universal Resource Locators (URLs)
		15. Internet Protocol (IP) address numbers
		16. Biometric identifiers, including finger and voice prints
		17. Full face photographic images and any comparable images
X		18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
X		19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code*)

1E. If you answered YES to any HIPAA identifier above, where will the data be stored?

__X__ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

- If checked, please provide the name of the server: __HSCS O drive___

__X___ a server managed by the principal investigator's department or school that is configured to store data regulated by HIPAA or highly sensitive data.

- If checked, please provide the name of the server: _ITS_ES3___
- If checked, see Instructions below

INSTRUCTIONS: The study team must verify with the UVa Office of Information Security, Policy & Records Office (ISPRO) that the server they plan to use is configured to store highly sensitive data. www.virginia.edu/ispro Email: IT-Security@Virginia.edu
Submit ISPRO approval with the new protocol submission. –CONFIRMED and on FILE.

HIPPA identifiers will be kept separate from the data used for analysis. Moderately sensitive data will however have a code, and a separate file will be used to link data to the identifiable information.

_____ a server managed by the sponsor or CRO in which the data will be sent and stored in an encrypted fashion (e.g. must be shared and stored via Secure FX, Secure FTP, HTTPS, PGP)

INSTRUCTIONS: The study team should confirm the security of the site with the sponsor, CRO or other outside group.
NOT ALLOWED if you have answered YES to any HIPAA identifier above and data will not be sent/stored in an encrypted manner.

_____ Cloud (UVaBox, UVa-Collab)

- If checked, please provide the name of the service: _____

INSTRUCTIONS: Not allowed if you have answered YES to any HIPAA identifier above.
NOTE: No research data may be stored in a non- UVa licensed cloud provider such as Dropbox, Google Drive, Survey Monkey etc.

1F. Will any of the data be collected or stored in hard copy format by the UVa study team (*e.g. on paper*)?
Yes

►IF YES, where will it be stored?

__X___ case report forms will be stored in a secure area with limited access.

__X___ questionnaires/ surveys will be stored in a secure area with limited access.

Questionnaires will only have the patient ID (code) with no HIPPA identifiers. All questionnaires will be kept in a locked filing cabinet of a locked room, with limited access. The study team will be the only members to access this information.

1G. The following procedures will also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique login ID and password that will keep confidential. The password should meet or exceed the standards described on the Information Technology Services (ITS) webpage about *The Importance of Choosing Strong Passwords.*
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa University Data Protection Standards will be followed
- http://www.virginia.edu/informationsecurity/dataprotection.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.

- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and University Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-health information that reveals an individual's health condition and/or history of health services use.
Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with a HIPAA identifier
Identifiable Health Information under HIPAA regulations is considered to be *Highly Sensitive Data*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Moderately Sensitive Data. The only HIPAA identifiers associated with data: full dates and or postal address information including town or city, state, and zip code.*

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See encryption solutions guidance. *Files on Health System Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVa Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the “F” and “O” managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract/ MTA is in place
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVa HIPAA covered entity unless disclosure is approved by the IRB and an MTA is in place prior to sharing of data

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Moderately Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device (e.g. smart phone)	
E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by Health System	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email work within the UVa HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately
Electronic Data Collection and Sharing	*Electronic Data Collection and Sharing*
(e.g. smart phone app, electronic consent using tablet etc.) MUST consult with ISPRO or Health System Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ Health System: Web Development Center: Contract must include required security measures.	
May NOT be stored in places like UVaBox, UVaCollab, QuestionPro. May also NOT be stored in non-UVa licensed cloud providers, such as Dropbox, Google Drive, Survey Monkey, etc.	
LOST OR STOLEN:	*LOST OR STOLEN:*
Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy (See Privacy Plan section of this protocol)	Must report in accordance with protocol/ in accordance with the Information Security Incident Reporting Policy (See Privacy Plan section of this protocol)

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
***The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, Nutrition Services (Morrison's), the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

__X___ HIPAA identifiers will be destroyed with the data after all retention requirements per sponsors' requirements, UVa Records Management Policies and IRB-HSR Record Retention Requirements have been met. If data and HIPAA identifiers from this study are to be kept and used in future research, a Database Protocol will be established to protect the data before this protocol is closed.

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes

This means that after the study is closed at UVa:

- You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc.) without additional IRB approval
- You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)
- You cannot share your research data with another researcher outside of your study team without additional IRB approval
- Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Age or Date of Birth if over the age of 89
4. Telephone numbers
5 Fax numbers
6. Electronic mail addresses
7. Social Security number
8. Medical Record number
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)

APPENDIX: Transfer of Data Outside of UVa

1. **Will any data be sent outside of UVa to any person at another institution other than the sponsor or the FDA (e.g. researcher outside of UVa)?** Yes- At the point of sharing data for final analysis, patient identifiers will not be necessary. Therefore, all data sent to collaborators will be completely de-identified

2. What identifiers will be sent with the data?-NO

YES	NO	
	X	1. Name
	X	2.Postal address information, other than town or city, state, and zip code
	X	3. Telephone numbers
	X	4. Fax numbers
	X	5. Electronic mail addresses
	X	6. Social Security number
	X	7. Medical Record number
	X	8. Health plan beneficiary numbers
	X	9. Account numbers
	X	10. Certificate/license numbers
	X	11. Vehicle identifiers and serial numbers, including license plate numbers
	X	12. Device identifiers and serial numbers
	X	13 Web Universal Resource Locators (URLs)
	X	14. Internet Protocol (IP) address numbers
	X	15. Biometric identifiers, including finger and voice prints
	X	16. Full face photographic images and any comparable images

	X	17. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
	X	18. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code*)

7. How will data be sent?

____ Paper forms via mail/ FedEx, UPS etc.

_X__ Email:

Not allowed if you have answered YES to any item above.

____FAX:

Not allowed unless receiving fax machine is in a restricted-access location, the intended recipient is clearly indicated, and that recipient has been alerted to the pending transmission and is available to pick it up immediately. Also verify FAX numbers before faxing and use FAX cover sheet with a confidentiality statement.

____ Devices such as flash-drive/ CD etc.:

Not allowed if you have answered YES to any item above unless you written approval from a VP/ Dean. The request for their written approval should be obtained using the Highly Sensitive Data Storage Request Form. You may also contact the UVa Office of Information, Security, Policy and Records Management at 243-6592 for assistance in completing this form.

____ Web Based Data Entry (e.g website, database, registry): NOT Encrypted and Password Protected;

Not allowed if you have answered YES to any item above.

____ Web Based Data Entry (e.g website, database, registry): Encrypted and Password Protected;
If checked, do you confirm that you have verified with host site that data will be sent and stored in an encrypted fashion (e.g. via Secure FX, Secure FTP, HTTPS, PGP)? Answer/Response:

8. Do you confirm that you will obtain a contract/ material transfer agreement with whomever you are sharing data with outside of UVa via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP) ospnoa@virginia.edu**?** Yes