COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

Protocol #: 20-2720
Project Title: Werewolf FLOW 50 During ACL Reconstruction: A Randomized Control Trial
Principal Investigator: Jay C. Albright, MD
Version Date: 11.22.2021

I. Hypotheses and Specific Aims:

Specific Aim: The aim of this study is to compare the outcomes, ease of use, and cost of the Werewolf FLOW50 device to our institutional standard of care which is does not include the use of electrocautery devices during anterior cruciate ligament reconstruction (ACLR) surgery in patients 12-18 years of age using a randomized control trial design.

We will compare the following outcomes between the Werewolf FLOW50 and our institutional standard of care:

1) postoperative arthrofibrosis based on MRI
2) knee range of motion
3) patient reported outcomes
4) complications
5) procedure time
6) procedure cost

This data collection is designed to assist orthopedic surgeons in determining optimal electrocautery techniques to use during anterior cruciate ligament reconstruction surgery in young patients.

Hypothesis: We hypothesize that a lower proportion of participants who undergo ACLR and are randomized to the Werewolf FLOW50 procedure will experience post-operative arthrofibrosis compared to those randomized to standard of care (control group).

II. Background and Significance:

Anterior cruciate ligament (ACL) rupture is an increasingly common diagnosis in the pediatric and adolescent population, possibly due to increased participation in sports and improved physician awareness and ability to diagnose. Although good post-operative outcomes are widely achieved with ACL reconstruction in young patients, known sequelae include arthrofibrosis, knee stiffness, and limited range of motion in the knee (Gage, 2019,

Ortho J Sports Med). The reported incidence of arthrofibrosis following ACL reconstruction has been as high as 26%; however, more recent advances in surgical techniques and rehabilitation protocols have reduced the incidence to approximately 5% (Christensen, 2018, Clin Sports Med; Mayr, 2004, Arch Orthop Trauma Surg).

The Werewolf FLOW50 (Smith and Nephew) adapts to multiple tissue types such as articular cartilage, meniscus, and ligamentous tissue, to resect targeted tissue while preserving healthy surrounding tissue. This technology may benefit surgeons during ACL reconstruction surgery in terms of ease of use, time efficiency, and also improved outcomes in patients. Therefore, the primary purpose of our study is to compare the rate of arthrofibrosis between patients randomized to the Werewolf FLOW50 device compared to a control group (institutional standard of care) during anterior cruciate ligament reconstruction (ACLR). Our secondary objectives include comparing knee range of motion, patient reported outcomes, complications, and procedure time/cost between groups.

III. Preliminary Studies/Progress Report:

No previous work at our institution compares the Werewolf FLOW 50 to standard electrocautery. Previous retrospective research (COMIRB 15-2207) and ongoing prospective research (COMIRB 18-1652) included/currently includes knee range of motion and postoperative complications post-ACL reconstruction surgery.

IV. Research Methods

A. **Outcome Measure(s)**:
   a. Primary outcomes
      i. <u>Presence of arthrofibrosis</u>
         1. Defined using:
            a. MRI data at 6 months post-operative
            b. Loss of ROM greater than 15 degrees at any time >3 months post-surgery
   b. Secondary outcomes
      i. <u>Safety</u>
         1. Lack of visible cartilage changes on MRI sequences at the MRI scan 6 months post-surgery
      ii. <u>Cost-effectiveness</u>
         1. Added cost of using the Werewolf device to the overall surgical case / percentage reduction in arthrofibrosis rate (relative to no arthroscopic cautery)
         2. Average cost of a second surgery for arthrofibrosis / percentage reduction in arthrofibrosis rate (relative to traditional arthroscopic cautery)

c. Secondary outcomes (standard of care)
    i. Surgical information standard of care
        1. Pain control technique:
            a. Combined femoral/sciatic nerve block
            b. Sciatic nerve block only
            c. Other: specify
        2. Graft type
            a. Quadriceps tendon – patellar autograft
            b. Other (exclude)
            c. Repair
        3. Procedures performed:
            a. Repair
            b. Reconstruction with QPA
            c. Lateral Meniscectomy
            d. Lateral Meniscal Repair
            e. Medical Meniscectomy
            f. Medial Meniscal Repair
            g. Other (specify)
        4. ACL Reconstruction Surgical Technique
            a. All-epiphyseal
            b. Hybrid: epiphyseal/transphyseal
            c. Transphyseal
    ii. Clinical Evaluation (obtained 6 months and 1 year post-surgery as standard of care)
        1. Date of Visit
        2. Lachman (manual, mm)
        3. KT-1000 (mm)
            a. Involved
            b. Non-involved
            c. Side-to-side difference
        4. Patient Reported Outcomes (research specific):
            a. Pediatric IKDC
            b. Lysholm Survey
            c. Standardized Questions to assess PT compliance
        5. Complications
            a. Excessive pain >3 months post-surgery
            b. Hardware
        6. Range of motion
            a. Flexion and extension (obtained via goniometric measurement)
    iii. Patient Variables (obtained at time of surgery as a part of standard of care)
        1. Athletic Involvement/Activity Level
        2. Height/Weight/BMI
        3. Skeletal maturity on pre-operative x-ray

a. Mature vs. Immature
4. Name
5. MRN
6. Date of birth
7. Gender
8. Race/ethnicity
9. Zip code
10. Insurance: Public vs. Private

iv. Screen Failures
1. Meets exclusion criteria
2. Opted out

B. Description of Population to be Enrolled:

a. Inclusion Criteria (Determined by medical record screening)

i. Ages 12-18 (inclusive) at time of surgery
ii. Scheduled to undergo ACL reconstruction performed at Children's Hospital Colorado or associated network of care site.

b. Exclusion Criteria (Determined by medical record screening)

i. Underlying congenital or musculoskeletal disorders
ii. Pregnant females, prisoners, and wards of the state
iii. Persons deemed incompetent and those who have limited decision-making capacity

C. Study Design and Research Methods

a. **Screening**
i. Subjects will be identified from patients presenting to the Children's Hospital Colorado Orthopedics outpatient clinics as well as patients presenting to the involved study sites orthopedic outpatient clinics, specifically to an orthopedic sports medicine provider, for treatment of ACL injury.

b. **Subject Enrollment**
i. Subjects will be approached for enrollment during their initial and/or pre-operative clinic visit or during the pre-operative time on the day of surgery. Enrollment may occur at any network of care site of Children's Hospital Colorado or via HIPAA compliant video conferencing with the inclusion of a witness. Eligible patients must undergo ACL reconstruction surgery at Children's Hospital Colorado.

c. Data Collection and Follow-Up

i. Surgical information will be collected from the operative report.

ii. Clinical follow-up information will be collected during the standard of care 6-month and 1-year post-operative clinic visit.
iii. The 6-month post-operative MRI (range= 5-8 months) will be completed at the Brain Imaging Center at Children's Hospital Main Campus in Aurora.

	Visit 1: Pre-op	**Visit 2: Surgery**	**Visit 3: 3 mos. post-op clinic visit**	**Visit 4: 6 mos. post-op clinic visit**	**Visit 5: 6 mos. Post-op MRI at Brain Imaging Center**	**Visit 6: 1 year post-op clinic visit**
Procedures	Study Enrollment R	ACL Reconstruction SOC	Clinic Follow Up SOC	Clinic Follow Up SOC	MRI R	Clinic Follow Up SOC
Visit Window	Pre-operative		±10 days	±10 days	5-8 months post-operative	±10 days
Informed Consent	R					
Inclusion & Exclusion Criteria	R	R	R	R	R	R
Demographic Form	R					
Knee Examination	SOC	SOC	SOC	SOC		SOC
Knee History	SOC	SOC	SOC	SOC		SOC
Medical History	SOC					
Pain Medication		SOC	SOC	SOC	SOC	SOC
MRI	SOC				R	
X-ray		SOC	SOC	SOC		SOC
Pedi IKDC and Lysholm Scale Questionnaires	R		R	R		R
Study documentation	R	R	R	R	R	R
Screen for adverse events	(R)	(R)	(R)	(R)	(R)	(R)
Protocol Deviation	(R)	(R)	(R)	(R)	(R)	(R)
Surgical Re-operation			(SOC)	(SOC)	(SOC)	(SOC)
Study Exit	(R)	(R)	(R)	(R)	(R)	(R)

**Also, at 4 weeks post-op we will be collecting 3 standardized questions from each patient to evaluate patient physical therapy compliance.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

The investigators forsee minimal risks to participants. The Werewolf FLOW50 is an FDA approved medical device to be used in the knee joint. he surgeon performing each surgery has used both the Werewolf FLOW50 device (according to FDA-approved indications for use) and no electrocautery device as standard of care during ACL reconstruction surgery.

There is minimal risk associated with the subsequent MRI. Participants may experience slight discomfort from the confined space, flashing lights in their eyes, or temporary warmth/reddening of the skin following MRI. Participants will be informed of these risks and discomforts and pregnant participants or those with any metal and/or electronic devices inside their bodies will not receive the MRI.

There is the risk of unintended disclosure of protected health information (PHI) to individuals outside the research team. To mitigate this risk, data points are entered into a password-protected, HIPAA compliant REDCap database accessible to only the PIs and study personnel. Children's Colorado affiliated and approved study personal will have access to all study information collected at all involved study sites. However, other study sites will only have access to the information collected on patients enrolled at their site. We believe this system will contribute to the protection of PHI. The only PHI collected will be visit dates; all participants will be linked to their information via a unique study identifier.

The PI will periodically review the status of this protocol. Any unanticipated problems will be disclosed to COMIRB within five days with a cover letter detailing the assessment and actions to be taken.

E. Data Management

Subjects will be assigned patient study identifiers. These identifiers will be used for the identification of all study materials, and will only be linked to the subject's name, medical record number, or other PHI through REDCap. REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly, web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado-Denver and was initiated at Vanderbilt University. The database is hosted at the University of Colorado-Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the DISC. The iterative development and testing process results in a well-planned data collection strategy for individual studies. Both REDCap and REDCap Survey systems provide secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of

entry. These systems offer easy data manipulation with audit trails and reporting for reporting, monitoring, and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

F. Human Subject Research Considerations

i. Involvement of Subjects

Participation in this study will not affect the pre, post, or intra-operative care of ACL reconstruction in any way other than either the use of the use of the Werewolf FLOW 50 device or not and MRI at 6 months postoperative. All involvement and participation will be completely voluntary. The MRI taking place at 6 months post-operative is the only study data point that is additional to standard of care measures.

ii. Planned Duration of the Entire Study

This will be an ongoing study with rolling enrollment of study subjects. We expect the study enrollment period to last about 2 years.

Project timeline		**Project Year (Quarterly)**		
Project/Activity		**1**	**2**	**3**
Regulatory/hiring				
Participant recruitment/enrollment				
5-8 Month Follow Up Data Collection				
Participants enrolled	WEREWolf	30	50	0
	Control	30	50	0
5-8 month monitoring completed (90% retention)	WEREWolf	0	27	45
	Control	0	27	45
Analyze Data				
Manuscript preparation/ scientific presentations				

iii. Duration of Participation for Each Subject

Participants will be enrolled in this study for up to 1 year. Data will be collected from each subject during their initial treatment visit as well as the 6 month and 1 year follow up time periods.

iv. Participation Discontinuation Criteria

Participation discontinuation will occur at the request of the study subject or their legal guardian. Discontinuation may also occur at the discretion of the provider or the principal investigator.

v. Potential Risks to Subjects

It is anticipated that study subjects do not face any potential physical or psychological harm as a result of participation in this study. While

recognized as being minimal, all potential risks are related to the unintentional disclosure of PHI to an outside or unapproved party.

vi. Plan to Protect Subjects/Mitigate Risks

Standard operative techniques will be used as usual to prevent surgical complications which are inherent risks to any ACLR surgery. This includes the use of sterile technique with surgical intervention beformed by a board-certified, fellowship trained, orthopedic surgeon.

As noted in "Data Collection Tools and Data Safety", subjects will be identified by study identifier only with all study related dates (the only PHI collected for research purposes) and other data will be stored in a secure REDCap database to mitigate the possibility of unanticipated disclosure. As REDCap is designed specifically for use with research, the risks of unanticipated disclosure of PHI are similar to those posed to patient information stored in electronic medical records.

G. Potential Scientific Problems:

The only foreseeable potential scientific problems relate to data collection and subject enrollment. It is possible that an insufficient number of subjects will be willing to participate in the study.

H. Data Analysis Plan

Power analysis

Based on existing studies, we expect that traditional arthroscopic cautery will result in a 12% rate of arthrofibrosis following ACLR. If we enroll 80 participants per group and assume 80% power and an alpha level of 0.05, the rate of arthrofibrosis would need to be 2% in treated group (10% reduction in rate compared to usual care) to detect a significant difference between groups.

Statistical analysis: primary outcome

In order to identify differences in arthrofibrosis between groups, we will construct 2x2 contingency tables and calculate associated odds ratios between groups. This will allow us to identify the odds of developing arthrofibrosis for the WEREWOLF group relative to traditional arthroscopic cautery.

If randomization is not sufficient and residual confounding effects are identified for group demographics or other patient characteristics, we will perform a binary logistic regression analysis where intervention group is the predictor variable, arthrofibrosis (yes/no) is the outcome variable, and relevant covariates are included. We will also perform a time-to-event analysis (Cox proportional hazards model), where the time of arthrofibrosis diagnosis is the outcome variable, and group as well as potential confounders are included as predictors.

For secondary outcomes, we will perform a similar series of analyses, but instead of arthrofibrosis as the outcome variable, we will include safety characteristics (cartilage changes as observed on MRI) as our outcome variable.

I. Funding

We are working with Smith and Nephew to provide support to complete the aims of the study.

J. Randomization Plan

Upon study enrollment and prior to surgery, participants will be randomized to WEREWOLF or traditional arthroscopic cautery groups. This will be performed using a block stratified randomization scheme, where age (≥16 years of age vs. <16 years of age at the time of surgery) and sex (female vs. male) are the stratification factors. Block stratified randomization procedures will be conducted according to standard procedures so that sample numbers are equally assigned to each group selected due to the relatively small sample size of the proposed study. The randomization table will be generated prior to study commencement, and individual participant assignments will be assigned by the research assistant, according to the table. Participants will be blinded to their treatment group for the duration of the study (1 year). If a participant self-withdraws or is withdrawn by the PI, they will be debriefed regarding their randomization at the time of withdrawal. The statistician for the study will be blinded to group assignment to reduce risk of bias.

K. Summarize Knowledge to be Gained:

There is no direct benefit to the patient or family from involvement in this database, but their participation can allows us to assess the use and outcomes of the Werewolf FLOW50 during ACL reconstruction surgery. This prospectively collected data will be stored for the use of retrospective studies in the future.

L. References