TITLE: Oral Losartan to Decrease the Risk of Postoperative Arthrofibrosis Following Primary Anterior Cruciate Ligament Reconstruction

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RUSH

PROTOCOL TITLE: Oral Losartan to Decrease the Risk of Postoperative Arthrofibrosis Following Primary Anterior Cruciate Ligament Reconstruction

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STUDY SUMMARY:

Investigational Agent-s -Drugs or Devices	None
IND / IDE / HDE #	N/A
Indicate Special Population-s	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners -or other detained/paroled individuals ☐ Students/Employees
Sample Size	144 all sites
Funding Source	Department of Orthopedic Surgery; Arthroscopy Association of North America (AANA)
Indicate the type of consent to be obtained	☒ Written Main eConsent ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Single Site Research Study ☒ Lead site– Rush University
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

ACRONYMS & ABBREVIATIONS:
ACE-I – Angiotensin converting enzyme inhibitor
ACL-Anterior cruciate ligament
ACLR -Anterior cruciate ligament reconstruction
ARB – Angiotensin receptor blocker
BMI-Body mass index
DUA – Data use agreement
HSS – Hospital for Special Surgery
MAT – Meniscal Allograft Transplantation
IRB – Institutional Review Board
IKDC-International Knee Documentation Committee
KOOS- Knee Injuries and Osteoarthritis Outcome Score
LOA-Lysis of adhesions
MUA-Manipulation under anesthesia
NYU – New York University
PROMs – Patient reported outcome measures
rACLR – revision anterior cruciate ligament reconstruction
RCTs- Randomized controlled trials
ROM-Range of Motion
RUMC – Rush University Medical Center
(TGF-βI) -Anti-transforming growth factor beta 1
GCP – Good Clinical Practice
MOR – Midwest Orthopedics at Rush

Purpose of the Study –
The purpose of this study to investigate the effect of using losartan (a blood pressure lowering drug with anti-scarring properties) on preventing primary postoperative arthrofibrosis (formation of abnormal scar tissue) in the knees in participants undergoing anterior cruciate ligament (ACL) repair surgery of their knee.

Background & Significance –
Anterior cruciate ligament (ACL) reconstruction (ACLR) is one of the most commonly performed orthopedic surgeries in the United States, with over 400,000 performed per year in the United States[1]. Most primary ACLRs do well, however there remains a 1%-8% failure rate necessitating revision ACLR (rACLR), depending on length of follow-up and definition of failure[2,3]. The majority of rACLRs result in a low graft failure rate, improvements in PROMs, and high return to sport[4–6].

Despite the overall success of primary ACLR and revision ACLR, arthrofibrosis remains a common postoperative complication. Newer estimates report a range of 3-4%, markedly

improved from earlier years with rates as high as 38%, likely due to advances in surgical techniques and accelerated rehabilitation protocols[7,8]. However, there remains the need to further decrease this complication, as arthrofibrosis significantly limits patient mobility, return to work and sport, with a current poor understanding of its pathophysiology[9]. It is believed that a core mediating factor of postoperative arthrofibrosis is mediated by transforming growth factor beta-1 (TGF-β1), a pro-fibrotic cytokine implicated in fibrosis and scarring in the cardiac, renal, pulmonary, and musculoskeletal systems[10–15]. Debilitating arthrofibrosis may necessitate a return to the operating room, specifically for manipulation under anesthesia (MUA) and/or arthroscopic lysis of adhesions (LOA).

Losartan, an angiotensin-II receptor blocker (ARB), approved by the Food and Drug Administration (FDA) for the treatment of hypertension and diabetic nephropathy, has garnered recent interest in the field of orthopedic surgery as an anti-fibrotic (anti-scarring) agent. Losartan's primary mechanism of action as an anti-hypertensive involves acting as a receptor antagonist for angiotensin II, a peptide produced by the liver which causes vasoconstriction, release of anti-diuretic hormone from the pituitary gland, and release of aldosterone from the adrenal glands, among other functions[16]. Losartan secondary function is to act as a TGF-β1 blocker. TGF-β1 has been implicated in pro-fibrotic pathways in multiple organs systems. Losartan, initially as a treatment for hypertension and diabetic nephropathy, was found to have benefits against fibrosis in the renal system[17–19]. As a result, the use of losartan has gained interest in several other fields in medicine, including plastic surgery for wound healing and keloid prevention, in ophthalmology to prevent corneal scarring, and orthopedic surgery[20–26]. The potential use of losartan presents an attractive anti-fibrotic prophylaxis candidate against the formation of postoperative arthrofibrosis following ACLR.

The purpose of this study to investigate the effect of using losartan (a blood pressure lowering drug with anti-scarring properties) on preventing primary postoperative arthrofibrosis (formation of abnormal scar tissue) in the knees in participants undergoing anterior cruciate ligament (ACL) repair surgery of their knee.

Subject Recruitment –

Patients will be recruited upon presentation to the outpatient office with an ACL rupture (regardless of number of prior surgeries) that are indicated for primary ACLR with graft choice per surgeon preference. If any chart filtering for prospective recruitment is required, the study will utilize CPT code 29888 (ACL reconstruction).

Rush University Medical Center is the lead site for this study. The goal of this study will be to recruit 144 participants, with approximately 48 participants from Rush University Medical Center, 48 participants from New York University (NYU) Langone, and 48 participants coming from Hospital for Special Surgery (HSS). Individual subjects will be followed for 12 months from their date of surgery.

The study will be open for 36 months after each site is open to accrual to allow all recruited subjects to have an ACLR surgery and to go through their data collection time-points postoperatively.

Inclusion Criteria:

- Must be undergoing a primary ACLR with or without the following:
  - Chondroplasty
  - Synovectomy
  - Loose body removal
  - Removal of hardware
  - Meniscal surgery (excluding meniscal allograft transplantation/MAT)
  - Lateral extra-articular tenodesis
- Must have skeletal maturity in the distal femur and proximal tibial physes
- Must be age 18 years or older at time of enrollment

Exclusion Criteria:

- <18 years at time of enrollment
- No diagnosis of ACL tear
- ACL repairs
- Revision ACL reconstructions
- Open distal femur or proximal tibia physes
- Major concomitant procedures (such as osteotomy, MAT, or cartilage restoration surgery)
- History of prior proximal or distal femur fracture (including those receiving nonoperative treatment)
- History of prior ipsilateral femur or tibia osteomyelitis
- Medical history
  - History of hypotensive disease, including postural orthostatic hypotension syndrome (POTS), autonomic dysreflexia, or Shy-Drager syndrome (aka multiple system atrophy), baseline hypotension <90 systolic or <60 diastolic mmHg.
  - History of significant hepatic disease (liver transplantation, cirrhosis of any cause, or any liver disease with Child-Pugh classification B or C) due to hepatic metabolism of ARBs.
  - Chronic kidney disease
  - Rheumatologic disorders on immunologic medications

  - Current medications including diuretics (i.e. furosemide), lithium, and spironolactone
  - Current hypertension with prescription of an ARB or ACE-I
- Allergy to losartan
- Current pregnancy or breastfeeding

Consent Process –

Potential participants are identified using medical chart and case review CPT code 29888 (ACL reconstruction) will be used for prospective patient identification. The study eligibility requirements will be reviewed by the PI and study staff. The potential participants are pre-selected as tentatively meeting the eligibility requirements for the study. Research study staff will reach out to eligible patients through a phone call or during their office visit explaining the study.

Potential participants are identified using medical chart and case review. The study eligibility requirements are reviewed by the PI and study staff. Potential participants are identified in clinic following clinical diagnosis. The study eligibility requirements and study details will be reviewed with the patient by the PI and study staff in-person. Randomization to the treatment arms of the study will occur at the time of informed consent.

Patients will be recruited for participation in this study in clinic at the time of their surgical discussion. Ideally, the informed consent discussion should be conducted when the study staff and potential participant has time to ask and answer questions. Information provided to the patient includes the rationale for the study procedure or treatment, the number of study visits and the study activities they will need to complete, risks involved, expected benefits, and alternatives to treatment including the likely results of no treatment and that their participation is voluntary and can be stopped at any time.

eConsent
The potential participant will be sent a valid Rush Institutional Review Board (IRB) approved stamped copy of the informed consent form for the study through an electronically secure and approved electronic platform, PatientIQ and delivered through their email. This could be executed on a dedicated clinical device or sent to the participant's device.

The potential subject will then be prompted to reply with the appropriate passcode in order to access the consent form, and then provide the passcode again with their signature (secured). A copy of the time stamped document will be sent to the study team through the electronic platform and a copy will be sent to the participant. This process could be executed on a dedicated clinical device or sent to the participant's device.

The process of consent will be documented in PatientIQ a form titled Informed Consent Process.

Randomization will occur at the time of informed consent using R statistical software.

Participants will be randomized to one of 2 study arms. These are Arm One: 72 participants enrolled in the treatment (losartan) group, or Arm Two: 72 participants enrolled in the control group (placebo). This will be in a double-blinded fashion so that participants and their clinical care teams are not aware of group selection.

Informed Consent Discussion
The PI, participating surgeon and staff, or clinical research study staff will contact the patient in clinic or via telephone to discuss the research study with them. Ideally, the informed consent discussion should be conducted when the study staff and potential participant has time to ask and answer questions. Information provided to the patient includes the rationale for the study procedure or treatment, the number of study visits, an overview of study activities they will need to complete, risks involved, expected benefits, and alternatives to participation.

The process may occur over a period of several discussions, culminating in the signing of a consent form with documentation in the patient profile or chart.

If the patient agrees to participate, their email address will be verified. The consent will be sent electronically through the secured platform, PatientIQ, to the patient's email. The potential subject will then be prompted to reply with their appropriate passcode in order to access the consent form, and then they will provide the passcode again with their e-signature (secured). No research activities will be performed prior to execution of the consent. A copy of the time stamped document will be sent to the study team through the electronic platform and a copy will be sent to the participant.

Study Design & Procedures–

This is a multi-center, double-blinded randomized controlled trial (RCT). The operating surgeon and patients will be blinded to the study arm selection.

The experimental arm (Arm 1) will receive 25mg losartan daily for 3 days followed by 50 mg losartan daily for 25 days. This is based on prior studies that recommend ramping up losartan when used for antifibrotic prophylaxis. The safety of utilizing losartan in healthy patients has been established in prior RCTs, particularly in plastic surgery.

The control arm (Arm 2) will receive a placebo tablet with the same appearance and frequency to that of the losartan group.

Both the losartan and placebo will be ordered through the Rush Investigational Drug Services pharmacy for RUMC based participants to pick up prior to their ACLR.

NYU Langone and HSS will obtain the study medications for participants at New York sites through their own research pharmacy.

All capsules will be size 1. Two types of losartan capsules will be compounded by combining a broken-up 25mg or 50mg losartan tablet and microcrystalline cellulose placebo filler to eliminate rattling of the broken tablet inside of the capsule. The 25mg losartan capsules will be yellow and the 50 mg losartan capsules will be blue. The placebo capsules will consist of microcrystal cellulose and will come in yellow and blue to appear identical to the losartan capsules

Subjects will log their medication adherence in a pill diary sent to them daily via email or text message through PatientIQ. Research staff will be able to track compliance through the completed daily forms that subjects fill out electronically. The notifications that subjects receive from PatientIQ to remind them to complete their pill diary form will have the secondary benefit of acting as an electronic pill reminder.

Given an onset of action of 6 hours, losartan will start the day of surgery and be dosed for 28 days postoperatively. The placebo group will follow an identical dosing schedule.

Additionally, as a part of the standard preoperative procedures at Rush University, all participants with pregnancy potential will undergo a pregnancy test on the day of surgery to allow for proper care during surgery and exclusion from the research study, as losartan is a known teratogen (causes birth defects).

Retrospective Data Collection
Demographic information collected will include age, sex, BMI, allergy information, medical comorbidities, smoking history, occupation, and sport type and level (recreational, high school, collegiate, professional). Surgical characteristics will also be collected including knee laterality, concomitant procedures, graft type, and fixation technique. This data will be collected from the patient record in Athena and PatientIQ.

Prospective Data Collection
Range of motion (ROM) will be documented preoperatively on the morning of surgery using a goniometer. ROM will also be documented at 2 weeks, 6 weeks, 3 months, 6 months, and 1 year postoperatively using a goniometer. At these visits, the Knee Injuries and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) subjective knee form, and Lysholm scores will also be administered.

The date of their return to sport, with specific characterization of their pre- and postoperative sport level will be documented. The date of their return to work, if employed, will also be documented, with notation of any modification of duties.

Postoperatively, any secondary procedures that patients undergo within the first year will be recorded. A particular emphasis will be on incidence of MUA and/or LOA, as the rate of arthrofibrosis in the study will be defined by the need for MUA and/or LOA. Indications for MUA/LOA will be standardized across sites; < 30˚ extension or < 60˚ flexion at 6 weeks postoperatively will be indicated for an isolated MUA, whereas < 10˚ extension or < 90˚ flexion at or greater than 3 months postoperatively will be indicated for arthroscopic LOA and MUA.

TGF-β1 levels will be collected from synovial fluid that will be drawn from each participant's ipsilateral knee. A volume up to 5 mL will be aspirated from the participant's knee for analysis using a single biomarker Enzyme-Linked Immunosorbent Assay (ELISA) for TGF-β1. If less than 5 mL of fluid is aspirated, the sample will still be sent for analysis as less than 1 cc of fluid is necessary to run a single biomarker ELISA. The baseline collection of 5 mL of synovial fluid will be performed intra-operatively and 5 mL of synovial fluid will be aspirated from the same knee at the first postoperative visit at 2 weeks post-operatively, with documentation of TGF-β1 levels at these time points using the same ELISA assays.

These assays will be performed at RUMC laboratory for RUMC participants, at the NYU Langone laboratory for NYU participants, and at the HSS laboratory for HSS participants.

Project Timeline and Schedule of Events

	Day of surgery	2 weeks	6 weeks	3 months	6 months	1 year post-operatively
ROM	Measurement with goniometer	Measurement with goniometer	Measurement with goniometer	Measurement with goniometer	Measurement with goniometer	Measurement with goniometer
TGF- β1 levels	Synovial fluid aspiration pre-incision intra-operatively	Synovial fluid aspiration	N/a	N/A	N/a	N/a
Rate of MUA	N/a	N/a	Documented event	Documented event	N/a	N/a
Rate of LoA	N/a	N/a	N/a	Documented event	Documented event	Documented event
PROM scores	Baseline scores completed in preoperative holding area	N/a	PROs administered	PROs administered	PROs administered	PROs administered
	N/a	Documented	Documented	Documented	Documented	Documented

Return to work and Sport rates						

Pill Diary Collection-
A pill diary will be created in PatientIQ to be sent daily to study participants on the day of surgery and for 4 weeks postoperatively to log their medication adherence. This will be sent to their email and via text message. Research staff will be able to log into PatientIQ to view patient compliance metrics and ensure subjects are taking their drug.

Risk/Benefit Assessment –
Side effects of losartan use include hypotension, orthostatic hypotension, acute kidney injury, hyperkalemia, angioedema, palpitations, syncope, dizziness, abdominal pain, nausea/vomiting, diarrhea, headache, lightheadedness, falls, and anemia [27].

Known drug interactions of losartan include other ACE-inhibitors or ARB medications, including but not limited to valsartan, erbasartan, lisinopril, enalapril, captopril, or ramipril. Other drug-drug interactions include diuretics such as furosemide, lithium, and spironolactone. These are included in the exclusion criteria of the study

Possible side effects/complications of the standard of care ACL surgery include: infection, stiffness, swelling, hematoma, wound dehiscence, neurovascular injury, fracture, graft failure or re-tear, deep vein thrombosis or pulmonary embolism

Possible side effects/complications of knee synovial fluid aspiration include: swelling, ecchymosis, infection, bleeding, iatrogenic injury

There is a potential risk of having the participant's privacy or confidentiality compromised. The participant's identities will not be identifiable in publications resulting from this investigation. Every reasonable effort will be made to protect the participant's information while their data is used as part of this study. There are no direct benefits to individual subjects for participating in this study. The alternative to participation in this study is not to participate in the study.

Data Sharing-
Data collected by NYU Langone will be housed on their own dual-factor authentication server in a Microsoft Excel data sheet. This will only be accessible by research staff at NYU. RUMC and HSS will follow the same protocol for their own data.

Data sharing between the institutions will be led by Rush University as the Data Coordinating Center. This will be facilitated by the Microsoft One Drive/Excel that is only accessible through either of the three institutions' servers and a data use agreement (DUA). The data to be shared will include all de-identified participant data that has been specified above in the Study Design and Procedures section. Specifically, shared data will include demographic data (age, sex, BMI, allergy information, medical comorbidities, smoking history, occupation, and sport type and level), surgical characteristics (knee laterality, concomitant procedures, graft type, and fixation technique), date of return to sport, level sport at preoperative and postoperative timepoints, date of return to work, modification of work duties, ROM, KOOS score, IKDC score, Lysholm score, data on MUA/LOA, and TGF- β1 levels. This data will be pooled together in a Microsoft Excel spreadsheet and shared amongst sites via Microsoft OneDrive.

NYU Langone and HSS will submit their own IRBs to their institutions and DUAs will be executed between the three institutions

Costs to the Subject-

Our Arthroscopy Association of North America (AANA) grant will sponsor the cost of the losartan or placebo prescription and the TGF-β1 ELISA assays. Subcontracts will be executed between the sites to ensure distribution of grant funds to each participating site to offset the study costs.

The Department of Orthopaedic Surgery will use grant funding to pay all costs for RUMC participants' synovial fluid aspiration, data collection and review.

Compensation of Subjects

There will be no compensation of subjects for this study.

Data Analysis and Statistical Considerations

The study will utilize standard statistical methodology to analyze the collected data. RStudio and Microsoft Excel will be utilized as primary statistics software.

For each quantitative variable (rate of MUA and/or LOA, knee ROM, and TGF-β1 levels), a one-sided independent t-test (parametric) or Mann-Whitney U test (nonparametric) will be used to determine differences between the losartan group and the placebo group. Determination of whether to use a parametric or non-parametric test will be performed using Shapiro Wilks tests and QQ plots, to assess normality of the data.

For PROMs, a multiple linear regression analysis will be conducted to determine differences between the losartan and placebo groups. Chi-squared tests will be used for nominal variables, including demographic information such as sex, comorbidities, smoking history, occupation. Survival analyses will be used for time to event data (e.g. one of the secondary procedures: MUA or LOA), and regression modeling will be employed to assess relationships in ROM and patient-reported outcome scores.

An alpha level of 0.05 will be used for all statistical analyses with a goal of a minimum study power of 0.80. Due to the nature of arthrofibrosis, a large sample size will be required to detect small differences in binary variables such as MUA/LOA. However, it is likely that differences in knee ROM, TGF-B1 levels, and postoperative PROMs will be more sensitive to differences between the experimental and control groups.

Based on a *priori* power analysis for an independent t-test with target alpha of 0.017 (adjusted using Bonferroni's correction) and power of 0.80 to detect a medium effect size (Cohen's d of 0.5), a total of 144 patients will be recruited for assessment of knee ROM, TGF-β1 levels, and rate of LOA/MUA.

A *priori* power analysis was also conducted for PROMs for a multiple linear regression model using an alpha of 0.05, power of 0.80, and medium effect size (Cohen's f^2 of 0.15). This yielded a required n of 55 patients.

All study participants will have each of the four data endpoints measured, so a total n of 144 will be used with 72 subjects in each study arm to obtain statistical significance.

Data & Safety Monitoring

There are minimal risks to subjects participating in this study, given the safety profile of low-dose losartan. Subjects will have 24/7 access to clinical staff at each participating surgeon's practice to report any concerns of an adverse event and to receive proper medical management. During business hours, this involves the surgeon or surgeon's PA team, and after hours and on weekends, this involves an orthopedic sports medicine fellow via AlertMD call system.

The contact points for these teams will be surgeon specific, and each subject will receive the contact information on the day of surgery with their standard postoperative instructions. Patients may also reach their surgeon's team via calling Midwest Orthopaedics at Rush at (815) 881-1304. If a subject reports known side effects of losartan (hypotension, orthostatic hypotension, syncope, dizziness, lightheadedness, falls, acute kidney injury, hyperkalemia, angioedema,

palpitations, abdominal pain, nausea/vomiting, diarrhea, headache, or anemia), the blinding of the subject will be broken to get them off the study drug. Upon stopping the study medication, the subject will receive a safety follow-up call from the study physician within a reasonable timeframe guided by the severity of symptoms. This will be to determine the cause of the participants symptoms and the best next step in medical management. If deemed due to the study medication, the drug will continue to be held and appropriate medical care should be sought by the participant. Another safety call will occur within 3 days of drug stoppage should it be deemed to be an adverse event from the study medication.

All adverse events will be recorded and reported to the site IRB per good clinical practice (GCP) and institutions guidelines. Any adverse events that are related to the study drug will be promptly communicated to the other sites by the lead site. Additionally, unanticipated events will be communicated between study sites through study documentation within the data that is shared between sites of all complications and unanticipated events. If an event is deemed unanticipated and there is a significant risk to other study participants as determined by the site's PI, a study wide redacted email will be sent to all PIs disclosing the specific event, what led to the event, and the PIs will discuss how to safely move forward or end study participation.

Study Drug Procurement and Study Drug Storage-

For the Rush site of this study, the Rush Oak Park Hospital compounding pharmacy will be responsible for the procurement of the study 25mg losartan capsules, the 50 mg losartan capsules, and the placebo capsules. All capsules will be size 1. Two types of losartan capsules will be compounded by combining a broken-up 25mg or 50mg losartan tablet and microcrystalline cellulose placebo filler to eliminate rattling of the broken tablet inside of the capsule. The 25mg losartan capsules will be yellow and the 50 mg losartan capsules will be blue. The placebo capsules will consist of microcrystal cellulose and will come in yellow and blue to appear identical to the losartan capsules.

The pharmacy has provided an official quote of $1,840 for all study medications for the Rush site. This is for 100 subjects (50 per group). The losartan and placebo tablets will be paid for in full using grant funds. There is no startup fee for this service at Oak Park Pharmacy. HSS and NYU Langone will be responsible for their own drug procurement and storage.

A free pharmacy courier service provided by Rush Oak Park hospital will be used to deliver these to RUMC. After that, the medications will be stored under lock and key in a secure location only accessible by Midwest Orthopaedics at Rush research study staff with badge access.

Rush's lead research assistant for the project will have access to the medication and to the unblinded list of patient data. Upon subject enrollment, they will be responsible for getting the correct medication for the participant based on their randomization group. They will label the medication bottles with blinded "losartan/placebo: starting on the day of your surgery take one yellow capsule by mouth daily for 3 days followed by one blue capsule by mouth daily for 25 days". After this, the medication will be blindly distributed to subjects while maintaining the blinding of the clinical team.

Data Storage & Confidentiality

Participant information will be collected and maintained in a excel data sheet housed on the Midwest Orthopedics at Rush (MOR) server, which is dual-factor authentication protected and accessible only to research staff. Subjects' identities will be coded via the use of a separate document key (electronic excel spreadsheet) correlating subjects' Rush medical record numbers with a study ID assigned for the sole purpose of this study.

This key electronic document will be maintained as a separate electronic file (excel spreadsheet) from data collection tool and will be housed in the MOR server, which is dual-factor authentication protected and accessible only to research staff.

Data sharing between institutions will be conducted via the Microsoft Office OneDrive cloud-based system that RUMC, NYU Langone, and HSS research staff will have access to. This is a dual-factor authentication protected server that will allow data sharing to occur between the two sites. All de-identified study data will be shared between the sites to allow for transparency. Rush will serve as the lead Data Coordinating Center.

All files related to the study will not be shared with non-study personnel.

According to Rush policy OP-0432 and CC-G04, study data must be maintained for 10 years in accordance with Illinois State Law. After this time the data will be destroyed by permanently and securely deleting electronic files on the Master key document (private health information) and the coded data collection tool.

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