# Phase 1/2 Prospective Double-blind, Placebo-controlled Randomized Clinical Trial Using Losartan to Treat Grade II and III Hamstring Strains

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UPMC LIFE CHANGING MEDICINE

Department of Orthopaedic Surgery
UPMC Rooney Sports Complex
UPMC Lemieux Sports Complex

# CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY


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***Why is this research being done?***
Investigators in the University of Pittsburgh Department of Orthopaedic Surgery are conducting a research study to evaluate the use of Losartan as a medication for grade II or III hamstring (muscle in the back of the thigh) sprains. Losartan is a prescription medication used to as a medical treatment for high blood pressure. The use of losartan in this research study is considered to be experimental.

Subjects will be randomized to receive either Losartan medication at the 50 mg dose or a placebo pill (inactive substance). Randomization is a process that assigns you by chance, rather than by choice. Randomization is like the flip of a coin and gives you equal possibility of being in either group. We will use a computer program to randomly assign you to one of the two groups and neither you nor your health care providers (doctor, physical therapist/ athletic trainer) will know which group you are in. In the case of emergency, however the study team will be able to determine which you have received. You will be given the supply of study pills to take once daily for 4 weeks.

The goals of this study are:

- To determine if Losartan is safe and tolerable, compared to a placebo;
- To determine if Losartan is effective in the recovery of hamstring muscle function after a grade II or III hamstring sprain;
- To determine the effect of Losartan how long it takes to return to prior level of function after a grade II or III hamstring sprain;
- To determine the effect of Losartan on another injury after a grade II or III hamstring sprain.

***Who is being asked to take part in this research study?***
You are being asked to participate in this study because you are 18 years of age or older, participate regularly in very strenuous (football, basketball, or soccer) or strenuous (racquet sports, skiing, manual labor occupations) activities including activities that requiring running and sprinting, have had a grade II or III hamstring injury in the past 7 days, and agreed to be randomized to one or two treatment groups. Approximately 10 patients will participate in this study. While you are enrolled in this study, you will attend physical therapy visits.

***What procedures will be performed for research purposes?***
The following activities will be completed throughout your participation in this study. Not all activities listed here will be completed at every visit. You will participate in 8 visits in-person and 4 – follow-up phone calls over a period of 12 months.

<u>Demographic Information</u>
Demographic Information that will be recorded include age, sex, weight, height, body mass index (BMI), education level, sports activity level, work activity, marital status, and smoking history. This form will be completed at the pre-treatment visit. (5 minutes to complete)

<u>Activity Level Questionnaires-</u> The following questionnaires will be completed at the pre-

treatment and follow-up visits. The Occupational Rating Scale of the Cincinnati Knee Rating System measures work activity by rating the duration or frequency of sitting, standing, walking, squatting, climbing, lifting, and carrying performed while working at a job. The Marx Sports Activity Scale consists of four activities (running, cutting, decelerating, and pivoting) rated by the frequency you perform the activity. (10 minutes to complete)

Medical History and Physical Examination

A medical history and physical examination will be performed for all subjects in this study at the pre-treatment visit. The medical history will include a review of the chief complaint, history of present injury, past medical history, allergies, medications, and social and family history. (15 minutes to complete)

An examination of the injury will be performed at the pre-treatment visit. You will be examined for any symptoms related to your hamstring injury including pain, bruising, swelling, and your ability to walk and run. (15 minutes to complete)

Vital Signs

Your vital signs will be measured by a qualified examiner. The examiner will take your pulse (heart rate) and blood pressure. Blood pressure will be measured in both arms and will be taken while you are seated, after you have been lying quietly on your back for 5 minutes, and while you are standing. Vital signs will be taken at the pre-treatment, 1 week, 2 week, 3 week, 4 week, 6 week, 12 week, and 6 month follow-up visits. (10 minutes to complete)

Pain Scale

You will be asked to rate your hamstring pain on a scale from 0 to 10. Your pain will be assessed at the pre-treatment, 1 week, 2 week, 3 week, 4 week, 6 week, 12 week, and 6 month follow-up visit. (2 minutes to complete)

Blood Draw

You will have of blood taken 4 times during the study. You will be sent to a UPMC Outpatient Lab for this blood draw. The blood will be taken from your arm. The amount of blood drawn will be enough to assess a chemistry panel with electrolytes (about 2 teaspoons). The blood will be taken prior to treatment and 2, 4, and 6 weeks after study medication is given to you. (15 minutes to complete)

MRI

An MRI (magnetic resonance imaging) will be used to determine the extent of your leg injury. MRI uses a large circular magnet to construct images of the internal structures of your leg and knee. You will undergo a MRI at the pre-treatment visit and 6 months follow-up. (1 hour to complete)

Losartan or Placebo

This study compares an active drug to a placebo. A placebo is an inactive substance made to look/taste like an active medicine. You will either be assigned to receive Losartan or a placebo. Research use a placebo to see if the study drug works better or

is safer than not taking anything. You will take the study medication daily for 4 weeks. You will bring the study medication with you to each in-person research visit. Pills will be counted by the study staff to check for medication compliance. Because Losartan is dangerous in pregnancy, female subjects will have a pregnancy test before starting the study pills and at each visit.

Medication Log

You will be asked to complete a medication log while you are taking the study medication. You will record when you took the study medication, as well as any other medications you make take during the same time period. This log will be reviewed with a member of the study staff when you return to the office for the 1 week, 2 week, 3 week, and 4 week follow-up visits. (15 minutes to complete)

Review of Exercise Log

Your physician will give you plan of stretching and strengthening exercises for physical therapy and rehabilitation. This plan will be supervised by the physical therapist or athletic trainer. The exercises are to be completed by you daily. For the research study, you will complete a log to indicate which exercise you have completed each day. This log will be reviewed at the 1, 2, 3, 4, 6, and 12 week visits with the research study team.

Hamstring Flexibility

To complete this test, you will lay on your back on an examination table. An examiner will move your leg by straightening your knee as far as it will go. The angle of your knee will be measured and recorded with a goniometer (protractor). This test will be repeated on both sides. This test will be completed at the pre-treatment, 1 week, 2 week, 3 wee, 4 week, 6 week, and 6 month follow-up visits. (10 minutes to complete)

Isometric Hamstring Strength

To complete this test, you will lay face down on an examination table. A dynamometer (device to measure force) will be placed on the lower leg, just above the ankle. The amount of force you create by pushing on the dynamometer will be measured. Your leg will be free to move back toward the table. You will push your leg as hard as you can, three times with a one-minute rest in between each. This test will be repeated on both legs. This test will be completed at the pre-treatment visit, 1 week, 2 week, 3 week, 4 week, week, and 6 month follow-up visits. (15 minutes to complete)

Isokinetic Hamstring Strength

For the isometric dynamometry, you will be seated in a device called the Biodex System III (Biodex Medical Systems, Shirley, NY) that measures the amount of force you exert while pushing on a force-sensing bar. You will be seated on the device and the force-sensing arm will be secured to your ankle. Testing will begin on with the non-involved leg followed by testing of the involved leg. The test consists of 3 practice trials, followed by 3 maximum effort trials (pushing as hard as you can) for contractions of the hamstring muscles (back muscles of your thigh). Each trial will consist of a 5-second contraction of the quadriceps muscles followed by a 60 second rest period. There will be a 1-minute rest period between the practice trials and the maximum effort trials. This

test will be completed at the 6 week and 6 month follow-up visits. (15 minutes to complete)

Telephone Call Follow-up

A member of the study team will call you to ask questions about your activity level and any symptoms you may have, including pain. You will receive 4 phone calls after your 6 week visit. Each call will last approximately 5-10 minutes.

**Study Chart**

This study chart shows all the study activities you will complete. Study procedures described in this consent form are listed along the left side of the chart. The study visit time points are listed across the top.

| | Pre-treat | Day 0 | 1 w | 2w | 3w | 4w | 6w | 12w | 4m | 6m | 9m | 12m | Time to Complete |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | | | |
| Demographic Questionnaire | X | | | | | | | | | | | | 5 minutes |
| Activity Level Questionnaries | X | | X | X | X | X | X | X | X | X | X | X | 10 minutes |
| Medical History | X | | | | | | | | | | | | 15 minutes |
| Vital Signs (heart rate and blood pressure) | X | | X | X | X | X | X | | | X | | | 10 minutes |
| Physical Examination | X | | | | | | | | | | | | 15 minutes |
| Blood Work | X | | | X | | X | X | | | | | | 15 minutes |
| Urine pregnancy test | | | X | X | X | X | | | | | | | 10 minutes |
| Numerical Pain Rating Scale | X | | X | X | X | X | X | X | | X | | | 2 minutes |
| Hamstring flexibility | X | | X | X | X | X | X | | | X | | | 10 minutes |
| Isometric hamstring strength testing | X | | X | X | X | X | X | | | X | | | 15 minutes |
| Isokinetic hamstring strength testing | | | | | | | X | | | X | | | 15 minutes |
| MRI | X | | | | | | | | | X | | | 1 hour |
| Randomization | | X | | | | | | | | | | | |
| Day of 1st Medication Dose | | X | | | | | | | | | | | |
| Medication Log Review | | | X | X | X | X | | | | | | | 15 minutes |
| Exercise Log Review | | | x | x | x | x | x | X | | | | | |
| Telephone follow-up | | | | | | | | X | X | | X | X | 5-10 minutes |
| | Legend: pre-treat = pre-treatment; w = week; m = months | | | | | | | | | | | | |

***What are the possible risks, side effects, and discomforts of this research study?***

Risks of Losartan

There is a risk that you may experience side effects of taking the medication Losartan during the treatment phase of this study. Side effects include diarrhea, dizziness, tiredness, upper respiratory tract infections, cough, sinus disorder, nasal congestion, indigestion, heartburn, pain, high blood potassium, low blood pressure, allergic reaction, and injury or death to an unborn fetus. You will be monitored by a study physician for these side effects throughout the course of the study.

Reproductive Risks

Losartan is contraindicated in pregnancy, as it is known to cause harm to an unborn baby. Pregnant females will be excluded from this study. Taking this medication while pregnant may cause injury or death to an unborn fetus. You will be counseled by the investigator of this risk and will be counseled to use appropriate birth control methods. You will be screened for pregnancy by blood test prior to being administered the study medication. You will also be screened for pregnancy with a urine pregnancy test at the 1 week, 2 week, 3 week, and 4 week follow-up visits.

To avoid risk to the fetus, it is important that female participants not become pregnant while you are participating in this research study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you should use an appropriate “double barrier” method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed “birth control” pills, injections, or implants. If you choose to be sexually active during this study, you understand that even with the use of these birth control measures pregnancy could still result. The risks of receiving the study drugs while pregnant include potential loss of pregnancy or possible birth defects. If you become pregnant while participating in this study, you must tell the study doctor immediately.

Breach of Confidentiality

Subject confidentiality will be maintained at all times, as with any other patient who receives treatment at the Center for Sports Medicine. All records will be assigned a case number. Information collected in this study will be stored in a locked file cabinet and will be accessible only to the research staff. The list linking the code number with your identity will be stored in a separate secure location. You will not be identified in any publications or presentation of the research results.

Risk of Blood Draw

The risks of taking blood include pain and bruising at the point the blood is taken.

Risk of MRI

There is the risk that the strong magnetic field of the MRI scanner may attract metallic objects toward the magnet. This may cause metallic objects within the body to move which may result in injury to the surrounding tissues. Additionally, some individuals may experience claustrophobia due to being a in confined space when in the MRI scanner.

Risks of Isometric and Isokinetic Strength Tests

The risks associated with the strength tests include mile muscle soreness and discomfort following the tests. In rare instances, individuals may experience a strained thigh muscle, which could result in muscle pain and swelling for several days. These risks will be minimized by allowing adequate time for warm-up, stretching, and familiarization with the test.

***What are the possible benefits from taking part in this study?***
You may not receive any direct benefit from this study. However, information learned in this study may lead to additional methods to treat future patients with hamstring injuries.

***If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?***
You will be promptly notified if, during the conduct of this research study, any new information about using Losartan to treat hamstring injuries is found.

***Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?***
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed **exclusively** for the purpose of this research study. You will be charged, in the standard manner, for any procedures performed for your routine medical care.

***Who will pay if I am injured as a result of taking part in this study?***
The investigators and their associates who provide services at UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe you were injured as a result of the research procedures being performed, please contact immediately the Principal Investigator or one of the co-investigators listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. You do not, however, waiver any legal rights by signing this form.

***Will I be paid if I take part in this research study?***
You will receive up to $410 for completion of all research activities. Payments are distributed as follows:

- **Baseline activities** (including consent, physical examination and vital signs, strength testing, questionnaires and assessments, MRI and bloodwork): $100
- **Weeks 1, 2, 3 and 4 activities** (including strength assessments, questionnaires and vital signs): $25 per timepoint

- **6 Week activities** (including strength assessments, questionnaires, vital signs and bloodwork): $50
- **6 Month activities** (including strength assessments, questionnaires, vital signs and MRI): $100
- **12 week, 4, 9 and 12 month** telephone questionnaires: $15 per timepoint.

No partial payments per timepoint will be given. To receive the full amount at each timepoint, all designated activities must be completed.

Payment to participants is considered taxable income regardless of the amount. If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a "Form 1099 – Miscellaneous" with the IRS and provide a copy to the taxpayer. We are required to give your name and social security number to the Accounting Office. Participants who do not provide a social security number may still participate in the research, but the IRS requires that 26% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 74% of the expected payment.

***Who will know about my participation in this research study?***

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet at the Center for Sports Medicine. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. Data may be stored on a computer on a password protected network drive that will only be accessible to study personnel. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

***Will this research study involve the use or disclosure of my identifiable medical information?***

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to information concerning the purpose of the treatment you underwent for your hamstring injury including; your medical care; non-operative treatment; surgical treatment; physical therapy information; any follow-up care related to your hamstring; and information from radiographs and MRI of your lower extremities. Information about your hamstring strength may be placed into your medical records.

A statement will be placed into your medical record related to your participation in the study stating you are enrolled in a research trial using losartan as a study medication. This statement will provide contact information for investigators in the event of an

emergency while you are on the study medication.

***Who will have access to identifiable information related to my participation in this research study?***
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the US Army Medical Research and Material Command may review your identifiable research information (which may include your identifiable medical information) for the purpose conducting and monitoring of this research study.

Authorized representatives of UPMC may review your identifiable medical information for the purpose of quality assurance monitoring.

Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

***For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?***
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of 7 years and for as long (indefinite) as it may take to complete this research study.

***May I have access to my medical information that results from my participation in this research study?***
A copy of the results of these tests will be placed into either your physical therapy chart or medical chart, depending on who recommended you participate in this study.

***Is my participation in this research study voluntary?***
Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.)

Whether or not you provide your consent for participation in this research study will

have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

***May I withdraw, at a future date, my consent for participation in this research study?***

You may withdraw, at any time, your consent for participation in this research study (However, if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.)

Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider.

***If I agree to take part in this research study, can I be removed from the study without my consent?***

It is possible that you may be removed from the research study by the researchers. You may be removed from the study, for example, you do not meet all the eligibility criteria prior to randomization or you become non-compliant with the medication schedule.

***VOLUNTARY CONSENT***

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form I consent to participate in this research study and provide my authorization to share my medical records with the research team.

_____
Participant's Name

_____ _____
Participant's Signature Date

***CERTIFICATION of INFORMED CONSENT***

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date