THE STEADMAN CLINIC AND STEADMAN PHILIPPON RESEARCH INSTITUTE

U.S. OLYMPIC & PARALYMPIC NATIONAL MEDICAL CENTER

Study Title: Biologically Regulated Marrow Stimulation by Blocking Fibrosis to Improve Cartilage Repair: A Randomized Double-Blind, Placebo-Controlled Study

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Combined Informed Consent and HIPAA Form

Research Information and Consent for Participation in Biomedical Research

Biologically Regulated Marrow Stimulation by Blocking Fibrosis to Improve Cartilage Repair: A Randomized Double-Blind, Placebo-Controlled Study
VHH IRB #2019-15

I. Overview:

You are being asked to take part in a research study. The information in this document should help you to decide whether you want to participate in this study. The sections in this Overview provide the basic information about the study. More detailed information is provided in the remainder of the document.

Study Staff: This study is being led by Dr. Marc J. Philippon, who is your hip surgeon at The Steadman Clinic. This person is called the Principal Investigator. Other approved research staff may act on behalf of the Principal Investigator. In the event of an emergency, you may contact Dr. Ashley Payne at (775) 229-3801 or Dr. David A. Kuppersmith at (970) 476-1100.

Study Details: This study is being conducted at The Steadman Clinic and Steadman Philippon Research Institute and is funded by The United States Department of Defense: Office of Naval Research. The purpose of the study is to test whether the quality of cartilage healing after hip microfracture can be improved by taking a low dose of a drug commonly prescribed for high blood pressure called losartan. The study procedures include: randomization into either the losartan group or the placebo group, a lab test that includes a blood draw 1-2 weeks after your surgery, completion of a subjective questionnaire at several time points over 18 months following surgery, and returning to The Steadman Clinic for an additional MRI 12 months after your surgery. At the end of the study, the research team will compare the losartan and placebo groups in terms of patient-reported outcomes and cartilage repair quality.

Participants: You are being asked to take part because you received hip surgery with Dr. Philippon, and a microfracture procedure was used to treat a cartilage injury. You will be asked to participate for 18 months following your surgery.

Voluntary Participation: Your participation in this research is voluntary. You do not have to participate and may stop your participation at any time. Your decision whether or not to participate will not affect your current or future dealings with Dr. Philippon, The Steadman Clinic, or Steadman Philippon Research Institute. **If you decide to participate, you are free to withdraw at any time without affecting that relationship.** If you decide not to participate, your treatment from Dr. Philippon and his team will continue unchanged.

Benefits, Compensation, and Risks: We do not know if you will receive any benefit from your participation. You will receive a $50 Amazon gift card at the completion of the 3-month clinic visit and a $150 Amazon gift card at the completion of the 12-month clinic visit and MRI. Total compensation for participation is $200 if you complete both on-site the research visits. The most common and most serious risks associated with taking losartan are side-effects that include dizziness, headache, renal failure, diarrhea, stomach pain, muscle cramps, leg or back pain, insomnia, cold or flu symptoms, and tiredness. Based on experience with losartan in previous patients, the research team believes it may provide benefit to subjects with your condition with reasonably limited side-effects. Your health will be monitored during the course of the study, and your medical team will provide guidance about how best to limit these potential side-effects, and what to do if they occur.

Confidentiality: Even if we publish the findings from this study, we will keep your study information private and confidential. Anyone with the authority to look at your records must keep them confidential.

II. Conflict of Interest

Your health care provider is an investigator on this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from a clinician who is not associated with this project. You are not obligated to participate in any research project offered by your clinician. Your participation in this research study is voluntary and you do not have to participate. The decision to not participate will not affect your clinical care now or in the future.

Neither Dr. Philippon, nor any members of the research team have any financial relationships with any manufacturer or supplier of losartan.

III. Why am I being asked to participate in this research?

You have been asked to participate in this research because you underwent hip arthroscopy at The Steadman Clinic, and your surgeon, Dr. Philippon, performed a technique called microfracture to treat cartilage damage in your hip.

Approximately 60 subjects may be involved in this research at The Steadman Clinic and Steadman Philippon Research Institute.

Even though you agree to participate in this study and complete the informed consent, it may be decided by the study doctor that your participation in this study is not allowed. You must meet the following eligibility criteria in order to participate in this study:

Inclusion Criteria: You are eligible to participate in this study if you meet the following criteria:

- Between 18-60 years of age;
- Underwent microfracture hip surgery for the treatment of grade 3 or 4 cartilage injury;
- Underwent standard baseline MRI at The Steadman Clinic.

Exclusion Criteria: You are not eligible to participate in this study if you:

- Are unable to consent yourself into the research study;
- Have less than 2 millimeters of hip joint space shown on x-ray;
- Have moderate degeneration or arthritis (degeneration of the cartilage tissue) in the operative hip joint;
- Had a hip surgery prior to your recent hip surgery;
- Had a previous fracture of the operative hip joint that resulted in bony deformity;
- Have a history of pigmented villonodular synovitis (joint disease characterized by inflammation and overgrowth of the joint);
- Have a history of synovial chondromatosis (noncancerous tumor that develops in the lining of the hip joint);
- Have a history of hip dysplasia (the hip joint becomes partially or completely dislocated);
- History of Avascular Necrosis (AVN), Perthes disease, or slipped capital femoral epiphysis (SCFE);
- Have a history of immune disorders, such as rheumatoid arthritis;
- Taking losartan or a medication with known losartan interaction, including phenobarbital, rifambin, or fluconazole;
- Have an allergy to any active or inactive ingredient in losartan;
- Have a condition that requires you to take losartan or any other hypertensive medication;
- Have a hypotensive condition diagnosed by your primary care physician.

IV. Study Procedures: What will happen during this study?

This research will be performed at The Steadman Clinic and Steadman Philippon Research Institute, including in clinical exam rooms and in the MRI department.

Losartan is a commonly used, FDA approved drug usually prescribed for people with high blood pressure or diabetic kidney disease. The effects and side-effects of the drug are well understood by doctors and scientists. Losartan is not approved for use after hip joint surgery to improve the quality of cartilage repair.

The doctors and scientists conducting this study believe that losartan can be helpful for patients undergoing the same surgical procedure you have just had.

Randomization and Medication Procedures:

If you decide to participate, the following procedures will be performed:

- The first step in this research study is to randomly assign you into the losartan group or the placebo group. A member of the study team on Dr. Philippon's clinical team will write the prescription, and you (or your caregiver) will pick up the study medication at Vail Valley Pharmacy in Edwards on either the first or second day after your surgery, Colorado which is 14 miles west of the Vail Hospital.
- You will have a 50% chance of being assigned into each group, and you will not know which group you're in until the completion of the study.
- The second day after hip surgery, in the evening, you will begin taking your prescribed medication (losartan or placebo), which is one tablet, twice per day, for 1 month.
- Your doses should occur as closely as possible to 8:00 AM and 8:00 PM each day.
- You will be asked to keep a medication log to document each dose you take during the month. You will also use this form to document any symptoms or side-effects that you may experience that are potentially related to the study medication.
- If you miss a dose, you should not double your next dose. Instead, you should resume the planned dosage at the next scheduled dosing time point.
- At your first clinic visit to TSC following completion of your medication, you will be asked to return the remaining capsules in the original prescription bottle. Your prescription will contain several more capsules than needed for 1 month of daily intake in case of capsule loss.
- A list identifying your group assignment will be kept securely within The Steadman Clinic, but your medical team will not know which group you are in. This is called a double-blind, placebo-controlled trial. Only one member of the study team, Vail Valley Pharmacy, and an independent medical monitor will know your group identity.
- You will be provided with a medication card that will indicate your study participation information about the possibility that you are taking Losartan, and instructions on how to obtain further information. This medication card can be provided to other health care providers during the course of this study.

Research Visits and Procedures:

At 7-10 days after beginning your medication course.

- Phone call with a member of the medical staff on the research team where you can report any symptoms or side-effects that you may experience. The most common signs or symptoms associated with losartan include chest pain, shortness of breath and heart palpitations.
- Staff will ask you to scan or fax a copy of your medication log to The Steadman Clinic. This can include taking a photograph and emailing to Dr. Philippon's team, if preferred.

- The study team will arrange a visit to The Steadman Clinic or a laboratory/clinic of your choosing to have a blood test. The results of this test will be shared with the medical staff on the study team to monitor your safety.
- Study funds will cover the cost of this lab work. If you or your insurance are billed any fees by accident, please contact Ashley Payne at apayne@thesteadmanclinic.com, and the study team correct this as quickly as possible.

At 18-24 days after beginning your medication course.

- Phone call with a member of the medical staff on the research team where you can report any symptoms or side-effects that you may experience.
- Staff will ask you about how your physical therapy is going.

At 32-38 days after beginning your medication course.

- Phone call with a member of the medical staff on the research team where you can report any symptoms or side-effects that you may experience.
- Staff will ask you about how your physical therapy is going.

TSC Clinic Visit 3 Months following surgery

- Dr. Philippon's surgical patients attend this as part of their regular care. You will undergo a physical exam to assess your hip's strength and range of motion.
- At this appointment you will have an opportunity to describe your health status with Dr. Philippon and/or his clinical staff.
- The study team may use the data collected into your medical record from this visit.
- You will be required to bring your medication log, and your medication bottle with any unused study medication to this visit.
- Either at home prior to the appointment, or using a tablet device in the clinic on the day of your appointment, you will complete a questionnaire regarding the health and function of your hip.
- The clinic visit will require approximately 1 hour to complete.

Hip Questionnaire Completion from Home at 6 and 18 Months following surgery.

- You complete a subjective questionnaire regarding your hip-related health. These questionnaires can be completed remotely from your home via computer or mobile device. You will receive the questionnaire link by email, and a member of the study team may call to remind you to complete this questionnaire.
- Each subjective questionnaire will take approximately 20 minutes to complete.

TSC Clinic Visit 12 Months following surgery

- The second on-site visit occurs 18 months following your surgery and will include a research-specific MRI of your hip.

- At this appointment you will have an opportunity to describe your health status with Dr. Philippon and/or his clinical staff, and you will undergo a standard hip physical exam. The study team may use the data collected into your medical record from this visit.
- Either at home prior to the appointment, or using a tablet device in the clinic on the day of your appointment, you will complete a questionnaire regarding the health and function of your hip.
- The clinic visit will require approximately 1 hour to complete.

The study team asks permission to access your medical record to collect the following health information for research purposes at the time of your evaluation:

- Gender
- Age
- Height
- Weight
- Smoking status
- Chronic diseases or conditions (not related to your current hip condition)
- Medication use, such as non-steroidal anti-inflammatory drugs
- Physical exam assessment including hip strength and range of motion
- Existing medical imaging (x-ray, MRI or CT).

The study team also asks permission to access your medical record to collect the following injury information from your imaging and surgical reports, and to use this for research purposes:

- Pre-existing injury details
- Severity of injury details
- Imaging findings (X-ray or magnetic resonance imaging)
- Injury type
- Previous treatment details (related to your current hip condition)

V. What are the potential risks and discomforts?

There are possible risks that may be associated with participation in this study. These risks are listed below, but it's possible that some risks are not yet known.

Side-effects Associated with Losartan:

A member of your medical care team will describe the possible side effects of losartan and answer any questions you have. The most common and most serious risks associated with taking losartan are side-effects that include dizziness, headache, diarrhea, stomach pain, muscle cramps, leg or back pain, insomnia, cold or flu symptoms, and tiredness. Some more rare risks associate with losartan include electrolyte abnormalities, renal failure, hypotension, severe vomiting, reactions with

NSAIDS, and pregnancy risks. If you experience any unexpected or unpleasant symptoms, please contact out to Dr. Philippon's team as soon as possible.

Risks Associated with Placebo Group Assignment:

The research team suspects, but is not certain, that losartan can provide a beneficial effect on cartilage healing after hip microfracture. If you are assigned to the placebo group, you may miss out on this possible beneficial effect.

Risk of Improper Disclosure of your Personal Information:

There is a possibility that your personal information will be accidentally or inappropriately breached during this research. The Steadman Clinic and Steadman Philippon Research Institute use many physical, technologic and administrative measures to protect your information. Locking offices and cabinets protect information on paper, while password-locked work stations and encryption protect electronic information. Whenever possible, information will be used and analyzed in a manner that does not contain any of your identifiable information. When results of this research are presented at scientific meetings and in medical journals, all information that can possibly identify you will be removed.

Risks or Discomforts Associated with MRI:

The MRI scan involves loud noises and positioning in a small space. You may feel claustrophobic, tired, or nauseated, especially if you are uncomfortable with tight spaces. The MRI scan does not involve the use of X-rays or injectable dyes. There are no known reports of increased cancer or birth defects associated with this procedure. However, the MRI scan exposes you to high magnetic fields, which can be dangerous if you have a pacemaker or certain metal implants.

Risks or Discomforts Associated with Questionnaires and Physical Exam:

There is a potential risk of emotional distress associated with completing questionnaires, and a potential risk for pain and/or discomfort associated with the physical exam. However, these risks should not exceed that experienced during normal activities of daily living.

VI. Are there reproductive risks to participation in this study?

If you are a woman: Participating in this research may involve risks to pregnant women and/or an unborn baby. To protect against possible side effects of the study drug, losartan, you may not take part in this study if you are pregnant or nursing a child. If you are a woman of childbearing ability, the study doctor recommends that you at least two method of birth control or to be abstinent (i.e., not have sex) throughout the study. Acceptable methods of birth control include: oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom. If you think that you have become pregnant during the study, you must tell the doctor immediately.

If you become pregnant while you are taking losartan, stop taking losartan and call your doctor immediately. Losartan may cause death or serious injury to the fetus when taken in the last 6 months of pregnancy.

VII. What are the costs for participating in this research?

There are no costs to you for the items and services which are experimental or for research purposes only.

VIII. Will I be paid for my participation in this research?

You will receive a $50 Amazon gift card after completion of the 3-month clinic visit, and a $150 Amazon gift card after completion of the 12-month clinic visit and MRI. If you do not finish the study, you will be compensated for the visits you have completed. If you complete the study, you will receive a total of $200. You will receive your payment by a member of the study team at the end of the research visit.

IX. What if I am injured as a result of my participation?

If you get ill or injured from being in the study, Dr. Philippon will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. David A. Kuppersmith or Dr. Marc Philippon at (970) 476-1100. If you believe your illness or injury to be an emergency, contact call 911.

If you are injured, you should let any health care provider who treats you know that you are in a research study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact the research doctors.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. The study staff will assist you in obtaining pre-authorization from your insurance company. Costs not covered by insurance could be substantial.

The Steadman Clinic and Steadman Philippon Research Institute have not set aside any money to pay you or to pay for your treatment if you get ill or injured from being in the study. There are no plans for The Steadman Clinic and Steadman Philippon Research Institute to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illnesses or injuries. The only exception to

this policy is if it is proven that your injury or illness is directly caused by the negligence of a Steadman Clinic and Steadman Philippon Research Institute employee.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

X. Can I withdraw or be removed from the study?

If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without affecting your future care at The Steadman Clinic. You will still receive standard of care treatment for your condition if you choose to withdraw.

You have the right to leave a study at any time without penalty. If leaving could affect your safety, the investigator will provide information about recommended steps for leaving the study.

The researchers also have the right to stop your participation in this study without your consent if they believe it is in your best interest.

XI. Future use of identifiable private information or identifiable biospecimen

Your personal identifiers might be removed from your identifiable private records. After removal of information that could identify you, your information could be used and/or distributed to another investigator for future research studies without additional consent from you.

XII. What about your privacy and confidentiality?

The people who will know that you are a research subject are members of the research team, and if appropriate, your physicians and nurses. No information about you, or provided by you, during the research, will be disclosed to others without your written permission, except if necessary to protect your rights or welfare (for example, if you are injured and need emergency care) or if required by law.

Study information which identifies you and the consent form signed by you will be looked at and/or copied for examining the research by:

- Food and Drug Administration (FDA) – to ensure the research is done properly.
- Department of Defense – study sponsor.
- Office for Human Research Protections (OHRP) – to ensure the research is done properly.
- Vail Health Institutional Review Board – to ensure the research is done properly.

A possible risk of the research is that your participation in the research or information about you and your health might become known to individuals outside the research. Your original signed consent document

will be kept in an unlabeled paper envelope and stored in a locked cabinet within The Steadman Clinic. Other personal information that will be collected for this study will be stored separately from the research data on a password protected excel spreadsheet within the clinic. Only authorized personnel from The Steadman Clinic will have access to your personal information. Some of the information used for this research is standardly collected for all hip surgery patients and this information will remain in your medical record for use by your clinical care team. The information collected for research only will be maintained for up to two years following completion of the study. De-identified data may be kept indefinitely.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

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.

XIII. What happens if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in this study. We will notify you as soon as possible if such information becomes available.

As part of being in this study, you will undergo an additional MRI. If the study team identifies anything important to your health or relevant to your optimal treatment course, the information will be provided to you. This could include abnormal findings on your MRI that may require further testing. If this occurs, the results will not be placed in your medical record at The Steadman Clinic and you may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

XIV. Who should I contact if I have questions about the research?

Contact the researchers Dr. Marc Philippon, Dr. Ashley Payne or Dr. Johnny Huard at 970-476-1100:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury (or a bad reaction to the study treatment), and/or
- if you have questions, concerns or complaints about the research.

XV. Who should I contact if I have questions about my rights as a research subject?

If you have questions about your rights as a research subject or concerns, complaints, or to offer input you may call Mary Crumbaker, Chief Ethics and Compliance Officer at Vail Health at 970-477-5197.

XVI. Authorization to use and disclose Protected Health Information

The purpose of this section is to give your permission to the research team to obtain and use your patient information. Your patient information will be used to do the research named above.

State and federal privacy laws protect your patient information. These laws say that, in most cases, your health care provider can release your identifiable patient information to the research team only if you give permission by signing this form.

You do not have to sign this permission form. If you do not sign it, you will not be allowed to join the research study. Your decision to not sign this permission will not affect any of your treatment, any other treatment, healthcare, enrollment in health plans or eligibility for benefits.

What information will be obtained and used?

"Patient information" means the health information in your medical or other healthcare records. It also includes information in your records that can identify you. For example, it can include your name, address, phone number, birthdate, and medical record number.

By signing this form you are giving permission to the following organization(s) to disclose your patient information for use in this research.

- Vail Health (includes Shaw Cancer Center, Howard Head and all Diversified Services clinic locations)
- Vail Valley Surgical Center
- The Steadman Clinic

What information will be released for research use?

If you give your permission and sign the last page of this form, you are allowing the health care providers indicated above to release the following medical records containing your Personal Health Information to the researchers for use in this project. Your Personal Health Information includes health information in your medical records, financial records and other information that can identify you.

The specific information that will be released and used for this research is described below*:*

- Medical history / treatment
- Consultation
- Diagnostic imaging report

- Radiology films (like X-rays or CT scans or MRI's)
- Laboratory / diagnostic tests
- Operative reports (about an operation)
- Patient-reported outcomes from questionnaires
- Clinical exam information (like hip strength or range of motion)
- Basic demographic information:
    - Gender
    - Age
    - Height
    - Weight
    - Body mass index (BMI)
    - Smoking status
    - Medical comorbidities (presence of two chronic diseases or conditions)

How will my patient information be used?

The following groups of people may also be able to see your health information and may use that information to conduct this research:

- The research team for the research described in the Consent Form;
- Vail Health Institutional Review Board (VH IRB);
- US Department of Defense (DoD);
- The independent medical monitor for this study;
- Others who are required by law to review the quality and safety of the research, including U. S. government agencies such as The U.S. Food and Drug Administration (FDA) or the Office of Human Research Protections;

Your patient information will be used and/or given to others for the following reasons:

- To monitor safety
- To do the research
- To study the results, and
- To see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

The researcher will use your patient information only in the ways that are described in the research consent form that you sign and as described in this HIPAA Authorization.

You can ask questions about what the research team will do with your information and how they will protect it. The privacy laws do not always require the receiver of your information to keep your information

confidential. After your information is given to an organization that is not subjected to the privacy laws, e.g. a research organization, there is a risk that it could be shared without your permission.

How long will this authorization be valid?

This permission for the researchers to obtain your patient information:

- Ends when the research is complete and any required monitoring of the study is finished.

Cancelling your permission:

You may change your mind at any time. To take back your permission, you must send your **written** request to:

Kate Wilmouth
Steadman Philippon Research Institute
181 W. Meadow Dr. Suite 1000
Vail, CO 81657

If you take back your permission, the research team may still keep and use any patient information about you that they already have. But they can't obtain more health information about you for this research unless it is required by a federal agency that is monitoring the research.

If you take back your permission, you will need to leave the research study. Changing your mind will not affect any other treatment, payment, health care, enrollment in health plans, or eligibility for benefits.

Consent to take Part in Research and Authorization for the Collection, Use, and Disclosure of Health Information

Signature of Subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to participate in this research and authorize the use of my health information as outlined above. I will be given a copy of this signed and dated form.

Signature of Subject	**Date and Time**
Print Name of Subject	

Statement of Person Obtaining Informed Consent and Research Authorization

I have carefully explained to the person taking part in the study what he or she can expect from their participation. I confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in their primary language. This research subject has provided legally effective informed consent.

Signature of Person Obtaining Consent	**Date (must be same as subject's)**
Printed Name of Person Obtaining Consent	