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

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Table of Contents

1.0 Steadman Philippon Research Institute Representatives 4
2.0 Protocol Signature Page 5
3.0 Study Synopsis 6
4.0 Terms and Abbreviations 11
5.0 Introduction 12
5.1 Background and Significance 12
5.2 Rationale 12
5.3 Safety of Administering Losartan to Normotensive Patients 14
6.0 Summary of Proposed Placebo Controlled Trial 16
6.1 Blinding 17
7.0 Study Medication Treatment 18
7.1 Losartan Potassium 18
7.2 Placebo Control 18
7.3 PenCol Compounding Pharmacy 18
8.0 Study Design 19
9.0 Study Objectives and Endpoints 20
9.1 Primary Objectives 20
9.2 Secondary Objective 20
9.3 Study Endpoints 20
9.4 Primary Endpoints: 20
9.5 Secondary Endpoints 20
10.0 Study Population 21
10.1 Description 21
10.2 Source of Subjects 21
10.3 Enrollment Criteria 21
10.3.1 Inclusion Criteria 21
10.3.2 Exclusion Criteria 21
11.0 Study Procedures 23
11.1 Visit 1: Day 1 Post-operative 23
11.2 Day 2 Post-operative (No Visit Required) 24
11.3 Day 7-10 Post-operative (No Visit Required) 24
11.4 Telephone Contact by Study Team Post-operative day 30- (No Visit Required) (approximately one month) 24
11.5 Visit 2: Three Months Post-operative Clinic Visit (+/- 4 weeks) 24
11.6 6 Months Post-operative -(No Visit Required) (+/- 4 weeks) 25
11.7 12 Months Post-operative -(No Visit Required) (+/- 8 weeks) 25
11.8 Visit 3: 18 Months Post-operative (+/- 8 weeks) 25
11.9 Unscheduled Visits and/or Subject Contact 25

12.0 Study Management of Adverse Events 26
12.1 Definition 26
12.2 Recording Adverse Events 26
12.3 Severity (Intensity) of Adverse Events 29
12.4 Expected and Unexpected Adverse Events 29
12.5 Serious Adverse Events 29
12.6 Reporting of Adverse Events 30
12.6.1 Appointment of a Non-Blinded Medical Monitor and FDA 30
13.0 Potential Risks to Study Subjects and Risk Mitigation 31
13.1 Risk of Losartan Administration 31
13.2 Risk of Placebo Administration 31
13.3 Risks Associated With MRI 31
13.4 Risks Associated with PRO Questionnaires: 32
13.5 Breach of Confidentiality 32
14.0 Stopping Rules/Termination of Study Enrollment 33
14.1 Termination of Enrollment by the Principal Investigator 33
14.2 Termination of Enrollment by the Medical Monitor 33
14.3 Removal of Subjects from the Study 33
15.0 Statistical Considerations 34
16.0 Principal Investigator's Ethical and Regulatory Obligations 35
16.1 Study Conduct: Ethics and Good Clinical Practice 35
16.2 Institutional Review Board 35
16.3 Informed Consent 36
Record Keeping and 36
16.4 Study Documents 36
16.4.1 Study Medication Accountability 37
16.4.2 Records Retention 37
17.0 Disclosure and Confidentiality 38
18.0 Financial Disclosures 39
19.0 Interim and Final Study Reports 40
20.0 Quality Assurance 41
20.1 Subject Completion 41
20.2 Protocol Amendments and Deviations 41
21.0 Declaration of Helsinki 42
22.0 References 43
23.0 Appendices 47
23.1 Appendix A: Informed Consent 47
23.2 Appendix B – Study Schemata 58

1.0 Steadman Philippon Research Institute Representatives

This Study is an Investigator Sponsored clinical trial to be carried out by The Steadman Philippon Research Institute using grant support from the Office of Naval Research, US Department of Defense.

Overall responsibility for the Study will be held by:

Principal Investigator	Steadman Philippon Research Institute
Marc Philippon, MD	181 W. Meadow Dr. Suite 1000
Managing Partner, The Steadman Clinic;	Vail, CO 81657
Co-Chairman, Steadman Philippon	970-476-1100
Research Institute	drphilippon@sprivail.org

Independent Medical Monitoring will be provided by an unblinded, appropriately certified physician responsible for overseeing the occurrence of adverse events and for providing medical advisory assistance to the Study Team.

Medical Monitor
TBD

The Study Team
In addition, there will be a team of Investigators and Research Associates selected by Dr. Philippon to whom appropriated duties will be delegated according to their specific qualifications. Collectively Dr Philippon and his designees are referred to as "The Study Team" throughout this protocol.

Primary Contact for the Study

Grant Dornan	Steadman Philippon Research Institute
Director of the Center for Outcomes-Based	181 W. Meadow Dr. Suite 1000
Orthopaedic Research (COOR).	Vail, CO 81657
	(970) 479-5868
	gdornan@sprivail.org

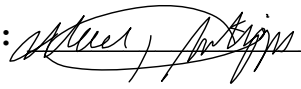
2.0 Protocol Signature Page

The signature below constitutes the approval of this protocol entitled, *Biologically Regulated Marrow Stimulation by Blocking Fibrosis to Improve Cartilage Repair: A Randomized Double Blind, Placebo Controlled Study* with attachments, and provides the necessary assurances that this trial will be conducted in compliance of all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and, regulatory requirements, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable US regulatory requirements.

Principal Investigator: Marc J. Philippon, MD

Print/Type

Title: Co-Chairman, Steadman Philippon Research Institute

Signed:  Date**:** 04/04/2019

3.0 Study Synopsis

Sponsor:	Investigator Sponsored Study
Study Title:	Biologically Regulated Marrow Stimulation by Blocking Fibrosis to Improve Cartilage Repair: A Randomized Double Blind, Placebo Controlled Study
Protocol Number:	2019-15
Study Design:	Randomized, double-blind, placebo controlled
Study Duration:	Eighteen (18) months following hip microfracture
Randomization:	Subjects are to be assigned to one of two treatment groups using a 1:1 (losartan/placebo) randomization scheme.
Study Arms/Medication	*Active Treatment:* Losartan potassium 12.5mg p.o. BID *Placebo Control:* Appearance matched tablet p.o. BID
Blinding Procedure:	Block randomization chart will be securely kept by an Unblinded Study Team member, and at the Vail Hospital Pharmacy (point of subject distribution) and with the unblinded Medical Monitor. All study subjects and other Study Team members including the Principal Investigator will be blinded to treatment through 18 months follow-up. In addition, any individuals engaged by the Principal Investigator to provide of radiographic, laboratory testing and and/or verification of data will be blinded to treatment.
Sample Size and Study Population:	A total of 40 male or female subjects ≥ 18 years of age will be recruited from up a single clinal site, where the Principal Investigator (Investigator Sponsor) conducts patient care. All subjects will have agreed to standard of care hip microfracture.

Objectives:	*Primary Objectives* To evaluate: 1. Cartilage quality as assessed by quantitative MRI at 18 months postoperatively compared between patients treated with losartan + microfracture and microfracture + placebo alone; 2. The safety of administering losartan in conjunction with microfracture surgery. *Secondary objectives* To evaluate: 1. Patient reported outcomes at 3, 6, 12, and 18 months postoperatively compared between patients treated with losartan + microfracture and microfracture alone (placebo).
Endpoints:	*Primary Endpoints:* 1. T2 mapping values and texture analysis metrics for quantitative MRI mapping; 2. Occurrence of adverse events. *Secondary Endpoints* 1. Descriptive quantification of patient reported outcomes in each treatment group.
Inclusion Criteria:	A subject may be included in the study only if he/she meets all of the following criteria: 1. Are aged 18-60 at time of surgery; 2. Tonnis grade 1 or less; 3. Present with a single, localized, grade 3 or 4 cartilage lesion of the acetabulum or femoral head treated with primary BMS (microfracture) performed by Dr. Marc Philippon.
Exclusion Criteria:	A subject will be excluded for the following reasons: **General** 1. Non-English speaking; 2. Diagnosed with inflammatory arthritis or other arthritis caused by autoimmune disease; 3. Taking losartan; 4. Allergic to any active or inactive ingredient of losartan; 5. Taking medication with known losartan interaction' 6. Are hypotensive as confirmed by the surgical anesthesiologist;

	Concerning the target hip have on preoperative assessment 7. Prior hip surgery; 8. Two or more cartilage lesions of grade 3 or 4; 9. Less than 2 mm of minimal hip joint space; 10. Osteoarthritis or diffuse change of cartilage; 11. Pre-existing bony deformity caused by previous fracture(s); 12. Synovial chondromatosis ; 13. Pigmented Villanodular Synovitis (PVNS); 14. Dysplasia (center edge angle <20 degrees); 15. Coxa profunda; 16. Protrusia Acetabuli.
Screening Tools: (At preoperative visit)	**Standard of Care Data Collected** Basic demographic data, medical and surgical history, medication review, age, gender, body mass index and chronicity of the injury, co-morbidities, smoking status, range of motion, strength and size of the cartilage lesion will be recorded. Circumduction evaluation exercises and range of motion restrictions will be evaluated. Patient Reported Outcomes (PRO) tools which will be repeated, at key study intervals will be performed and a T2 MRI of the hip will be performed as standard of care diagnosis.
Subject Follow-up:	All adverse events will be assessed during Study Medication administration and for 5 days (+/- 3) days after medication completion. After Study Medication administration only those adverse events related to the target hip will be collected. In addition, the following data will be collected: **Visit 1: Post Op Day 1:** Subject discharge for the hospital is anticipated to occur on POD1. At discharge the subject will be provided with a blood pressure cuff and be trained on "at home" blood pressure monitoring and recording. They will also be provided with a prescription for Study Medication which will be written in a blinded format for either losartan or placebo. Subjects will be instructed to visit the Vail Hospital Pharmacy to obtain the correct, blinded Study Medication. Study Medication Logs, and Blood Pressure Logs will be provided, with instructions for completion. Subjects will be instructed to undergo post-operative physical therapy, and they will be provided with a document outlining recommended content. They will also be provided with a

	prescription for a basic metabolic panel to be drawn by their local laboratory within 7-10 days post medication initiation. **POD Day 2** Subjects begin taking Study Medication **POD Day 7-10 (No Visit Required)** Subjects visit their local laboratory and a Basic Metabolic Panel is drawn to include: Glucose, Calcium, Sodium, Potassium, Carbon Dioxide (CO_2), Chloride; Blood Urea Nitrogen (BUN), and Creatinine. In addition, each subject will be contacted by a Study Team member to confirm compliance, and Study Medications are being logged. All adverse events and protocol deviations will be recorded. **POD Day 35 (+/- 3 days) Telephone Contact by Study Team Post- (No Visit Required)** Study Medication is expected to be completed at this time. A Study Team member will contact each subject to confirm completion. Subjects will be asked to send to the Study Team, a copy of the Study Medication Log. All adverse events and protocol deviations will be recorded. **Visit 2: POD 3 Months (+/- 4 weeks)** Subjects will be asked to complete the following questionnaires either on paper or in electronic format. • SF-12 – Short Form General Health Survey; • Patient Satisfaction; • Harris Hip Score (HHS); • Vail Hip Score (VHS); • Hip Outcome Score (HOS); • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); • Tegner Activity Scale; and • VAS Pain - Visual Analogue Scale for Pain. Subjects will receive a focused physical exam, review of all medications, strength testing and range of motion (ROM) assessment. Adverse events related to the target hip and protocol deviations will be recorded. **POD 6 Months Post-operative -(No Visit Required) (+/- 4 week**

	A Study Team member will contact each subject. Subjects will complete electronically each questionnaire as above. Adverse events related to the target hip and protocol deviations will be recorded. **POD 12 Months Post-operative -(No Visit Required) (+/- 8 weeks)** A Study Team member will contact each subject. Subjects will complete electronically each questionnaire as above. Adverse events related to the target hip and protocol deviations will be recorded. **Visit 3: POD 18 Months Post-operative Visit (+/- 8 weeks)** All procedures performed in POD 3 months will be repeated. In addition, subjects will undergo a Morphological and quantitative T2 MRI to be performed at Steadman Philippon Research Institute. Adverse events related to the target hip and protocol deviations will be recorded.
Statistical Methods	Intent-to-treat analysis will be performed. We will compare group means, with the hypothesis that greater post-operative PROs and higher graft quality as assessed with quantitative imaging will be observed in the microfracture plus losartan group compared to microfracture alone. Analysis of Covariance (ANCOVA) or Linear mixed-effect models with random intercepts will be used to compare groups while adjusting for the baseline measurement of each subject. Sample size for this study was determined via a statistical power analysis using published data We aim to power this study to detect an effect size between the microfracture alone and microfracture plus losartan groups that is equal to the observed between-group effect size calculated from Apprich, et al (d=1.107). The significance level will be set at α=0.05. Assuming 2-tailed testing and requiring 90% statistical power, 19 patients per group are sufficient to detect the effect size of interest. We aim to enroll 20 subjects per group. Power calculations were performed using G*Power (version 3.1; Universität Düsseldorf).

4.0 Terms and Abbreviations

Abbreviation	Term
BMS	Bone Marrow Stimulation
BRBMS	Biologically Regulated Bone Marrow Stimulation
COOR	Center for Outcomes-based Orthopaedic Research
CRSM	Center for Regenerative Sports Medicine
FAI	Femoro-acetabular Impingement
MRI	Magnetic Resonance Imaging
OA	Osteo arthritis
POD	Post-operative Day (e.g. POD 1, POD 2)
PRO	Patient Reported Outcome
RCT	Randomized Control Trial
TGF-β1	Transforming Growth-Factor Beta 1

5.0 Introduction

5.1 Background and Significance

The Steadman Clinic and the Steadman Philippon Research institute are proposing a prospective clinical study to collect safety and efficacy information on the use the drug, Losartan, (an FDA approved medication indicated for the treatment of hypertension, diabetic neuropathy and hypertension and left ventricular hypertrophy) to test the antifibrotic properties of this TGF-β1 blocking agent in reducing the formation of fibrocartilage and increasing formation of hyaline cartilage post hip microfracture. It is proposed that if more durable repair tissue (hyaline cartilage) is formed, patients should experience better, long-term clinical results. This study is to be used for scientific exploration only. There is no intent to use study results to support any change in the labeling of the drug.

This study to be a double blinded, placebo-controlled study of clinically meaningful patient reported outcomes including measurements of pain and function. In addition, a T2 MRI will be utilized to monitor and characterize the regeneration of fibrocartilage and hyaline cartilage in the hip joint at 18 months hip microfracture surgery. All adverse events will be recorded and monitored by an unblinded Independent Medical Monitor.

5.2 Rationale

It is well documented that Osteoarthritis (OA) is a leading cause of disability in the United States. Hip OA causes pain, decreased hip range of motion, and lower quality of life. [(1)] The Center for Disease Control and Prevention has reported osteoarthritis affects over 30 million adults in the US.[(2)] It is estimated that one in four people will develop symptomatic hip osteoarthritis in their lifetime. Untreated, OA leads to advanced cartilage disruption in the joint often necessitating a total hip replacement. [(3)]

The prevalence of total hip replacement was estimated to be at least 2.6 million individuals in the United States; the prevalence among adults fifty years of age or older was 2.3 %. [(4)] The cost of hip replacement continues to increase, with the current cost averaging $30,124 USD causing a significant socio-economic burden.[(5)] In addition, joint replacement surgeries are becoming more prevalent in patients younger than 60 years of age. [(6)] With the increasing rate of total hip replacement in younger patients, there is a need to develop innovative approaches to improve hip cartilage repair in order to prevent or at least postpone the first hip replacement.

Full thickness chondral defects rarely heal without intervention. Techniques used to treat chondral defects and hopefully avoid hip replacement include arthroscopic microfracture (or bone marrow stimulation (BMS)), osteochondral autografts, osteochondral allografts, and autogenous cell transplantation.[(7-9)] Microfracture is the most commonly used first-line

treatment technique for symptomatic chondral lesions in hip joints. Microfracture, is easy to perform, minimally invasive, and the least expensive treatment for cartilage defects [10-12]. The surgical procedure consists of removing the calcified layer and creating small controlled holes through the subchondral bone to reach the cancellous bone. [10, 12, 13] The marrow clot fills the chondral defect which is believed to provide bone marrow mesenchymal stem cells that subsequently promote cartilage repair. [14, 15]

However, microfracture is cost effective only if results are favorable. Reports show that microfracture has produced good outcomes in patients with grade 3 or 4 cartilage lesions of hip joint, however clinical and imaging outcomes vary. Many scientists and clinicians are critical of microfracture because the cartilage repair tissue is a hybrid of hyaline and fibrocartilage. It has been reported that fibrocartilage is the predominant repair tissue following the use of the microfracture and bone marrow stimulation techniques. [13, 14, 16] Fibrocartilage is not native to the hip joint and is morphologically intended to attach bones and limit join mobility. Hyaline Cartilage is native to all human joints and is morphologically intended to provide durable, smooth, lubricated movement.

Given the clear gap in treatment alternatives between microfracture and expensive alternative biological therapies, there is a clear need to explore mechanisms by which the outcomes of microfracture can be approved. An enhanced microfracture treatment, or second generation of bone marrow stimulation, could be very important in providing an effective, low cost treatment alternative.

The addition of Biologically Regulated Marrow Stimulation (BRMS) through the use of an approved pharmaceutical agent (which blocks the production of fibrotic tissue) could lead to better outcomes for patients. We are proposing to explore this possibility through this proposed study where FDA approved losartan will be given for one month after hip microfracture.

Losartan, in addition to being an angiotensin receptor blocker, is also a transforming growth factor β (TGF-β1) blocking agent. It is known that (TGF-β) is a central mediator of fibrogenesis and that anti-fibrotic agents are reported to enhance articular cartilage repair by promoting hyaline cartilage while preventing the fibrosis that typically leads to fibrocartilage. Although TGF-β1 is widely believed to be essential for articular cartilage homeostasis, [17, 18] it has been recently reported that TGF-β1 is overproduced in osteoarthritic joints. [19] Recent publications have shown a protective effect on hyaline cartilage in TGF-β receptor II conditional knock-out mice, and that a higher concentration of TGF-β1 might be one of the causes of osteoarthritis.[20, 21] Further, it was reported that cartilage injury causes activation of TGF-β activated kinase-1 (TAK- 1), resulting in inflammation of the joint and degenerative

changes in the cartilage, [22] and inhibition of TAK-1 can prevent inflammation-related cartilage degeneration in an osteoarthritis model.[23] Furthermore, Price et al reported that systemic losartan use inhibited inflammation in the animal arthritis model through suppressing tumor necrosis factor alpha in synovial tissues. [24] Several studies have shown that oral intake of losartan can inhibit tissue fibrosis by blocking TGF-β1- pSmad2/3 signaling pathway, in musculoskeletal applications.[25-28]

5.3 Safety of Administering Losartan to Normotensive Patients

The proposed protocol requires randomization of individuals to be treated either with losartan 12.5mg twice daily or placebo for one month following micro fracture surgery. Subjects will be excluded if they are symptomatically hypotensive, require medication with known interactions with losartan (to include all antihypertensive medication) or are currently taking losartan for any reason. It is therefore informative to explore the safety of losartan in normotensive subjects.

In 1983, Burnier et al [29] reported on their review of the literature in order to define appropriate dosing of antihypertensive medications in circumstances when new medication is being developed. They reported that similar pressor mechanisms are active in hypertensive and normotensive subjects. Doses sufficient to block the pressor effect of Angiotensin I in normal volunteers were identical to those needed to treat hypertensive patients. Although studies examined the renin system response of various ACE inhibitors including captopril 5, 20, 25, 100 and 200mg, enalapril 1.5, 2.5, 10 and 20mg, as well as unspecified doses of pentopril, this finding underlines the similarities in pressor response between normal and hypertensive individuals.

A number of clinical studies have been performed reporting on the use of antihypertensive agents on 138 normotensive subjects. The following is a brief summary of the effects of healthy individuals highlighting key data in support of the established safety of administering losartan (angiotensin II receptor antagonist) to normotensive individuals.

Upon its introduction into Phase I testing in the 1990s, Burnier et. al. [30] published a further review examining the clinical pharmacology of losartan, specifically addressing the effects on the renin-angiotensin system, blood pressure and heart rate, renal hemodynamics, renal tubes, and uric acid excretion of healthy, normotensive subjects. This review included studies of a total of 126 normotensive individuals and includes the publications by Christen, [31], Munifo,[32] Goldberg, [33] Diog,[34] Brunier[35] and Nakashima.[36] It was found that administration of losartan was associated with a dose-dependent increase in plasma renin activity and plasma angiotensin II levels, with no significant changes in plasma aldosterone obtained with doses smaller than 120mg. It was also reported that losartan increased uric acid

excretion (as much as by 30%) and hence decreases serum uric acid levels. However, there was no significant effects on heart rate of healthy, normotensive subjects receiving up to 120mg of losartan. Results showed that there was little or no effect on the blood pressure of normotensive individuals (unless the subjects are markedly salt-depleted).

This finding confirmed by the dose-ranging study performed by Doig et. al, [34] which included 5, 10, 25, 50, and 100mg doses of losartan or matched placebo given to 12 normotensive men subjected to limited-sodium diets. More pronounced reductions of blood pressure were seen at doses of 50 and 100mg. Recording of side effects concluded that, at all doses, losartan was well tolerated, and side effects were consistent with other angiotensin-converting enzyme inhibitors, albeit infrequent. Lightheadedness was the most commonly reported adverse symptom, occurring more prevalently at higher doses of losartan, and was determined to be mainly posture-related. An asymptomatic and rise in transaminase levels in one subject at and increase in urea and creatinine in association with nausea in another subject was found. Both adverse events occurred within 24 hrs. of 100mg losartan administration.

Across all studies examined, no significant effects on normotensive subjects were reported at the dose proposed in this study (12.5 mg). In addition, adverse response was seen early in the course of losartan administration, and there is no evidence of cumulative response over time. However, it should be noted that Azizi et. al [37] studied the additive effects of combined angiotensin-converting enzyme inhibitors (in this case, captopril) in 12 healthy individuals with the angiotensin II antagonist losartan and found that combined administration had major additive effects on plasma renin rise with additional reduction of blood pressure. This finding has informed our decision to exclude from the study, all patients taking medications having known interaction with losartan.

6.0 Summary of Proposed Placebo Controlled Trial

Our objective is to determine in a placebo controlled if the administration of losartan post microfracture will result in reduced fibrosis in healing tissue and will improve hyaline cartilage repair. Patients who have undergone microfracture for a focal chondral defect of the femoral head or acetabulum will be considered candidates for enrollment. A member of the Study Team will review the patients' record to determine if all inclusion/exclusion criteria are met. Each potential subject will be fully informed regarding all aspects of the proposed study and will be required to review and sign a full, IRB approved, informed consent document attached as Appendix A.

Forty patients who have consented to participate will be assigned, 1:1 via block randomization, one of the two blinded study groups.

1) n=20: standard microfracture + losartan [TGF-β1 blocker]); or
2) n=20 standard microfracture + placebo.

Losartan and the inactive placebo are collectively referred to as Study Medication.

A Study Team member will then inform the pharmacist of the patient's assigned group and the patient will pick up study medication prior to leaving the hospital following microfracture. This is expected to occur on post-operative day one (POD1). Subjects will self-medicate for one month following surgery either 12.5mg losartan twice daily or placebo twice daily. A log recording medication administration (Medication Log) will be maintained daily by the subject during the administration month.

Subjects will also be given a blood pressure cuff to take home to for twice daily self-monitoring and recording of blood pressure while the Study Medication is being administered, after which time blood pressure should be measured once weekly until the 3-month visit.

Subjects will be instructed to undergo physical therapy and a document describing the recommended content of that therapy will be provided.

At 7-10 days postoperatively subjects will be required to undergo a standard Basic Metabolic Panel. Results will be faxed to the Principal Investigator or designee. Subjects will also be interviewed by telephone by a Study Team member to document possible protocol violations, all adverse events, subject blood pressure and compliance with blood draw and study medication.

At the conclusion of study medication, subjects will be contacted by the Study Team to confirm completion of medication. The occurrence protocol deviations and of all adverse events will be documented.

At three months post operatively, subjects will be seen for a visit The Steadman Clinic. A copy of the Medication Log will be retained by the Study Team, and subjects will complete Patient Reported Outcomes (PROs) either on paper or electronically. These tools are described in more detail in Section 13.5 of this protocol. All medical history will be updated including all medications. Vital signs will be recorded, and subjects will undergo strength testing and range of motion assessment by the Principal Investigator or a designee. Protocol deviations and all adverse events related to the target hip will be collected.

At six and twelve months post operatively, subjects will be required to complete from home the assigned PROs electronically. Subjects will be contacted by phone and protocol deviations and all adverse events related to the target hip will be collected.

At eighteen months postoperatively, subjects will be seen at the Steadman Clinic. PRO questionnaires will be completed. Medical history will be updated including all medications. Vital signs will be recorded, and subjects will undergo strength testing and range of motion assessment by the Principal Investigator or a designee. In addition, morphological and quantitative T2 MRI will be performed to assess the regrowth of new cartilage tissue. protocol deviations and all adverse events related to the target hip will be collected.

After all subjects have reached 18 months follow-up, primary and secondary outcomes will be analyzed as described in **Section 17** of this document. Unblinding of the Study Team and the Subject will occur.

6.1 Blinding

All study subjects and Study Team members responsible for subject evaluation, data management and analysis (Including the Principal Investigator) will be blinded to treatment through 18 months follow-up. In addition, any individuals engaged by the Principal Investigator to provide of radiographic, laboratory testing and and/or verification of data will be blinded to treatment.

One Study Team Member responsible for group assignment, the pharmacist responsible for medication distribution and the Independent Medical Monitor will be unblinded.

7.0 Study Medication Treatment

7.1 Losartan Potassium

Losartan potassium is an angiotensin II receptor (type AT1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1- [p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Losartan will be sourced through PenCol Compounding Pharmacy, located in Denver, Colorado. provided to subjects in its approved, marketed generic form. Scored tablets containing 25 mg of active ingredient (losartan) will be split by the pharmacy to provide individual dosage of 12.5 mg, to be taken by subjects twice daily (BID). Directions for Use can be found in using the following link.
https://www.bioportfolio.com/resources/drug/15151/Losartan-Potassium-Sandoz-Inc.html
.

7.2 Placebo Control

Appearance matched placebo medication will also be compounded at PenCol Compounding Pharmacy, located in Denver, Colorado.

7.3 PenCol Compounding Pharmacy

PenCol is accredited by the Pharmacy Compounding Accreditation Board (PCAB). This accreditation confers the most comprehensive compliance assurance in the pharmaceutical industry, with standards based on U.S. Pharmacopeial Convention (USP) guidelines. This process includes an extensive on-site survey conducted by an independent expert and annual verification ensures compliance with the non-sterile and sterile pharmacy compounding process defined by USP <795> and USP <797>. The address and contact information for PenCol is provided below.

1325 South Colorado Boulevard
Suite B-024
Denver, CO 80222
Phone: 303.388.3613

The compounding pharmacy will work directly with the Vail Pharmacy within Vail Health Hospital. All subjects will obtain their medication (or placebo) directly from Vail Pharmacy.

8.0 Study Design

This is a prospective, randomized, placebo controlled, double blind study. to be conducted at the Steadman Clinic and the Steadman Pilippon Research Institute. A total of 40 subjects will be randomized 1:1 to receive either standard microfracture of the hip + losartan or standard microfracture of the hip + placebo.

Subjects will be blinded to medication treatment. To maximize the objectivity of follow-up evaluations, all Study Team members involved in study assessments or documentation will be blinded through 18 months follow-up.

9.0 Study Objectives and Endpoints

9.1 Primary Objectives

To evaluate:

1. Cartilage quality as assessed by quantitative MRI at 18 months postoperatively compared between patients treated with losartan + microfracture and microfracture + placebo alone;

2. The safety of administering losartan in conjunction with microfracture surgery.

9.2 Secondary Objective

To evaluate:

1. Patient reported outcomes at 3, 6, 12, and 18 months postoperatively compared between patients treated with losartan + microfracture and microfracture alone (placebo).

9.3 Study Endpoints

9.4 Primary Endpoints:

1. T2 mapping values and texture analysis metrics for quantitative MRI mapping;
2. Occurrence of adverse events.

9.5 Secondary Endpoints

1. Descriptive quantification of patient reported outcomes in each treatment group.

Investigators and Study Sites

10.0 Study Population

Patients who have undergone microfracture for a focal chondral defect of the femoral head or acetabulum will be considered candidates for enrollment. A member of the Study Team will review the patients' standard of care record to determine if all inclusion/exclusion criteria are met. Patients meeting the study's inclusion/exclusion criteria will then be approached by this same study member with the opportunity to provide informed consent to enter this study. This meeting will take place during the patient's first post-operative physical therapy visit in a private setting.

10.1 Description

Qualified subjects who personally give informed consent will be screened for eligibility. Only subjects who meet all eligibility criteria will be randomized and treated with either losartan or placebo.

10.2 Source of Subjects

Study subjects will be identified and recruited from the practice of the Principal Investigator. No external recruitment or advertising is to be engaged.

10.3 Enrollment Criteria

10.3.1 Inclusion Criteria

Patients who:

1. Are aged 18-60 at time of surgery;
2. Tonnis grade 1 or less;
3. Present with a single, localized, grade 3 or 4 cartilage lesion of the acetabulum or femoral head treated with primary BMS (microfracture) performed by Dr. Marc Philippon.

10.3.2 Exclusion Criteria

Patients who are

General

1. Non-English speaking;
2. Diagnosed with inflammatory arthritis or other arthritis caused by autoimmune disease;
3. Taking losartan;
4. Allergic to any active or inactive ingredient of losartan;
5. Taking medication with known losartan interaction'
6. Are hypotensive as confirmed by the surgical anesthesiologist;

Concerning the target hip have on preoperative assessment:

7. Prior hip surgery;
8. Two or more cartilage lesions of grade 3 or 4;
9. Less than 2 mm of minimal hip joint space;
10. Osteoarthritis or diffuse change of cartilage;
11. Pre-existing bony deformity caused by previous fracture(s);
12. Synovial chondromatosis;
13. Pigmented Villanodular Synovitis (PVNS);
14. Dysplasia (center edge angle <20 degrees);
15. Coxa profunda;
16. Protrusia Acetabuli.

11.0 Study Procedures

Patients who present for treatment and in whom operative treatment has been planned, will as part of their pre-operative evaluation undergo a standard of care medical review. Basic demographic data will be collected, including age, gender, body mass index, chronicity of the injury, and surgical data will be queried. Additional data including medical co-morbidities, smoking status, medication use, will be collected. History of hip trauma, range of motion, strength, size of the cartilage lesion, circumduction evaluation exercises and range of motion restrictions will be evaluated. As standard of care, patients complete several Patient Reported Outcomes (PRO) tools which will be repeated, at key study intervals as described in the following section of this document, should the patient consent to participate in the study. Subjects will also undergo a T2 MRI of the hip as standard of care diagnosis.

These routine baseline measurements will be used to evaluate preliminary eligibility. If eligibility seems likely, a member of the Study Team will briefly describe this study and gauge the patient's interest in participation.

A full Study Schemata is provided in Appendix B.

11.1 Visit 1: Day 1 Post-operative

Each potential subject will be fully informed of all requirements of participation as well as the voluntary nature of participation. If they are interested in participation, they will be asked to sign the Informed Consent Form (ICF) as approved by the reviewing Institutional Review Board. One copy of the completed Informed Consent Form will be given to the subject and the original must be retained as a source document. Subjects will be randomized only after informed consent has been obtained. A unique subject study ID will be assigned upon signature of Informed Consent. The subject study ID number will be recorded on all pertinent study records, as described in Section 15.5 of this document

Subject discharge for the hospital is anticipated to occur on POD. At discharge the subject will be provided with a blood pressure cuff and be trained on "at home" blood pressure monitoring and recording. They will be instructed to undergo physical therapy and receive a document outlining the recommended content of that therapy. They will also be provided with a prescription for Study Medication which will be written in a blinded format for either losartan or placebo. Subjects will be instructed to visit the Vail Hospital Pharmacy to obtain the correct, blinded Study Medication. Study Medication Logs will be provided, with instructions for completion.

Subjects will also be provided with a prescription for a basic metabolic panel to be drawn by their local laboratory within 7-10 days post medication initiation.

11.2 Day 2 Post-operative (No Visit Required)

Subjects begin taking Study Medication

11.3 Day 7-10 Post-operative (No Visit Required)

Subjects visit their local laboratory and a Basic Metabolic Panel is drawn to include:

- Glucose;
- Calcium;
- Sodium;
- Potassium;
- Carbon Dioxide (CO_2);
- Chloride;
- Blood Urea Nitrogen (BUN); and
- Creatinine.

In addition, each subject will be contacted by a Study Team member to confirm that the blood draw has occurred, and Study Medications are being logged. The occurrence of protocol deviations and all adverse events will be recorded.

11.4 Telephone Contact by Study Team Post-operative day 30- (No Visit Required) (approximately one month)

Study Medication is expected to be completed at this time. A Study Team member will contact each subject to confirm that the Study Medication has been completed and logged. Subjects will be asked to send to the Study Team, a copy of the Study Medication Log. The occurrence of protocol deviations and all adverse events will be recorded.

11.5 Visit 2: Three Months Post-operative Clinic Visit (+/- 4 weeks)

Subjects will be asked to complete the following questionnaires either on paper or in electronic format.

- SF-12 – Short Form General Health Survey;
- Patient Satisfaction;
- Harris Hip Score (HHS);
- Vail Hip Score (VHS);
- Hip Outcome Score (HOS);
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC);

- Tegner Activity Scale; and
- VAS Pain - Visual Analogue Scale for Pain.

Subjects will receive a focused physical exam, review of all medications, strength testing and range of motion (ROM) assessment. Protocol deviations and adverse events related to the target hip will be recorded.

11.6 6 Months Post-operative -(No Visit Required) (+/- 4 weeks)

A Study Team member will contact each subject. Subjects will complete electronically each questionnaire as above. Adverse events related to the target hip and protocol deviations will be recorded.

11.7 12 Months Post-operative -(No Visit Required) (+/- 8 weeks)

A Study Team member will contact each subject. Subjects will complete electronically each questionnaire as above. Adverse events related to the target hip and protocol deviations will be recorded.

11.8 Visit 3: 18 Months Post-operative (+/- 8 weeks)

All procedures performed in Visit 3 will be repeated. In addition, subjects will undergo a Morphological and quantitative T2 MRI to be performed at Steadman Research Institute according to a specific and consistent imaging protocol Adverse events related to the target hip and protocol deviations will be recorded.

11.9 Unscheduled Visits and/or Subject Contact

In the event that additional visit(s) or subject contact is required other than those described in the protocol, the information must be documented in the appropriate study document.

12.0 Study Management of Adverse Events

12.1 Definition

Adverse Event – An adverse event (AE) is any untoward medical occurrence in a subject administered a Study Medication and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of whether or not related to the Study Medication (ICH E2A II/A/1, 21 CFR 312.32).

All pre-existing medical conditions will be recorded on the medical history study document. Starting with the administration of the Study Medication any new experience that was not present at baseline or worsening of an event present at baseline in intensity or frequency, is considered an adverse event.

Note: Unchanged, chronic conditions are NOT adverse events and should not be recorded.

It is recognized that subjects will exhibit (throughout follow-up) symptoms of the underlying disease process of that fluctuates in severity and duration.

Adverse events will include those occurrences, which when compared to before treatment meets any of the following criteria:

- Represent a new event or escalation of an event;
- Require a new escalation in treatment;
- Lasts longer;
- Experienced more frequently;
- More intense;
- Different in character (e.g. stabbing vs. ache);
- Experienced in a different part of the body; and/or
- Brought on by activity that previously did not cause the symptom.

12.2 Recording Adverse Events

Adverse events that occur up to 35 days +/- 3 days after the beginning Study Medication administration will be recorded. Terms should be recorded consistently, using acceptable medical terms. When possible, a diagnosis should be identified as the AE (i.e., disease or syndrome) rather than the component signs and symptoms, and recorded on the case report form (e.g., record congestive heart failure rather than dyspnea, rales and cyanosis). However, signs and symptoms considered unrelated to encountered syndromes or diseases are to be

recorded as individual AEs (e.g., if congestive heart failure and severe headaches are observed at the same time, each experience is to be recorded as an individual AE). The AE should not be recorded as a procedure or clinical measurement (i.e., a laboratory or vital sign) but should reflect the reason for the procedure or diagnosis.

Death is considered to be an outcome of an AE. The cause of death (rather than the term "death") should be recorded on the serious AE and death report case report forms.

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. At each required visit (or whenever reported) during the study, all AEs that have occurred since the previous visit must be recorded on the AE case report form.

All AEs, regardless of seriousness, severity, or presumed relationship to the treatment must be recorded using medical terminology

All AEs must be followed until resolution or until a stable clinical endpoint is reached. All measures required for AE management and the ultimate outcome of the AE must be recorded in the study document. All adverse events that occur in the study population will be tabulated and summarized.

Date of Onset and Resolution

The date of onset is the time at which the subject reports that the incident began. This may or may not be the date on which the Study Team became aware of the event. The date of resolution is the date at which the event was no longer apparent to the subject and/or the Study Team. This may be unknown if at the end of the study the event is not resolved. In this case, the event will be indicated to be unresolved.

Incidence

An AE may be classified as "intermittent" or "continuous if has no periods of abatement.

Relationship to Study Medication

The Principal Investigator is required to assess whether there is a reasonable possibility that the Study Medication caused or contributed to an AE.

Many terms and scales are used to describe the degree of causality between a Study Medication and an event. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A, III/A/1).

Determination of whether there is a reasonable possibility that a treatment caused or contributed to an AE includes assessing temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

As is recommended in FDA draft guidance document, Safety Reporting Requirements for INDs and BA/BE Studies (2010), we define four degrees of relatedness: "unrelated", "probably not related", "suspected adverse drug reaction" (SADR) or "adverse reaction".

Unrelated (clearly not related to the research)
The occurrence of the AE is not reasonably related in time, OR the AE is considered unlikely to be related to the treatment (biologically implausible).

Probably not related (doubtfully related to the research)
The administration of the treatment and the AE are not considered reasonably related in time AND the AE could also be explained by causes other than the treatment (concurrent illness/underlying disease, other drugs or procedures).

Suspected Adverse Drug Reaction (SADR)
Suspected adverse reaction means any AE for which there is a reasonable possibility that the treatment caused the AE. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the treatment and the AE. A SADR reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a treatment.
The Principal Investigator should consider if exposure to the treatment and the AE are reasonably related in time AND the treatment is more likely than other causes to be responsible for the AE or is the most likely cause of the AE.

Adverse Reaction
An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the treatment caused the event.

If the event is felt by the Principle Investigator to be either a SADR or an adverse reaction, every effort will be made to identify the event as related to the Study Medication. Adverse events that are generally felt to be attributable to the Study Medication occur in close temporal relationship to the onset of dosing. A discussion of AEs that are common with the Study Medication is found in the Section 15.1 of this document

All adverse reactions and SADRs will be followed until resolution or the Investigator judges the experience to be chronic or stable.

12.3 Severity (Intensity) of Adverse Events

The severity of the adverse events should be assessed based on the following grading scale:

- Grade 1 (Mild): Adverse event that is noticeable to the subject and may require additional therapy;
- Grade 2 (Moderate): Adverse event that interferes with the subject's activities and requires intervention or additional therapies;
- Grade 3 (Severe): Adverse event that is intolerable, or necessitates additional therapy or places the subject at immediate risk of harm;
- Grade 4: Adverse event that is life-threatening or disabling (hospitalization);
- Grade 5: Adverse event that results in Death.

12.4 Expected and Unexpected Adverse Events

"Expected" AEs are those that have been previously reported as associated with the disease process. All others are to be recorded as "Unexpected".

12.5 Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Principal Investigator, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event.

An AE or suspected adverse reaction is considered "life-threatening" if, (in the view of the Principal Investigator) its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious and/or unexpected adverse event(s) may present as either a local or systemic response, or both, which may present as an anaphylactic response associated with generalized urticaria, shortness of breath, or respiratory or circulatory arrest.

Subjects will be instructed to contact the study site immediately if a systemic reaction occurs between scheduled study visits. Subjects may be assessed initially over the phone and may be asked to return to the study site for an additional visit to assess the reaction.

12.6 Reporting of Adverse Events

12.6.1 Appointment of a Non-Blinded Medical Monitor and FDA

An Independent Medical Monitor will be selected to oversee study safety.. This individual is to be an appropriately certified physician experienced in the management of blood pressure.. He/she will be unblinded to Study Medication.

The portion of this study which is greater than minimal risk involves administration of losartan or placebo for 1 month following enrollment in the study. All adverse events will be monitored by the blinded Study Team during this time period.

The Principal Investigator will be responsible for confirming the severity of all adverse events. All serious and unexpected adverse events will be reported to the unblinded Independent Medical Monitor within 24 hours of their disclosure to the Principal Investigator. The Medical Monitor will review data or events reported by the Study Team within 72 hours of disclosure to the Medical Monitor.

During this time appropriate care will be given to the study subject. If managing adverse events requires unblinding to the any member of the Study Team, the appropriate team member will disclose the group identity to the necessary medical provider.

The IRB will be notified of unanticipated and serious adverse events within 5 business days of identification. This reporting may come from the Study Team, the Independent Medical Monitor, or both.

If a subject experiences a serious and unexpected adverse event while taking losartan, FDA will be notified by telephone or facsimile within 7 days, and in writing within 15 days hours (after the Principal Investigator's initial receipt of the information).

Each written notification may be submitted on FDA Form 3500 or in a narrative format and shall bear prominent identification of its contents, i.e., "Med Watch Safety Report".

13.0 Potential Risks to Study Subjects and Risk Mitigation

Expected risks to subjects in this study include all those currently associated with osteoarthritis and as sequala to microfracture surgery. Additional risk to subjects which might arise as the result of study participation are discussed below.

13.1 Risk of Losartan Administration

A full description of expected side effects can be found in Losartan's directions for use https://www.bioportfolio.com/resources/drug/15151/Losartan-Potassium-Sandoz-Inc.html Known side effects include dizziness, headache, diarrhea, stomach pain, muscle cramps, leg or back pain, insomnia, tiredness and cold or flu symptoms such as stuffy nose, sneezing, sore throat, fever and cough. In addition, there is a chance that administration of losartan will not improve the outcomes of microfracture.

Subjects will be fully informed about expected side effects of losartan and will be instructed to inform the Primary Investigator should these symptoms become apparent. Informed consent will include information revealing that it is unknown if losartan will improve the outcomes of microfracture.

13.2 Risk of Placebo Administration

If results of this study reveal that administration of losartan improves the results of microfracture, subjects randomized to placebo may miss these benefit(s).

Subjects will be fully informed regarding the expected outcomes of standard microfracture surgery and will be told that they have only a 50% chance of being randomized to receive losartan. In addition, subjects will be told that the advantages of receiving losartan following microfracture are unknown.

13.3 Risks Associated With MRI

The MRI scan involves exposure to loud noise, and positioning in a small space. Subjects may feel claustrophobic, fatigued or nauseated especially if they 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. The MRI scan exposes the subject to high magnetic fields, which can be dangerous for those with pacemakers and some metal implants.

All participants will be offered music and/or earplugs to reduce the noise level produced by the MRI machine. Participants with a pacemaker, hearing aid, aneurysm clips or artificial heart valves, and other forms of loose metal implants will be excluded from the study as assessed by

a pre-MRI questionnaire administered as part of the eligibility screening prior to enrollment. The screening will be conducted again the day of the MRI, to ensure the participant can still safely undergo an MRI. It is possible that a participant will become unexpectedly ineligible for an MRI between the first and second testing days (e.g. if they receive a pacemaker after the first testing day). In this case, the participant will be allowed to continue with motion capture and DSX testing but will not have an MRI taken.

13.4 Risks Associated with PRO Questionnaires:

Completion of the PRO questionnaires should take each subject approximately 20-30 minutes. There is a risk that subjects may find this laborious and experience emotional distress.

To mitigate this experience, subjects will be fully informed and instructed on how to complete each questionnaire. Subjects can also elect to taking "breaks" during questionnaire completion. Subject will also be offered the option of completing questionnaires electronically at home.

13.5 Breach of Confidentiality

There is a possibility that personal information could 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. Deidentifying study information, assignment of an alpha-numeric study identifier, locking offices and cabinets, password-locked work stations and encryption protect electronic information. Information will be used and analyzed in a manner that does not contain any of identifiable information. When results of this research are presented at scientific meetings and in medical journals, all information that can possibly identify subjects will be removed.

All electronic PRO data is encrypted using the AES-256 encryption algorithm, and high-grade SHA-256 RSA encryption is used for https connections over TLS. Secure network access is enforced by multi-tiered firewalls, custom system configurations and multi-zones networks.

14.0 Stopping Rules/Termination of Study Enrollment

The triggering of stopping rules will result in prompt discontinuation of subject enrollment and notification of the Medical Monitor and IRBs. Although enrollment will cease, all subjects enrolled up until that point will continue to be followed according to the protocol for evaluation for duration of the clinical trial. Enrollment will be reconvened only when permission is granted by the IRB.

14.1 Termination of Enrollment by the Principal Investigator

The Principal Investigator may terminate study enrollment at any time for any of the following reasons.

1. Any unexpected serious or life-threatening AE that cannot be determined to be unrelated to Study Medication;
2. It is determined that the protocol precipitates multiple subject non-compliance issues beyond reasonably missed follow-up.

14.2 Termination of Enrollment by the Medical Monitor

The Medical Monitor may terminate enrollment due to the emergence of significant safety signals.

14.3 Removal of Subjects from the Study

Principal Investigators may remove a subject from the study if:

1. Subject demonstrates poor compliance with study protocol;
2. There is concurrent illness or required medical treatment that interferes with study assessments;
3. The Principal Investigator determines that the subject's health, safety or welfare is at risk.

For subjects taking losartan, symptomatic hypotension, significant electrolyte imbalance, acute renal failure, or severe nausea or vomiting precluding medication compliance will result in immediate discontinuation of the subject's course of medication.

15.0 Statistical Considerations

Patients will be randomized with a 1:1 allocation ratio into either the microfracture plus losartan versus microfracture alone group. Block randomization will be used with block sized of n=8 to ensure that groups are of approximately equal size at study completion, even if some patients are lost to follow-up or unenrolled.

Intent-to-treat analysis will be performed. We will compare group means, with the hypothesis that greater post-operative PROs and higher graft quality as assessed with quantitative imaging will be observed in the microfracture plus losartan group compared to microfracture alone. Analysis of Covariance (ANCOVA) or Linear mixed-effect models with random intercepts will be used to compare groups while adjusting for the baseline measurement of each subject.

The effect size of microfracture plus losartan compared to microfracture alone with respect to patient reported outcomes is unknown, so a sample size calculation was performed based on anticipated quantitative

Anticipated effect sizes for the group difference with respect to MRI-assessed cartilage quality were derived from the literature, however a paucity of helpful literature was found in the hip literature. Sample size for this study was determined via a statistical power analysis using published data from Apprich, et al [(38)], who compared patients treated with microfracture of the talus versus patients treated with matrix-associated autologous chondrocyte transplantation (MACT).

The primary outcome metric reported in Apprich, et al was a semi-quantitative scale of diffusion-weighted imaging (DWI) acquired by MRI and the paired differences between DWI of the repaired tissue and healthy reference cartilage for each patient was reported for each treatment group. We aim to power this study to detect an effect size between the microfracture alone and microfracture plus losartan groups that is equal to the observed between-group effect size calculated from Apprich, et al (d=1.107).

The significance level will be set at α=0.05. Assuming 2-tailed testing and requiring 90% statistical power, 19 patients per group are sufficient to detect the effect size of interest. We aim to enroll 20 subjects per group. Power calculations were performed using G*Power (version 3.1; Universität Düsseldorf).

16.0 Principal Investigator's Ethical and Regulatory Obligations

The Principal Investigator is responsible for ensuring that the trial is conducted according to the signed investigator statement, the study protocol and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of the Study Medication. The Principal Investigator shall confirm informed consent for each subject to whom losartan or placebo, is administered. A discussion of the Principal Investigator's minimal responsibilities follows.

16.1 Study Conduct: Ethics and Good Clinical Practice

Principal Investigator will administer Study Medication only to subjects under his personal supervision or under the supervision of an appropriate Study Team designee responsible to the Principal Investigator.

This study must be carried out in compliance with the protocol and in accordance with the Good Clinical Practice, ICH Guidelines and the Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The Principal Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the applicable regulatory requirements and to the principles of Good Clinical Practice to which it conforms.

16.2 Institutional Review Board

The Principal Investigator shall assure that an IRB that complies with the requirements set forth in ICH and FDA guidelines will be responsible for the initial and continuing review and approval of the proposed clinical study. The Principal Investigator shall also ensure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others. Except when the changes constitute minor administrative ones or where necessary to eliminate apparent immediate hazards to human subjects, the Principal Investigator will not make any changes in the research without IRB approval.

Before implementing this study, the protocol, the proposed informed consent form and other subject information, must be reviewed and approved by the Institutional Review Board (IRB).

Other Principal Investigator responsibilities relative to the IRB include the following:

- Submit all protocol amendments to the IRB for review;

- Report to the IRB any information about serious AEs reported in other studies associated with treatment;
- Provide the IRB with any other information it requests before or during the conduct of the study;
- Report to the IRB all adverse events as required by the approving IRB(s);
- Maintain a file of IRB/study-related information;
- Update the IRB on a minimum of a yearly basis;
- Maintain IRB approval during the duration of the study.

16.3 Informed Consent

Principal Investigators must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document.

No subject can enter the study before his/her informed consent has been obtained.

The Informed Consent Form must be submitted by the Principal Investigator for IRB approval.

16.4 Record Keeping and Study Documents

Study documents used to record demographic, procedural, and follow-up data, as well as any adverse clinical events that may occur during the study must be retained by the Principal Investigator.

The Principal Investigator must verify personal oversight of the clinical trial and confirm that all data recorded is accurate and current.

All data entries must be made only by the Principal Investigator and/or other site trained personnel. Training will be documented and logged in the site study binder.

16.4.1 Study Medication Accountability

It is the responsibility of the Principal Investigator to ensure that all Study Medication is inventoried and accounted for throughout the study and recorded in appropriate documents kept in the site study documents.

16.4.2 Records Retention

All correspondence related to this clinical study should be kept in appropriate study files at the clinical site. Records of subjects, study documents, product inventory, and IRB and Study Team correspondence pertaining to the study must also be kept on file.

The Principal Investigator must retain protocols, amendments, IRB/EC approvals, signed and dated consent forms, source documents, medical records, case report forms, device accountability records, all correspondence and all other documents pertaining to the conduct of the study.

17.0 Disclosure and Confidentiality

By signing the protocol, the Principal Investigator agree to keep all study documents in strict confidentiality and to request similar confidentiality from his/her staff and the Institutional Review Board. study documents (Protocols, and other material) will be stored appropriately to ensure their confidentiality.

18.0 Financial Disclosures

The Principal Clinical Investigator and other key Study Team members shall provide the IRB with sufficient, accurate financial information. Disclosures shall be promptly updated if any relevant changes occur during the course of the Study and for 1 year following the completion of the study.

19.0 Interim and Final Study Reports

Principal Investigators shall furnish all progress reports required by the IRB.

20.0 Quality Assurance

20.1 Subject Completion

Any subject who does not return for a scheduled follow-up evaluation will be contacted by telephone by the Principal Investigator, or his or her designee, to determine the cause for the missed appointment. Two telephone calls will be made and documented in the study binder, in addition to sending a certified letter requesting the subject to contact the office and return for his/her evaluation. If a returned letter receipt or an undeliverable response is received, this notice will be retained in the subject's study binder that will note the subject is lost to follow-up. If the study subject wishes to withdraw from the study, the reason(s) for discontinuation will be recorded in the subject's chart and on the appropriate study document.

20.2 Protocol Amendments and Deviations

No changes in the study procedures shall be effected without documentation by signed protocol amendments. Documentation must include the date and justification for the change and approved by the reviewing IRB prior to implementation of the amendment.

All deviations from the protocol will be recorded from the beginning through the completion of Study Medication administration. The Principal Investigator will be required to assess if any deviation has resulted in additional subject risk, and/or data integrity.

21.0 Declaration of Helsinki

The study will be conducted according to the guidelines established in the Declaration of Helsinki (World Medical Association 1964). Good Clinical Practices (GCPs) and local ethical and legal requirements. Subjects will be free to withdraw from the study at any stage without prejudice to their subsequent treatment.

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23.0 Appendices

23.1 Appendix A: Informed Consent

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 Ashley Payne at (970) 306-3171.

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 18 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 18-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, 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 40 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.**

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);**
- **Have a history of hip coxa profundal or protrusion acetabuli (deformity of the hip socket that causes stability issues);**
- **Have a history of immune disorders, such as rheumatoid arthritis;**
- **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.
- 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, you will begin taking your prescribed medication (losartan or placebo), which is one tablet, twice per day, for 1 month.
- You will be asked to keep a medication log to document each dose you take during the month.
- 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.

Research Visits and Procedures:

- At 7-10 days after beginning your medication course, you will visit 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.

- At 7-10 days after beginning your medication course, you will have a 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.
- You will be given a blood pressure monitoring device for your home use. With this device you will monitor your blood pressure twice per day for two weeks, and then once per week until the end of the course of medication (30 days total). Blood pressure will be maintained on a paper log.
- Return to the study site 2 times over the next 18 months.
- The first on-site visit is your standard 3-month follow-up appointment that all of Dr. Philippon's surgical patients attend 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.
- 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. The study team may use the data collected into your medical record from this visit.
- Each on-site visit will take approximately 1 hour.
- You will be asked to complete a subjective questionnaire regarding your hip-related health at 4 different time points (3, 6, 12 and 18 months). These questionnaires can be completed remotely from your home via computer or mobile device.
- Each subjective questionnaire will take approximately 20 minutes 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 (listed in Section I):

A member of your medical care team will describe the possible side effects of losartan and answer any questions you have. In addition to the risks listed in Section I, some more rare risks associate with losartan include 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 measuring your blood pressure at home or 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. 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.

VII. 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 18-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.

VIII. 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. Marc Philippon at (970) 476-1100. If you believe your illness or injury to be an emergency, contact call 911.

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.

IX. 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.

X. 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.

XI. 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.

XII. 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.

XIII. 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.

XIV. 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.

XV. 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**
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

23.2 Appendix B – Study Schemata

	Standard of Care Used for Screening	**Visit 1 POD 1**	**Telephone Contact**	**Telephone Contact Day 35**	**Visit 2 3 months**	**Telephone Contact**	**Telephone Contact**	**Visit 3 18 Months**
Window		**(or upon discharge)**	**7-10 days post discharge**	**+/- 3 days**	**+/- 4 weeks**	**6 months +/- 4 weeks**	**12 months +/- 8 Weeks**	
I/E Criteria	X							
Vitals, H&P	X				X			
BMI	X							
Demographic Info	X							
Medical History	X				X			
Trauma Chronology	X							
Circumduction eval	X				X			
ROM	X				X			
T2 MRI	X							X
Strength Testing	X				X			
SF-12	X				X	X	X	X
Patient Satisfaction	X				X	X	X	X
HHS	X				X	X	X	X
VHS	X				X	X	X	X
HOS	X				X	X	X	X
WOMAC	X				X	X	X	X
Tegner Activity Scale	X				X	X	X	X
VAS	X				X	X	X	X
Informed Consent		X						
Randomization		X						
Medication Pick -up		X						
Blood Pressure Cuff, Medication and BP Logs. PT instructions		X						
Compliance Check			X	X				
Protocol Deviations			X	X	X	X	X	X
Adverse Events			X	X	X*	X*	X*	X*
Basic Metabolic Panel			X					
*As related to the target hip only								