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*COMIRB Protocol*

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**Project Title: A Double-Blinded Randomized Clinical Trial Evaluating Platelet Rich Plasma versus Hyaluronic-Acid in the Short-term Treatment of Symptomatic Early Osteoarthritis of the Hip**

**Version Date 1/8/2017**

**Principal Investigator: Dr. Omer Mei-Dan**

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## 1. Hypotheses

Intra-articular injections with autologous platelet rich plasma and hyaluronic acid will reduce pain and improve function in patients with early hip osteoarthritis (null hypothesis).

## 2. Specific Aims

The objective of this study is to compare the clinical efficacy of intra-articular injections of autologous platelet rich plasma (PRP) vs. hyaluronic acid (HA) for symptomatic early osteoarthritis (OA) of the hip. Secondarily, this study aims to determine the feasibility and safety of treating early OA of the hip with HA and PRP.

## *3.* Background and Significance

Osteoarthritis (OA) has become one of the most common painful conditions affecting adults and the most frequent cause of mobility disability in the United States and Europe (1). Primary OA is an aging disease which normally develops between 35-60 years of age. However, in some cases OA develops secondary to dysplasia or trauma, affecting patients much younger. Unfortunately, there are currently no agents available that can halt OA progression and reverse any existing damage. Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) have suboptimal effectiveness, and there are some concerns regarding their safety, in light of the well-described gastrointestinal and cardio-renal side effects.

It has been recognized that inflammatory and/or metabolic imbalances in cartilage may contribute to the progression of cartilage to osteoarthritis. In turn, pharmacological treatments considered disease modifying osteoarthritis drugs (DMOAD) have attempted to manipulate these processes (1-2). Research has focused on factors that affect chondrocyte metabolism and the mechanism of cartilage matrix degradation, including anti-apoptotic agents following cartilage trauma (3-4). Lately, attention has turned to growth factors, which could possibly enhance cartilage production and decrease catabolic activity. The biggest remaining challenge is the development of appropriate effective therapy administered within the window of opportunity. Currently, the most suitable route for administering such therapy appears to be intra-articular injections that allow accumulation of critical doses of the drug within the damaged area and also reduce the risk of systemic side effects.

Moreover, Early ARthritis THerapies (EARTH) multicenter clinical studies have been developed to evaluate acute interventions strategies following severe joint injuries such as ACL tear or intra-articular fractures in delaying or preventing the onset of posttraumatic OA. The underlying hypotheses is joint injury initiates a series of events resulting in more rapid joint degeneration that culminates in early

disabling OA, and that early intervention prior to the development of irreversible changes may modify the disease course (5).

### a. Autologous Platelet-Rich Plasma (PRP)

The therapeutic use of autologous platelet-rich plasma (PRP) constitutes a relatively new biotechnology that has been a breakthrough in the stimulation and acceleration of soft-tissue, bone and cartilage healing (6-7-8). The application of PRP has been extended to many different fields, including orthopedics, sports medicine, dentistry, cosmetic and periodontal medicine, plastic, and maxillofacial surgery [7]. The efficiency of this process lies in the local and continuous delivery of a wide range of growth factors and proteins, mimicking the needs of the physiological wound healing and reparative tissue processes [6]. In this process a preparation rich in growth factors (PRGF) combines the advantage of an autologous fibrin clot that will aid in hemostasis as well as provide growth factors in high concentrations to the site of a tissue defect. The platelet-rich plasma preparation encourages the release and slow delivery of growth factors from harvested platelets, activated by endogenous thrombin, and is used as a biological enhancer in the healing of fractures, lumbar fusions, cartilage defects, muscle tears, and tendon lesions, thus promoting initiation and early maturation of bone and soft tissue formation [2-7] which involves a more physiologic repair with less scar tissue [5].

Growth factors offer promising treatments for enhanced regeneration of cartilage in focal articular cartilage defects or in situations of more widespread cartilage loss such as those that occur in OA. Numerous anabolic growth factors stimulate chondrocytes synthesis of proteoglycans, aggrecan, type II collagen, induce synoviocyte and MSC proliferation, drive chondrogenic differentiation of mesenchymal stem cells (MSCs), and decrease the catabolic effects of cytokines such as interleukin-1 (IL-1) and the matrix metalloproteinases (MMP) (8).

The source of the new PRP preparation consists of a limited volume of plasma enriched in platelets, which is obtained from the patient. Once the platelet concentrate is activated a myriad of growth factors and proteins are released, progressively, into the local environment, contributing to the accelerated postoperative wound healing, tissue repair, and vascularization (8-9).

The application of PRP in cartilage repair is relatively new and therefore limited publications are available investigating its use. Chondrocytes and MSCs exposed to PRP both have increased cell proliferation and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared with controls (10). Synoviocytes from patients with OA cultured in PRP demonstrated increased hyaluronic acid production and secretion, suggesting that PRP could potentially serve as an endogenous source of chondroprotection and joint lubrication after intra-articular application [11]. In a rabbit model, osteochondral defects were

treated with either autogenous PRP in a poly-lacticglycolic acid (PLGA) carrier, PLGA alone, or left untreated [12]. The PRP group demonstrated a higher extent of cartilage regeneration as well as an increased production of the glycosaminoglycans in the ECM.

In a cohort of 30 patients comparing injections of PRP with hyaluronic acid (HA) in the management of OA, the success rate for the pain subscale reached 33.4% for the PRP group compared with 10% for the HA group ($p = 0.004$) [13 ]. Additionally, the percent reductions in the physical function subscale and overall WOMAC at 5 weeks were also associated solely with treatment modality in favor of PRP with $p = 0.043$ and $p = 0.010$, respectively.

Kon et al. treated 115 knees of patients with four intra-articular PRP injections given every 21 days and followed the patients for 12 months [14]. Patients evaluated in this study included 58 with degenerative chondral lesions (Kellgren-Lawrence 0), 33 with early OA (Kellgren- Lawrence I–III), and 24 with advanced OA (Kellgren- Lawrence IV). A substantial improvement in International Knee Documentation Committee (IKDC) and EuroQol (EQ-VAS) scores was noted at the end of therapy and at both the 6- and 12-month time points. The IKDC subjective scores as well as the EQ-VAS scores also demonstrated major improvements at the end of therapy. The authors concluded that treatment with PRP is safe and effective at improving pain, function, and quality of life in patients with degenerative articular pathology.

A separate study by Dr. Mei-Dan showed that osteochondral lesions of the ankle treated with intra-articular injections of PRP and HA resulted in a decrease in pain scores and an increase in function for at least 6 months, with minimal adverse events. Platelet-rich plasma treatment led to a significantly better outcome than HA.[15]

Recently, an RCT (randomized control trial) evaluating the effect of PRP on early osteoarthritis of the knee showed significant clinical improvement at both 6 months and 1 year. Platelet-rich plasma seemed to result in no change by MRI per knee compartment in at least 73% of cases at 1 year. No adverse effect was reported with the use of PRP (18).

### b. Hyaluronic Acid (HA)

Synovial hyaluronic acid is a high–molecular weight glycosaminoglycan that acts as a fluid shock absorber, protecting cells and the intracellular collagen network from mechanical stress. The purpose of intra-articular injections of HA is to return the lost viscoelasticity to the joint, being frequently applied with some good results, although several contradictory findings have also been reported (20). Results from a clinical trial involving 306 patients showed that at the 40-month visit, significantly more patients responded to intra-articular injections of HA compared with placebo in the management of knee OA symptoms ($p=0.004$) (21). Furthermore, a recent

meta-analysis including 54 trials and involving more than 7,500 patients has also provided information about the therapeutic trajectory of HA for knee OA. Interestingly, HA was found to be efficacious by 4 weeks, reaching its peak effectiveness at 8 weeks but exerting a residual detectable effect at 24 weeks

Multiple studies have shown that viscosupplementation (VS) with HA in the hip is as effective as in the knee. (27-30). Migliore et al.'s prospective study on the symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip showed statistically significant improvements in all outcomes measured (Lequesne index, visual analog scale [VAS], and NSAID consumption) at 2 and 6 months follow-up. This series was based on 30 patients receiving from one to three intra-articular injections of hylan G-F 20. There were no systemic adverse events (26). In another prospective study of 14 patients with hip osteoarthritis, each patient received three weekly injections of 2 mL of a hyaluronan derivative. There were no systemic adverse effects. There were statistically significant improvements in all measured outcomes (31). Tikiz et al compared low molecular weight (LMW) hyaluronan (Ostenil) and high molecular weight (HMW) hylan G-F 20 (Synvisc) in the treatment of hip osteoarthritis. Fluoroscopic guidance was used to inject 32 hips (25 patients) with LMW hyaluronan and 24 hips (18 patients) with HMW hyaluronan. VAS, Lequesne index, and Western Ontario and McMaster Osteoarthritis Index (WOMAC) were measured at baseline, 1, 3, and 6 months. Again, there were no systemic adverse effects. Both LMW and HMW hyaluronan preparations tested produced statistically significant improvement in all outcomes out to 6 months: 40% reduction in VAS, 48% reduction in Lequesne index, and 40% improvement in WOMAC scores. No significant difference was found between higher- and lower weight hyaluronan groups (32). A prospective study by Gaston et al of intra-articular hip viscosuplementation with synthetic hyaluronic acid for osteoarthritis measured efficacy, safety, and comparison with preinjection radiographs. Fifteen hips were injected weekly for 3 weeks with Suplasyn hyaluronan. Harris Hip Score and weight bearing anterior posterior (AP) pelvis films were done at baseline and 3 and 6 months. The results showed a statistically significant improvement in Harris Hip Score at 3 months, which continued out to 6 months. Analysis of radiographic data (using Kellgren and Lawrence grades, as well as minimum joint space width) showed that those with fewer initial radiographic changes had a trend towards an increased benefit from hip viscosupplementation. Again, there were no systemic adverse effects (33).

### c. Preliminary Studies

The application of PRP in cartilage repair is relatively new and therefore limited publications are available investigating its use. Recently, a randomized controlled study comparing HA versus PRP in the short term treatment for symptomatic knee osteoarthritis showed plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a

comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee (22). Another study evaluating the effects of PRP in osteoarthritis of the knee together with MRI reported significant clinical improvements at 12 months post injection. According to MRI results, there was no change in the appearance of osteoarthritis 1 year after platelet-rich plasma therapy in 83.3% of all cases when compared with baseline (N = 12) with lateral femoral and tibial compartment involvement. Similarly, there was no change in 73.3% of the cases with medial compartment involvement, although these values did not reach statistical significance. The appearance of medial compartment osteoarthritis improved in 1 knee (6.7%) after 1 year. This is in contrast to some longitudinal studies that suggest an annual decrease of up to 4% to 6% of cartilage volume in knee osteoarthritis compartments (18).

Recently, Gobbi et al evaluated the effect of PRP in 50 patients with osteoarthritis. At 12 months follow up, patients had improved clinical symptoms with no adverse effects reported [23].

In a pilot study of 100 patients with osteoarthritis of the knee receiving intra-articular PRP injections, favorable results with pain reduction and improved function were reported. Patients were followed up at 2, 6, 12, and 24 months. Statistically significant improvement was observed in all the variables (24).

Mei-Dan et al. evaluated the effect of intra-articular injections of PRP and compared to HA in osteochondral lesions of the talus. Both groups significantly improved clinical symptoms. When comparing both treatments groups, PRP produced a significantly greater improvement than HA (15). Minor discomfort and mechanical pressure were common reports at the injection site in both groups.

Battaglia et al recently reported the outcomes of injection of PRP for OA of the hip. Twenty patients, with a mean age of 52 years, who presented symptomatic OA of the hip were treated with a total of 3 intra-articular injections of PRP. Patients were prospectively evaluated at 1, 3, 6, and 12 months follow up. All patients had significantly improved clinical symptoms. No major complications or adverse events occurred at the moment of injection or in the follow-up period. Ten patients reported a slight pain during or after the injection, which spontaneously resolved in 1 or 2 days (37).

## 4. Research Methods

### a. Dosing and Treatment Regimens

All eligible patients will receive three injections per randomization table into the symptomatic hip. If a patient has bilateral symptomatic hip OA, both hips will be randomized to the same treatment group.

### i. Hyaluronic Acid

Hyaluronic acid is categorized as a medical device by the FDA, is commercially available from several manufacturers, and is currently FDA approved for the treatment of osteoarthritis in the knee. However, it is a well-accepted treatment modality, for many other intra-articular indications, and is utilized by many surgeons, nationally and globally, for the treatment of hip, shoulder, ankle, sub-talar and other joints. HA is typically supplied in 2 -3 mL prefilled syringes, and injected in a series of 3 to 5 consecutive intra-articular injections at weekly intervals. Most patients feel some relief after 3 injections. For this protocol, Supartz hyaluronate will be used (see attached package insert). Supartz hyaluronate has been approved as a Class 3 medical device by the FDA since 2001 for treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, such as acetaminophen. Supartz is manufactured by Smith & Nephews, Inc. in Memphis, TN, and will be provided for free by the principal investigator to subjects who are randomized to the HA arm in this study.

Supartz hyaluronate is a sterile, viscoelastic non-pyrogenic solution of purified, high molecular weight (620,000-1,170,000 daltons) sodium hyaluronate (hyaluronan) with a pH of 6.8-7.8. Each one mL of SUPARTZ contains 10 mg of sodium hyaluronate (hyaluronan) dissolved in physiologic saline (1.0% solution). The sodium hyaluronate is extracted from chicken combs. Sodium hyaluronate is a polysaccharide, containing repeating disaccharide units of glucuronic acid and N-acetylglucosamine.

SUPARTZ hyaluronate is supplied as a sterile, non-pyrogenic solution in 2.5 mL pre-filled syringe, and will be administered by intra-articular injection using a 22-23 gauge needle, once a week (1 week apart) for a total of 3 injections. The therapeutic scheme of HA supplementation varies according to the molecular weight of the drug. One injection per week for 3 weeks is the most commonly used approach in contemporary literature (47).

The full 2.5 mL is injected in one joint. Strict aseptic administration will be used. The prefilled syringe is intended for single use and will be discarded after the injection. The content of the syringe will be used immediately once the container has been opened.

SUPARTZ is not FDA approved for hip viscosupplementation but like all HA brands, it is being utilized by surgeon, nationally and globally, for other joints, including the hip, shoulder, ankle, CMC etc. It is the standard of care to use HA to other joints than the knee, in our institution.

### ii. PRP

The FDA does not require an IND and does not object to licensed medical practitioners using autologous Platelet-Rich Plasma as long as the PRP is not shipped across state lines, packaged for individual use only, and no labeling claims are made (see attached communication from the FDA).

Several phlebotomy and processing kits are FDA approved for safe and rapid preparation of PRP, and are commercially available. Dose, preparation and regimen of intra-articular injections of PRP have been variable in the literature. Doses vary between one to three injections, given consecutively within one or two week intervals (37).

For this protocol, we will use the FDA approved Endoret ® kit from Biotechnology Institute SL (see attached documentation). Kits will be purchased with the Principal Investigator's startup funds. Each kit consists of components necessary to collect whole blood from the patient into tubes containing anticoagulant and to separate the centrifuged sample into fractions (including the one containing platelet-rich plasma). The content in each set consists of 4 extraction tubes, 2 fractioning tubes, 1 activator ampoule, 1 activation syringe (use to activate the PRP), 1 PTD (a rubber band placed in the arm to pump up the veins), 1 tourniquet for the blood draw, and 1 butterfly phlebotomy needle. Each PRP preparation requires a total of 36 mL of peripheral blood. Blood will be obtained via direct venipuncture using the provided tourniquet and butterfly needle. Blood will be collected into four 9 mL extraction tubes containing 3.8% (wt/vol) sodium citrate. Tubes are centrifuged at 640 rpm for 8 minutes at room temperature. The 1 mL plasma fraction located just above the buffy coat is then aspirated from each tube and dispensed into the fractioning tube. This PRP preparation process takes place under laminar airflow (cleaner than surgery room) located at the Boulder outpatient's clinic where it is currently being utilized in a regular daily PRP injection setup. The clinic is amenable for sterile procedures. Immediately prior to injection, calcium chloride is drawn up from the activator ampoule with the activation syringe and is added to the PRP fractioning tube. The activated PRP is then injected in its entirety into the hip joint. All the preparation is performed under strict aseptic technique.

### b. Outcome Measure(s)

Standard of care diagnostic AP hip x-rays will be performed in patients with clinical suspicion of symptomatic OA of the hip. Lesions will be classified according to Kellgren-Lawrence classification. Kellgren and Lawrence grading scale defined as follows:

- 0 = normal;
- 1 = doubtful narrowing of joint space and possible osteophytic lipping;
- 2 = definite osteophytes and possible narrowing of joint space;

- 3 = moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour;
- 4 = large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour (25).

Once the diagnosis has been confirmed, eligible patients will be approached for participation in this study. After written consent was obtained, study subjects will be randomized and treated either with three PRP or three HA injections. Consent will be performed at the office encounter. Consent will be obtained by research personnel trained on the study protocol. Medical questions related to consent will be deferred to the PI or Co-Investigators (all MD or PA). This may include explaining in more detail the intra-articular injection procedure, the outcomes that they should expect, and complications that may arise. We will also make sure the patient understands that if they decide not to enroll, it will not alter the physician-patient relation. Patient will also have the option to withdraw from the study without altering the physician-patient relation at any time point of the study.

The PI of this study will be the Treating Physician. He will be unblinded to the treatment and will only be involved in the initial assessment of the patient and the actual injections. All follow up visits, clinical assessments and outcome scores will be performed by a co-investigator, who will be either a medical fellow or Physician Assistant (PA), and will be blinded to the treatment throughout the study period. All study subjects will be blinded to the treatment. All subjects, regardless of the treatment they are randomized to, will have 36 mL of blood drawn on each of the three injection days. Only subjects randomized to the PRP treatment will receive their processed autologous PRP. Blood from subjects randomized to HA will be discarded without processing. Subjects will be asked to close their eyes or direct the view away from the injection to prevent them from seeing the injected material, which would provide clues about the treatment received. To maintain the study blind for the research staff, no information about the treatment arm or the injected material will be entered into the EPIC Medical Record System.

The primary efficacy outcome will be defined as the percentage of patients having a 50% decrease in the summed score for the WOMAC pain subscale from baseline (visit 1, prior to injection) to month 6. Follow up for patient's scores will be performed at 6 weeks, and 3, 6, 12, 18 and 24 months. Ortech, a UCD OIT approved web based system will be used to collect patient reported outcomes. Outcome surveys collected includes the International Hip Outcome Tool (IHOT); Hip Disability and Osteoarthritis Outcome Score (HOOS), from which the WOMAC subscale will be derived; and the Non-arthritic hip score. All patient reported outcome (PRO) surveys have been validated and are widely used in the study of hip osteoarthritis.

Physical examination will be performed to assess the range of motion (ROM) of the hip joint. This will include extension, flexion, internal rotation, external rotation, internal rotation at 90 of hip flexion, external rotation at 90 degrees. Other tests that will be performed include FABER test, and bicycle kicks. Difference in ROM will be statistical compared at different time points between groups and intra-groups to determine improvement or not with time. Improvement in range of motion (degrees), compared with base line, will be analyzed between and within groups.

### c. Safety Measurements

The nature, onset, duration, severity, and outcome of all adverse events, as well as any association of an adverse event related to the study medication, will be assessed and documented at each visit. Patients will be asked to avoid intake of NSAIDs. If symptoms require pain medications during the initial follow up period (6 months after 3$^{rd}$ last injection) NSAID consumption will be recorded, as well as other pain medications taken. The use of rescue medication will be recorded daily by patients on a rescue medication log. Patients will be asked to maintain the log of rescue medication used for the first six months after the last injection. At final evaluation, total number of (rescue) medication used during this time period will be statistically analyzed between and within groups. That would also be compared to average monthly usage prior enrolment (base line). Patients will be allowed to have non-NSAIDs rescue medication as needed to treat pain. This includes acetaminophen and in select cases opioids such as Vicodin or Percocet.

To evaluate the safety profile of the treatments, all complications and/or adverse events will be recorded with their level of severity and their causal relationship to the study treatment.

## 5. Description of Population to be Enrolled

This study aims to enroll 80 subjects, 40 subjects for each of the two treatment arms. We considered these 80 patients could be included in a 6-month period time. Dr. Mei-Dan and Dr. Dayton have a busy clinic, which would allow including 4 patients per week for the study. Dr. Dayton normally sees patients with both hip and knee OA. Dr. Mei- Dan only sees patients with hip pathology.

### a. Screening Procedures

Study subjects will be recruited from current patient population or first time patients of Dr. Omer Mei-Dan and Dr. Michael Dayton. They will be identified and recruited for during routine office visits. All AP and lateral pelvis x-rays will be performed as

standard of care, and they will be used to assess and confirm eligibility. Patients will be recruited based on the following eligibility criteria

**Inclusion Criteria**

- Male or female age 30-72 inclusive.
- Symptomatic early OA of the hip (Kellgren-Lawrence Grade 1-2-3) documented by x-ray taken within the past 6 months.
- Women of childbearing potential will be allowed to enroll but must be willing to practice one highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS] condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

**Exclusion criteria**

- Patients with polyarticular disease.
- Patients with major conditions such as poorly control diabetes, CHF, COPD or untreated depression
- Patients with known blood disorders (such as thrombopathy, thrombocytopenia, anemia with hemoglobin **<**9g/dL).
- Patients who had intra-articular treatment with steroids within 6 months of randomization in this study or received more than 3 previous intra-articular steroid injections to the effected hip.
- Patients who are pregnant or nursing at the time of consent.
- Patients with inflammatory arthritic conditions (e.g. rheumatoid arthritis)
- Non-English speaking patients. (Patient Reported Outcomes are validated in English and is the language utilized with the electronic PRO collection system.))
- Patients who had previous hip surgery
- Additional disabilities in any of the lower limbs that would interfere with any of the clinical assessments.
- Chronic use of NSAID (defined as taking NSAID regularly every week for the last 6 months), steroids or chemotherapy drugs
- Treatment with aspirin or NSAIDs within 2 days prior to randomization
- Patients with a BMI over 30. Due to the fact that this study utilizes an injection technique which may be inaccurate in obese subjects.

# 6. Study Design and Research Method

## a. Study Procedures

Patients with clinical diagnosis of early symptomatic OA of the hip, based on physical exam findings and x-rays will be given the option to enroll in the study. The protocol will have two stages (Screening and treatment stage, and follow up stage with data collection) as described below.

## b. Screening and Treatment Stage

### i. Consent Procedure (visit 0)

Informed consent will be obtained by a study team member who is an orthopedic surgeon or PA, all of whom are intimately familiar with every aspect of the protocol. Consent will be obtained in a physician office or other private room. A signed and dated copy of the consent will be given to the subject. Patients will have the option to take the consent document home and review it before consenting to participate in the study. Patients will have the option to combine the consent visit (visit 0) with the baseline visit (visit 1).

### ii. Enrollment and first injection (visit 1)

1. The patient will be given a full verbal and written explanation regarding the trial and treatment.
2. Consent will be given to the patient. Patient will have the option to enroll immediately or come back within a week.
3. Enrolled patient will fill out the baseline surveys using Ortech. Ortech is web based and will be available using a laptop or iPad, designated exclusively to this research study. Information provided by the patients will only be accessible to authorized PI and Co Pi. Access to Ortech will require a log in and password that will be provided to only authorized study members.
4. Physical examination will be performed and outcome measures (ROM, FABER, bicycle kicks) will be documented in Epic.

### iii. Randomization.

Randomization will be double blinded. A computer generated randomization table will be utilized to randomize patients to either the PRP or HA treatment group. The randomization table will be generated prior to study start. Two blocks of 40 patients with equal number of patients randomized

to each treatment will be utilized to facilitate an interim analysis after 40 patients have been randomized.

Individual randomization information will be contained within sealed, opaque, sequentially numbered envelopes. Allocation will be monitored diligently to preserve concealment.

Each patient will choose a randomization envelope numbered from CH1 to CH40 for the first block of 40 patients and CH41 to CH80 for the second block. This number will correlate to either the PRP treatment or HA group according to a pre-defined randomization table.

A Randomization Log will be maintained as an Excel file. The following information will be recorded: randomization number and subject initials, subject name, medical record number (MRN), consent and enrollment date, randomization date, initials of person randomizing subject, and treatment assignment. The PI will keep this essential document in a locked file cabinet, as it is the primary source document that links the subject's identity to the confidential Randomization ID. The subject maintains this Randomization ID for the remainder of the trial and, thereafter, the Randomization ID is used on all research files, CRFs, Randomization Lists, Envelopes, and other research documents.

A research assistant or Dr. Mei-Dan will fill out the Randomization Log. None of them are involved in the follow up examination. None of the blinded examining physician will have access to the Randomization Log.

### iii. Subject Randomization Log:

The Randomization Log will list randomization numbers 1 through 80. Each randomization number will correspond to the treatment group as determined by the randomization table. It will also contain patient name and initials, MRN, consent and randomization date, and initials of the research team member randomizing the patient. Below is shown an example of the excel sheet that will be used.

| Randomization # & Initials | Subject Name | MR # | Consent & Enrollment Date | Treatment Assignment | Date Randomized | Randomized By (Initials) |
|---|---|---|---|---|---|---|
| CH1 | | | | PRP | | |
| CH2 | | | | PRP | | |
| CH3 | | | | HA | | |
| CH4 | | | | PRP | | |
| CH5 | | | | HA | | |
| CH6 | | | | PRP | | |
| CH7 | | | | HA | | |
| CH8 | | | | PRP | | |
| CH9 | | | | PRP | | |
| CH10 | | | | HA | | |
| CH11 | | | | HA | | |
| CH12 | | | | HA | | |
| CH13 | | | | PRP | | |
| CH14 | | | | HA | | |
| CH15 | | | | PRP | | |
| CH16 | | | | HA | | |
| CH17 | | | | PRP | | |
| CH18 | | | | HA | | |
| CH19 | | | | HA | | |
| CH20 | | | | HA | | |

Randomization Envelopes:

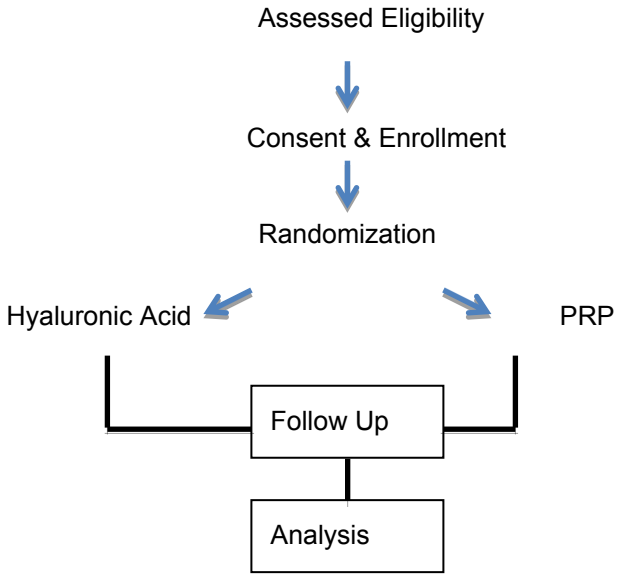
Envelopes will have the following information:

Study: A Randomized Clinical Trial Evaluating Platelet Rich Plasma versus Hyaluronic-Acid in the short-term Treatment of Symptomatic early OA of the Hip
PI: Omer Mei-Dan, MD
Site: Colorado University
Randomization #: **CH-F-1**
Study ID #: _____
Date envelope opened: _____
Time opened: _____
Person opening the envelope: _____
Note: Envelopes will be stored in a restricted access locked

Each envelope will have a randomization assignment insert. The treatment assignment and other relevant randomization data should be recorded on the Randomization CRF and the opened envelope and corresponding insert should be filed in the restricted access study file along with the Randomization Log.

Randomization #: CH-F-1 Treatment Assignment: PRP
Study ID #: _____
Date envelope opened: __ __ /__ __ / __ __
Time opened: __ __ : __ __ (24 hour clock)

Signature of the person who is randomizing the subject: _____




### iv. Treatment

Study subjects in both treatment arms will receive a total of 3 intra-articular injections, one week apart. All subjects will have physical exams performed to assess their hip function.

### v. Injection Procedure

Prior to all intra-articular injections, all subjects will have their blood drawn to maintain the double-blind. If patient is randomized to HA the blood drawn will be discarded. If patient is randomized to PRP this blood will be immediately processed to produce the PRP for injection.

PRP will be prepared in a sterile fashion and as described by Sanchez et al (13).

The blood draw will be performed at the CU Sports Medicine clinic in Boulder which is satellite outpatient clinic of the Department of Orthopaedics. Blood will be drawn in a conventional sterile way.

Patient's name and DOB will be asked to ensure identity. All specimen tubes will be marked with his/her identification. Protective sterile gloves will be used to protect the physician, nurse from bodily fluids. All of the tubes will be set out by the order of the draw and any necessary tools (tourniquet and alcohol swabs) will be nearby. Blood draw will be done from the most common point - the median cubital vein-which runs on the inner part of the forearm. A tourniquet will be placed on the upper part of the arm, tight enough to make the vein bulge. The vein will be gently pat and prep. The 21 gauge needle will be inserted into the vein with a smooth, fast motion. The vacutainer (blood specimen tube) will be pushed into the holder, keeping the needle steady. The vacutainer will automatically start filling with the right amount of blood needed for a specific specimen (18ml).The needle will then be pulled out at the same angle it was inserted. Immediately the needle will be disposed in the proper place and gauze will be applied to the patient's wound, pressing firmly to apply pressure.

The blood will be placed in the centrifuge. Tubes will be centrifuged at 640g for 8 minutes. This will be performed in the centrifugation machine FDA approved Endoret Kit. Once separation was done, it will be taken to the laminar flow where preparation for the PRP under sterile conditions will be started. In case the patient was randomized for the HA arm, the blood will be disposed and will not be placed in the centrifuge. The 1 mL plasma fraction located just above the buffy coat will be aspirated from each tube and dispensed into an empty tube under vertical airflow conditions. Seconds before the infiltration, calcium chloride will be added to a final concentration of 22.8 mM (50 micro-ml per 1 ml of PRP). The activated concentrate will then be injected into the hip joint. The platelet concentration in this type of PRP is 2 to 3 times the blood platelet count, which is considered to be moderately elevated and have yielded the best clinical results in the literature.

All patients will be asked to close their eyes or direct the view away from the injection just prior to injection, to further ensure subjects will be blinded to type of treatment applied.

All injections will be performed by the Treating Physician, Dr. Omer Mei-Dan to allow the rest of the study team to remain blinded. All clinical follow up evaluations will be performed by a co-investigator, who will be either a medical fellow or PA, and who will be blinded to subject's treatment arm.

An intra-articular injection of PRP or HA will be performed, according to treatment group the subject was randomized to.

Injection will be performed with the patient lying supine. Ethyl Chloride will be used as a topical anesthetic at the injection site if patient desires. The anatomical landmarks technique (Mei-Dan et al, Arthroscopy 2013) will be utilized to identify the correct location for the injection. In case of overweight subjects where landmarks are harder to assess, ultrasound-guided injection technique will be utilized. For the anatomical landmarks technique, the antero-superior iliac spine and the greater trochanter will be identified and marked with a marking pen. Then a cross is drawn, using both bone landmarks to identify the correct area for the injection. The injection area is draped in a sterile fashion. A 16 gauge needle is inserted in the cross area until bone is felt. The inner needle is removed. While the study subject is prepared for the injection, an unblinded research assistant (or Dr. Mei-Dan) prepares the PRP or HA per instructions in the laboratory, out of sight for the subject. Subject's will be asked to close their eyes or direct the view away from the injection, the syringe with sterile PRP or HA is screwed into the needle that was placed in the joint, and the material is injected into the joint. The needle is then removed, and a Band-Aid is applied to the entry point.

### c. Follow Up Stage

1. There will be six follow-up visits at 6 weeks, and 3, 6, 12, 18 and 24 months.
2. Physical exams including ROM, FABER and bicycle kick will be performed at each of these visits by the blinded Examining Physician.
3. Patients will complete the online patient reported surveys at 6 weeks, and 3, 6, 12, 18 and 24 months. These can be done from home or at the follow up visit.
4. Standard of care AP hip x-rays will be taken at the year 1 and year 2 visits.

### d. Risks

All x-rays used for this study are done as standard of care in the management of hip osteoarthritis.

All patients will have the risk related to intra-articular injection. This include, pain at the injection site, erythema. As with every joint injection, joint infections could potentially occur. However, in our experience, with more than 10,000 injections over the course of 6 years, using this technique, no infection has occurred.

Intra-articular injections with PRP can result in cutaneous rashes or urticaria, pain at the injection site, or erythema. All of which are considered very rare based on previous level 1 studies (13-15).

Intra-articular injections with HA can result in transient increases in inflammation in the injected joint. Pain, swelling, redness/warmth/bruising at the injection site, or headache, may occur. A very serious allergic reaction to this drug is rare.

Clinically significant findings will be documented as adverse events in the study documents and graded on a three point scale (mild, moderate, severe). Relationship of the adverse event to the treatment will be assessed (unrelated, possible, related).
Mild – joint pain after 48 hours from injection (patient is expected to have some sort of joint discomfort after injection for a day or two). Possible local irritation of skin, or hematoma.
Moderate –joint pain or reaction starting after a few days or lasting more than 4 days. Skin infection or long lasting irritation.
Severe- joint infection.

### e. Data Collection

A total of 9 visits (10 visits, if consent is done as a separate visit) are expected during a 24-month time period, for patient follow up. The first 3 visits, one week apart, will include physical examination and treatment with PRP or Hyaluronic acid injection. After the 3rd injection, subjects will be seen for clinical evaluation and survey assessment per schedule of

assessment below. Radiographs taken at patients' initial evaluation for their hip, and radiographs taken at one year and two year follow-up visits are done as standard of care in the management of hip osteoarthritis.

The three injection visits (1 through 3) will take approximately 45 minutes. This includes time for the baseline patient reported outcomes, physical examination, blood draw, and injection. Follow up visits (4 through 9) last around 30 minutes and will include patient reported surveys and physical examination. Study subjects will have the option to complete the surveys at home using the web based outcomes assessment software (Ortech). For subjects who don't have a computer, the surveys will be printed out and the subject can fill out a hard copy and return it.

The hip module in Ortech will be used to collect patient reported outcomes. Clinical hip scores will be determined automatically with Ortech. These include the International Hip Outcome Tool (IHOT); Western Ontario and McMaster (WOMAC) osteoarthritis index, which will be derived from the HOOS; and the Non-arthritic hip score.

| Schedule of Assessments | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit # | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Day/Month*** | | Day 0 | Day 7 (+1week /- 2 days) | Day 14 (+1 week/- 2 days) | Week 6 (+/- 1 week) | Month 3 (+/- 2 weeks) | Month 6 (+/- 2 weeks) | Month 12 (+/- 1 month) | Month 18 (+/- 1 month) | Month 24 (+/- 2 months ) |
| Informed Consent | X | | | | | | | | | |
| Patient Reported Outcomes (Ortech): IHOT, HOOS, non-arthritic hip score | | X | | | X | X | X | X | X | X |
| Physical exam (incl. ROM, FABER, bicycle kicks) | | X. Performed before inoculation | X Performed before inoculation | X Performed before inoculation | X | X | X | X | X | X |
| Hip x-ray | | X** | | | | | | X | | X |
| Randomization | | X | | | | | | | | |
| Blood draw (PRP kit) | | X | X | X | | | | | | |
| Injection | | X | X | X | | | | | | |
| AE assessment | | X | X | X | X | X | X | X | X | X |
| Pain Meds | | X | X | X | X | X | X | X | X | X |

* Visit 0 and Visit 1 may occur on the same day.
** Visit 0 x-rays can be performed up to 6 months prior to subject's consent date as standard of care.
*** A month is defined as a calendar month.

### f. Participant Discontinuation Criteria

Patients may be withdrawn from the trial for one of the following reasons:

1. Noncompliance with the protocol procedures.
2. The patient has been given other or additional treatment, which may interfere with the study treatment (such as intra-articular steroid injection).
3. The patient wishes to withdraw from the trial.
4. A severe adverse reaction by treatment applied is evident. Such as joint infection which requires IV antibiotics and possible surgical irrigation and drainage.
5. Patient becomes pregnant prior to completion of the third injection.
6. The investigator may withdraw patients from the trial if it is in the best interest of the patients. The reason for withdrawal shall be clearly described and the patient shall, whenever possible irrespective of the reason for withdrawal, as soon as possible be called for a final visit. All relevant assessments shall be completed, preferably according to the schedule for the final visit.

## 7. Risks associated with study

### a. Risks

All x-rays taken while the patient is enrolled in the study are performed as routine medical care in the management of painful hip osteoarthritis. No additional x-rays are required.

Intra-articular injections have been proposed to be a safe procedure, with low complication rate, if performed while taking adequate precautions (48). Risk related to the intra-articular injections are: infection with an incidence of 1 in 50,000 inoculations, pain at the injection site and erythema.

Intra-articular injections with PRP, as with every intra-articular injection (and not due to the PRP itself) can result in cutaneous rashes or urticaria, pain at the injection site, or erythema. All of which are considered very rare based on previous level 1 studies (13-15).

Intra-articular injections with HA can result in transient increases in inflammation in the injected knee. Pain, swelling, redness/warmth/bruising at the injection site, or headache, may occur. All which are rather rare.

PRP or HA can result in cutaneous rashes or urticaria, pain at the injection site, or erythema. These are a considered very rare based on previous level 1 studies (13-15). Clinically significant results will be reported as adverse events and will be graded on a three-point scale (mild, moderate, severe). Relationship of the adverse event to the treatment will be assessed by a safety officer (Dr. Vik Patel) not related to the study and The PI of the study and will be judged as not related, possibly related or related.

As with every joint injection, a joint infection could potentially occur. However, in our experience with more than 10,000 injections over 6 years, and using the described technique, this has never occurred.

### b. Complications and Pain associated with Study

All injections and follow up visits will be performed at the CU Sports Medicine Clinic in Boulder, which is satellite outpatient clinic of the Department of Orthopaedics. The Boulder clinic, being a well-equipped outpatient set up, with many injections performed on a daily basis, would have additional rescue devices, in case of need. Adverse events and pain medications used will be reported and monitored during each follow up visit and patients are reminded to contact the principal investigator with every possible question or adverse event they might sustain.

We will assist in arranging care for any injuries patients may sustain by participating in this study. However patient's insurance will be billed for any care that is provided.

### c. Recording and Reporting Adverse Events

The study investigators will monitor all subjects enrolled for any potential adverse effects (AE) associated with the treatments provided. Additionally, Dr. Vik Patel (who is not involved in the study) will perform regular evaluations of adverse effects and will serve as a safety officer.

In the event that AE occurs the following will be documented.

- Nature of adverse effect.
- Clinical adverse events will be graded on a three- point scale (mild, moderate, severe).
- Statement as to why it is considered unanticipated or anticipated but with change in nature or severity or frequency of occurrence from baseline.
- Statement as to the degree to which it is considered treatment related (unrelated, remote, possible, probable), and why.
- Results of any diagnostic tests that were performed.
- Description of any treatment implemented.

- Statement of subject's current clinical status.
- Investigator's signature and date.

Local side effects and irritations such as cutaneous rashes or urticariae, painful injection site, local heat, swelling, painful hip, and erythema will be recorded.

The investigator will supply a report for the COMIRB, CCTSI, if the adverse effects are unanticipated or if anticipated adverse effects change in intensity, frequency, or duration.

### d. Data Security

All data will be stored on servers used by University of Colorado Denver Department of Orthopaedics. These servers are located on the Anschutz Medical Campus. They have power backups, cooling systems, several firewalls, and restricted access to the physical location. Servers are encrypted with PGP encryption at 128-bit SLL encryption level, and RAID storage backs.

Access to the servers will be over a secure password protected connection only provided to the research team.

All web-based surveys using Ortech will be completed over a secure and encrypted connection. Ortech has been thoroughly vetted by UCD OIT, including a penetration test, to assess its security.

### e. Risk/Benefit Assessment

#### i. Hyaluronic Acid

Benefits obtain with injection of HA in the treatment of early OA of the hip have been shown by multiple studies as shown above (27-32). Improvement on pain relief, range of motion, Visual Analog Scale for pain and the decreased need for NSAIDs on the daily basis have been shown. (26-32). In over 11 published studies on VS of the hip using HA, there were no systemic adverse effects. Self-limited local adverse events occurred in 5% to 8% of patients and included mild transient sensation of heaviness in the hip and mild short-term increase in pain in the hip. The most common adverse effect listed was mild self-resolving soreness at the injection site (30). VS (HA) of the hip for osteoarthritis appear to be safe and effective in more than 25 years of use in Europe. Although no double-blind placebo controlled studies were found in a search of the medical literature, more than 11 studies suggest that VS (HA) in the hip is as effective as VS in the knee. It appears to be a safe and reasonable alternative to NSAID or intra-articular steroids for the treatment osteoarthritis pain. VS in the hip may delay the need for hip

replacement surgery. VS in the hip appears to work better in patients with fewer radiographic changes of OA.

### ii. PRP

The benefits of PRP in the treatment of OA have been shown in different studies. Recently Patel et al showed in a double-blinded randomized placebo-controlled clinical trial that PRP is more effective than placebo for the treatment of OA of the knee (34). Those patients receiving PRP injections did statistically better at 6 months follow up. Adverse effects were reported as minors including syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia, pain, and stiffness post injection. All these adverse effects were of short duration lasting no more than 30 minutes. None of the adverse effect reported were of high severity or warranted concern. Cerza et al also compared the effects of PRP to HA on gonarthrosis in a controlled randomized study (35). Compared to HA, those patients treated with PRP had a significant effect shortly after the final infiltration and a continuously improving sustained effect up to 24 weeks; clinical outcomes were better compared with the results with HA. No adverse effects were reported in any of both groups. Wang et al evaluated the effect of PRP on gonarthrosis of the knee. Over 322 patients included in the study (36), none reported adverse effects. At 6 months, the patients reported a significant improvement in pain, stiffness, function, and the Lequesne Index.

## 8. Data Analysis Plan

A power analysis was performed to determine the sample size of patients that should be included to determine statistical difference, if present, at different time points within group and between groups.

We expect a mean difference of 5.6 (±14), 17.9 (±15) and 28.6 (±15) between HA and PRP at 6, 12 and 24 weeks respectively on WOMAC subscale score. With an anticipated effect size of 0.8 and a desired statistical power level of 0.8, we calculated a minimum sample size of 40 patients at 12 weeks and 20 patients at 24 weeks.

To determine statistical difference in HA group, we expect a mean clinical improvement of 20, 18 and 10 on the WOMAC subscale score respectively at 6, 12 and 24 weeks. A minimum sample of 24 patients on the HA group was calculated

To determine statistical difference in PRP group, we expect a mean clinical improvement of 30, 40 and 40 on the WOMAC subscale score respectively at 6, 12 and 24 weeks. A minimum sample of 21 patients on the PRP group was calculated

The study's null hypothesis is that PRP and HA would improve patient's outcome. We will first analyze clinical improvement at different time point for each treatment group. This quantitative analysis will be performed using a Paired T test. Secondly, we will compare improvements between two treatment groups to determine statistical difference between two groups. This difference will be assessed using a Wilcoxon non parametric test.

To assess the safety of both treatment groups, adverse effects and complications for each treatment group will be recorded. A chi square test will be performed to determine statistical difference among different groups.

The grade of OA using the Kellgren-Lawrence classification will be documented for each patient on each of three radiographs performed during the study. Two orthopedic sports surgeons, sub specialized in hips, will assess each AP pelvis radiograph pre-treatment, 12 and 24 months post-injection. Clinical outcomes scores will be reported, pre-injection, 12 weeks, 6, 12, and 24 months post- injection. Improvement will be assessed using a Chi Square test for categorical scores and t-test for continuous scores.

## 9. Summarize Knowledge to be Gained

The study is designed to objectively evaluate whether intra-articular injections with autologous platelet rich plasma (PRP) and HA will improve OA symptoms and prevent progression of OA in patients suffering from early osteoarthritis of the hip. Radiographic evaluation will aid in determining the rate progression of early OA after treatment.

This will be the first study in the literature comparing HA vs. PRP in the treatment of early symptomatic OA. Considering the necessity to develop non-operative treatments or "chondroprotection" therapies, this will be a great contribution in the orthopedic community suggesting that early intervention prior to the development of irreversible changes may modify the disease course.

Dissemination of results will occur via publication in a peer - reviewed journal in the field of orthopedic surgery.

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