Platelet-Rich Plasma Therapy for Patellar Tendinopathy: A Randomized Controlled Trial Correlating Clinical, Biomechanical and Novel Imaging Biomarkers

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Protocol Revision History

Version Date	Summary of Revisions Made:
01 Jun 2016	Original version
21 Sep 2016	Replacing the Biodex Medical Systems with Kiio Sensor for the
30 Jan 2017	Clarify the 32 week visit will include completing questionnaires at home; the inclusion of a recruitment website.
18 Apr 2017	Recruitment efforts are being expanded to include additional sites.
13 Mar 2018	Inclusion of 10 healthy/normal subjects. Added Appendix A (Patellar Tendinopathy: Clinical and Biomechanical Assessment Protocol).
29 Jul 2020	Clarification to subject recruitment/identification to allow for the use of Workbench Research Recruitment Templates in HealthLink; Addition of remote consenting procedures
23 Dec 2021	Adding a data sharing plan with Dr. Kijowski at NYU

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1.0 PROJECT SUMMARY

BACKGROUND AND RATIONALE

Patellar tendinopathy (PT) is a common disabling overuse injury that is highly prevalent in sports, especially amongst jumping athletes. PT affects 32% of elite basketball players and may lead to considerable long-term morbidity, resulting in a negative effect on their career with up to 50% of athletes forced to quit their sport. Treatment of PT remains challenging, and no currently available conservative therapies directly address the underlying pathophysiology of tissue degeneration. We will conduct a 52-week double-blinded randomized controlled clinical study to investigate the efficacy of PRP and to determine if the intervention truly provides better improvements in pain and function and enhanced tissue healing when compared to less expensive minimally-invasive treatment options.

OBJECTIVES

The overall goal of this proposal is to find an effective treatment for PT. To achieve this, we will conduct a double-blinded randomized controlled trial (RCT) to investigate if platelet-rich plasma (PRP) is effective for treating PT (4-6). Clinical (pain and function scores) and biomechanical (knee strength) measures will be correlated with disease modification changes assessed using conventional and novel quantitative magnetic resonance imaging (MRI) and ultrasound (US) techniques.

ELIBIGILITY

This research will target adults, ages 18 to 39 years, diagnosed with chronic (>3 months) patellar tendonitis. Diagnosis will require a clinical examination consistent with PT and/or MRI or ultrasound confirmation of PT. In addition, 10 healthy/normal subjects who are not diagnosed with chronic PT will be enrolled into a control cohort.

STUDY DESIGN

Sixty-six patients with PT will be randomized to one of three study arms. Subjects in Group 1 (PRP) will receive a single US-guided (USG) injection of 5 mL autologous PRP into the patellar tendon, subjects in Group 2 (DN) will undergo USG dry needling of the patellar tendon, and subjects in Group 3 (SH) will undergo a sham control USG dry needling in the subcutaneous tissue only (not intratendon) at the level of the patellar tendon. The efficacy of the different treatment options will be assessed by pain- and function-dependent, PT-specific Victorian Institute of Sport Assessment Patella (VISA-P) quality of life scores, Tegner activity level scores, knee strength measurements, and conventional and novel MRI and US imaging at baseline, 16, 32, and 52 weeks post-treatment.

Ten subjects without PT will comprise the healthy/normal or control cohort. The control subjects will undergo the clinical and biomechanical assessments and conventional and novel MRI and US imaging during a single study visit.

REQUIRED SAMPLE SIZE

With 20 subjects, the expected power of our study based on hypothesized changes over time and the pooled SD of the changes in VISA-P scores. To allow for 10% drop out, we will recruit 22 subjects per group. Based on the estimated SD for the changes in the VISA-P scores reported in the previous study, we are conservatively inflating our pooled SD estimate. The data collected from the 10 control subjects will be used to compare normative data to the data collected from the test population.

2.0 INTRODUCTION

Patellar tendinopathy is one of the most common disabling conditions of the knee affecting both active individuals and competitive athletes (1, 2). PT is a degenerative tendon condition resulting in localized anterior knee pain affecting the proximal patellar tendon (7). The etiology of pain related to this chronic degenerative disorder remains unclear. The degenerative features of tendinopathy, however, are similarly seen in lateral epicondylitis (8), plantar fasciitis (9), and Achilles tendinopathy (10). The pathophysiology of PT is thought to be multifactorial, including overuse microtrauma, which leads to tendon disorganization and increased vulnerability to further injury and possible rupture (7). Chronic pain from PT is costly to elite athletes by reducing peak performance, forcing early career retirement, and in the later stages of life, adopting a sedentary lifestyle which leads to other chronic diseases such as hypertension and heart diseases (2). Thus, finding a reliable treatment option would change the way we approach PT and other chronic overuse injuries. Platelet-Rich Plasma: PRP is an emerging minimally invasive treatment option that uses concentrated autologous platelets, rich in healing factors (4-6). Recent exponential use of PRP has been in the area of sports-related tendon overuse injuries (5, 6, 11-13). Currently, it has been estimated that about 100,000 elite athletes are injected with PRP annually, but the frequency of use is likely under reported (14). The main growth driver came from the media's attention on well-known professional athletes reporting a quicker and durable return to activity after PRP rather than foundational evidence-based decisions from a well-designed randomized control trial (RCT). Moreover, clinicians are often faced with increasing demand by their patients for PRP, ranging from the weekend warrior to the disabled worker, without much leverage to argue for or against its use. There are only two existing but limited two-armed RCTs of PRP that have shown equivocal results in chronic overuse injuries (15-18). Despite limited scientific evidence, PRP usage has been and will continue to grow exponentially*. Therefore, rigorous clinical trials are needed to investigate the efficacy of PRP and to determine if the intervention truly provides better improvements in pain and function and enhanced tissue healing when compared to less expensive minimally-invasive treatment options.* PRP Mechanism of Action: Platelets are vital in initiating the tissue healing process (12, 19). When activated by injury, platelet alpha-granules are released to incite soft tissue healing (20). PRP augments the native healing process at the site of tissue degeneration through the action of concentrated healing growth factors such as PDGF, VEGF, FGF, and TGF- β1 (12). Fibroblast response and collagen formation occur in the healing response phase with tenocyte development and alignment healing (12). In chronic conditions, such as PT, few circulating platelets, and therefore low growth factor concentrations, are present, especially for tendons that receive only 30% of a muscle's blood supply (21). Therefore, delivering concentrated healing growth factors may benefit hypo-vascular soft tissue structures such as tendons. Small clinical studies have reported that PRP injections for PT decrease pain, increase function and have the potential to modify diseased tendon (15-18). However, PRP has not been

rigorously evaluated as a therapy for PT. The proposed project will be the first to assess pain- and function-dependent, knee-specific quality of life and in-vivo assessment of compositional, ultrastructural, and mechanical properties of PT post-treatment with PRP in a Level 1, RCT with subject and assessor blinding. The valuable data gained will significantly add to the knowledge base of disease modifying effects of PRP for tendinopathy. Positive findings of PRP compared to control would help establish an optimal protocol for the nonsurgical management of PT. In addition, no study has assessed the correlation between novel imaging biomarkers with validated clinical outcomes in response to therapy, which would provide a powerful imaging assessment tool to objectively monitor tissue healing.

3.0 STUDY AIMS/STUDY OBJECTIVES

The purpose of this research is to find an effective treatment for PT that addresses the underlying pathophysiology of tissue degeneration.

3.1 Specific aims include:

- 3.1.1 To evaluate the efficacy of PRP by reporting improved pain- and function-dependent, PT-specific Victorian Institute of Sport Assessment Patella (VISA-P) quality of life scores, Tegner activity level scores, and knee strength at baseline, 16, 32, and 52 weeks post-treatment.
- 3.1.2 To demonstrate treatment-related changes in pathologic imaging features of PT using conventional MRI (thickness and T2 signal intensity) and US (thickness, echogenicity, and hyperemia).
- 3.1.3 To investigate the relationship between changes in novel quantitative MRI (single-component and bicomponent ultra-short echo-time T2* (UTE-T2*)) and US (shear wave speed (SWS), a proxy for elasticity) parameters of PT and clinical and biomechanical improvement following treatment.

4.0 SELECTION OF PATIENTS

4.1 Study Population: This research will enroll 10 healthy normal adults and 66 adults diagnosed with chronic patellar tendonitis.

4.2 Eligibility criteria (healthy/normal)

- 4.2.1 Age between 18 and 39 years
- 4.2.2

4.3 Eligibility criteria (Subjects diagnosed with chronic patellar tendonitis)

- 4.3.1 Inclusion criteria
  - 4.3.1.1 Age between 18 and 39 years
  - 4.3.1.2 Chronic (>3 months) PT
  - 4.3.1.3 Clinical examination consistent with PT
  - 4.3.1.4 MRI or US confirmation of PT
  - 4.3.1.5 Pain score of 3 or greater on a 10-point VAS
  - 4.3.1.6 Self-report failure of supervised physical therapy

4.3.1.7 Self-report failure of at least 2 of the most common treatment options for PT (e.g. NSAIDs, relative rest, ice and bracing).

4.3.2 Exclusion criteria (All subjects)

4.3.2.1 Inability to comply with study follow-up requirements
4.3.2.2 History of bleeding disorders or other hematologic conditions
4.3.2.3 Knee pain from other possible etiologies (e.g., degenerative joint disease, meniscal tear, ligament injury or reconstruction)
4.3.2.4 Full or partial patellar tendon tear
4.3.2.5 Current use of anticoagulation or immunosuppressive therapy
4.3.2.6 Prior knee trauma requiring medical attention or surgery
4.3.2.7 Self-reported pregnancy
4.3.2.8 Worker's compensation injury
4.3.2.9 Daily opioid use for pain
4.3.2.10 Contraindication to MRI.
4.3.2.11 Systemic diseases such as Diabetes and connective tissue diseases.
4.3.2.12 Prior PRP or DN procedure.
4.3.2.13 Women that are pregnant

5.0 Research Design and Methods

5.1 Subject Identification and Recruitment: Potential subjects will be identified through the UW Orthopedics/Sports Medicine and UW Physical Therapy Clinics (Research Park, East and West) and surrounding Sports Medicine clinics. Study staff with UW Health electronic health record (Health Link) access may search patient list templates made available to them as part of their research access to Health Link to help identify potential subjects for study enrollment evaluation. Those that appear to meet eligibility criteria will be introduced to this research opportunity by someone involved in their care. Patients that agree will be contacted by research team personnel to learn more about participation. Recruitment flyers will also be posted in these locations.

The healthy normal subjects will be recruited from the IRB approved database of healthy volunteers (2017-0004, Reeder, PI). These subjects will be contacted by the database manager either by phone or email and will be provided with information about participation. Those interested in participating will be referred to a study team member to learn more about participation and to be scheduled for an initial study visit.

Recruitment efforts will also include the use of UW campus mass emails, fliers, UW website, social media, and postcards. Flyers will be posted in the UW Sports Medicine Clinics (Research Park and East), UW Physical Therapy Clinics (Research Park, East and West), University Health Services, as well as in sport facilities in the area (Natatorium, SERF, Health Clubs, etc). Recruitment flyers and postcards will also be made available to physical therapists and athletic trainers in the area and at other colleges and universities that provide a letter of support for this research.

Recruitment material will be made available at events such as local fun runs/races. We will also search medical records using ICD9 codes for potential subjects. One mailing will occur to potential subjects, which will include a letter or postcard describing the study. All recruitment material will include a brief summary of the purpose of the research, the number and duration of study visits, the contact information for the research team, and compensation.

5.2 Consent: The consent process will occur prior to administration of research procedures at the baseline visit. Potential subjects will meet with a study team member to review the information in the consent form including study procedures, risks associated with participation, alternatives to participation and whom to contact for additional information. After the subject has provided signed consent, any relevant laboratory tests will be obtained and confirmed prior to final enrollment in the study. Any questions will be addressed prior to the start of any research procedures and all subjects will be reminded that participation is optional and they can change their mind at any time.

During the COVID-19 pandemic, consent procedures will be conducted by phone, when possible, to minimize face-to-face contact subjects have with the research team. A copy of the consent form will be mailed or emailed to subjects prior to the scheduled consent phone call. If emailed, the consent form will be encrypted. A study team member will call potential subjects at the scheduled time to review the information in the consent form including study procedures, risks associated with participation, alternatives to participation and whom to contact for additional information. Any questions will be addressed during the course of the phone call and subjects will be encouraged to contact the study team with any questions or concerns they might have at any time. Upon completion of the consent process, a copy of the signed consent form will be provided in one of the following ways depending on each subject preferences and capabilities:

- Electronic signature will be provided using DocuSign
- Subject will be asked to scan a copy of the entire consent document and email it back to the study team.
- Subject will be asked to take a photo of the signature page and email a copy to the study team.
- If subjects are unable to provide an electronic copy of the signed consent form, they will be asked to bring a copy of the form to the research visit.

5.3 Research Procedures: Subjects enrolled in the chronic PT cohorts will be asked to complete four study visits at baseline, 16 weeks, 32 weeks, and 52 weeks. Subjects enrolled in the control cohort will complete 1 study visit. Health questionnaires (VISA-P Tegner, medication log, side effect log) will be mailed to subjects diagnosed with chronic PT only. A table outlining research visits is below. The following research procedures will be administered:

5.3.1 Randomization: The 10 healthy/normal subjects will not be randomized and will not receive any injections. The subjects diagnosed with chronic patellar tendonitis will be randomized to one of three study arms. Subjects in Group 1 (PRP) will receive a single US-guided (USG) injection of 5 mL autologous PRP using a 22G, 1.5 inch needle and after 20 needle passes targeting hypoechoic and hyperemic areas within tendon and bone attachment if involved. Subjects in Group 2 (DN) will undergo USG dry needling with 20 passes using a 22G, 1.5 inch needle targeting hypoechoic and hyperemic areas within tendon and bone attachment if involved. Subjects in Group 3 (SH) will undergo a sham control USG dry needling with 20 passes using a 22G, 1.5 inch needle placed in the subcutaneous tissue only (not intratendon) at the level of the patella tendon.

5.3.2 PRP Preparation and Administration (randomized subjects only): At the injection session, a nurse will perform a standard antecubital blood draw (15mL) using a 15 mL syringe and an 18G needle from the PRP group at the contralateral arm. The blood draw will occur only once. The study coordinator will then place the sample in the Arthrex ACP System and spin the blood sample using a two-stage spinning: the 1st separates red blood cells from platelets, and the 2nd concentrates the platelets to yield approximately 6mL of concentrated, autologous platelets. This layer of platelet rich plasma will be placed in the syringe by the centrifuge machine. Centrifuging will be repeated if desired concentration level is not achieved, but this has not occurred clinically and we do not anticipate inadequate platelet concentration level. All blood and equipment handling will follow universal precautions.

Platelet counts from subjects' whole blood and PRP processed blood will be analyzed. Platelet counts in whole blood vary by individual. The optimal quantity of platelets and growth factors required for tissue healing is not known, but a clinically effective concentration has been described as being greater than 4 times baseline autologous whole blood platelet concentrations (Marx RE: Platelet-rich plasma: Evidence to support its use. J Oral Maxillofac Surg 2004;62:489-496.). Therefore, platelet concentration yield may have important implications in clinical outcome correlation. In order to validate consistent platelet concentration yields across subjects, we will sample 1mL of whole blood (approximately one lab Vacutainer) and an additional 1 mL of platelet rich plasma for lab analysis of platelet to be completed by the UWHC Clinical Laboratory. This extra 1 ml of whole blood will be drawn at the same time that the 15 ml described above is drawn. After results are analyzed, the specimens will be discarded into biohazard waste.

The plasma poor platelet portion will be discarded in biohazard waste and destroyed day of procedure. The 5ml of platelet rich plasma will be injected into the subject's PT.

There will be no subject identification number associated with the blood before it is placed in the centrifuge system. It is a closed system. It spins the blood of one subject only. There is no risk of cross contamination.

The specimens will not be kept or stored. The blood will be analyzed on the same day as the procedure is being performed. This will not require storing of the specimen and prevent erroneous labeling of platelet concentration with a different subject.

The skin will be cleansed with an alcohol wipe and Hibicleanse. Lidocaine skin heals will be placed for local analgesia. The Patellar tendinopathy area will be identified using the US 15-6MHz linear array transducer. Under continuous US evaluation, 1 mL of the prepared solution will be injected into the diseased area of the PT itself using a 22G, 1.5" long needle. Then, up to 4.0 mL of the solution will be peppered along a short segment of the tendon into the areas of palpated tenderness and US documented pathology for a total of 5ml. After the injections, the subject will rest for 5 minutes. Participants will be telephoned after 3 days to enquire about side effects or adverse events.

Dry Needling (DN) Procedure: This is a therapeutic procedure that involves the same injection procedures under ultrasound guidance as in the PRP group but no PRP will be injected inside the patellar tendon.

Sham (SH) Placebo Procedure: Same needle size is used under ultrasound guidance as in PRP and DN groups but we will not inject PRP nor place needle inside the patellar tendon. Rather, the needle will be placed in the soft tissue next to the patellar tendon.

5.3.3 Blinding (randomized subjects only): Subjects and assessors will be blinded to the subject group allocation. Subjects in the DN and SH groups will also undergo phlebotomy to maintain blinding. Subjects will be identified to study personnel using a unique study number only and results of the imaging studies will be blinded, batched, and evaluated in a randomized manner.

5.3.4 Clinical and Biomechanical Assessment (see Appendix A) - All subjects: The clinical symptoms of all subjects will be assessed using the validated pain- and function-dependent, PT-specific Victorian Institute of Sport Assessment Patella (VISA-P) quality of life score and Tegner activity level scale. Knee flexor and extensor muscle isometric torque strength will be assessed using an isokinetic dynamometer (Kiio Sensor). Patellar tendon wave speeds will be measured with an experimental device during any or all of: strength tests with the Kiio sensor, squats, vertical jumps, walking, and running. The walking/running tasks will only be performed with subjects who have experience with treadmill walking/running. The wave speed measurement device will be placed on the surface of the skin. It consists of a piezoelectric actuator that induces waves in the tendon and miniature accelerometers that track wave propagation.

5.3.5 MRI Protocol: All subjects will undergo a non-contrast MRI examination of the knee on an MR750 3T scanner (GE Healthcare, Waukesha, WI) using an 8-channel extremity coil. Subjects will be in the scanner for approximately 45 minutes.

5.3.6 US Protocol: All subjects will undergo an US examination of the patellar tendon using both LOGIQ E9 (GE Healthcare Waukesha, WI) and Aixplorer (Supersonic Imagine, Aix-en-Provence, France) imaging systems with a 15-6MHz linear array transducer. Use of two US imaging systems will allow comparison of SWS measurements across different vendor platforms, which would be important for repeatability in future large-scale clinical trials. Imaging will take approximately 60 minutes total to complete.

5.3.6 Review of Medical Records (All subjects):

The following information will be collected from the randomized subjects: Patient age, height, weight, history of PT pain, duration of symptom related to PT, past medical history, past surgical history, medication history and current use, medication allergy.

The following information will be collected from the healthy/normal subjects: Patient name, height and weight, phone number, lifestyle and health history.

*Randomized subjects only

Procedure	Measurements	Assessment Time (weeks) 0	16*	32*	52*
Signed Consent and Randomization		✓			
PRP Procedure*	Collection, processing and administration	✓			
VISA-P Tegner*	Pain and function score of PT	✓	✓	✓	✓
Symptoms/Biomechanics	Knee Strength testing	✓	✓		✓
MRI	Single/bi-component UTE-T2*, PT volume	✓	✓		✓
Conventional US	PT thickness, echogenicity, hyperemia	✓	✓		✓
SWI	SWS measurements	✓	✓		✓
Medication/PT Log*	Pain medicine use, eccentric exercise adherence	✓	✓	✓	✓
Side Effects Log*	Side effects	✓	✓	✓	✓
Exit Interview	Satisfaction score, qualitative assessment of study experience				✓

5.4 Risks

5.4.1 PRP Preparation and Administration: The main risk associated with this process is temporary pain and swelling during the phlebotomy procedure to collect the sample and at the injection site during the treatment phase. Sterile technique will be employed during all phases of this process which will minimize any opportunity for the sample to be contaminated or the collection/injection site to be infected.

5.4.2 MR Imaging: The risk from a non-contrast enhanced MRI exam is minimal and is primarily related to claustrophobia and discomfort with positioning. Thorough screening will be completed to ensure subjects with contraindications to MR are identified. Only qualified staff will be involved with conducting the MR exam.

5.4.3 US Imaging: There are no physical risks associated with US imaging.

5.4.4 Subjects could injure themselves by stumbling or falling while walking or running on the motorized treadmill. These tasks will be familiar to subjects who are asked to perform them, so the risks are relatively minor. Additionally, there is a risk of minor skin irritation from the wave speed measurement device.

5.5 Benefits: There are no benefits expected for the study participant. However, positive outcomes from this study would establish an effective non-surgical treatment option for PT and demonstrate that disease modification of PRP-treated PT with clinical improvements in pain and knee strength is directly related to improvements in the imaging features of the healing tendon.

5.6 Criteria for Removal from Study: Enrolled patients will be removed from the study in the following circumstances:

- The patient is unable to complete all research procedures
- The subject withdraws consent

- Exclusion criteria are discovered after informed consent has been obtained but prior to the research examination.

6.0 Data and Safety Monitoring

The procedures administered for this research will be done in a manner that is consistent with clinical care. Therefore, an internal monitoring plan that includes the PI and all co-investigators will be implemented. Study team members will meet quarterly to discuss study progress including enrollment, data acquisition, and adverse events. In the event any unanticipated problems occur during the course of this research, they will be reported to the Institutional Review Board (IRB) in accordance with posted policies.

7.0 Privacy and Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects will be assigned a unique study number upon enrollment that will be used to label their research data in lieu of directly identifiable information. All subject data collected during participation in the study will be kept in a locked file cabinet within a Department of Radiology office or a password-protected database that uses departmental servers and will only be accessible to study team members. Coded data and images will be shared with Dr. Richard Kijowski at New York University. The Department of Radiology Radius team will serve as the honest broker and will code and share date with NYU. After the study is completed, all data will be de-identified for the purposes of research presentations/publications. The study MRI and US examinations will be archived on the standard clinical PACS system which is password protected behind the UWHC firewall. The study data and records will be maintained for up to 5 years after the conclusion of the study, at which point the PI will destroy the key to the coded identifiers, thus permanently anonymizing the data.

8.0 Statistical Considerations

A similar study involving patients with PT estimated the pooled standard deviation (SD) of the changes in VISA-P score over time to be between 15 and 19 and the minimal detectable change in score to be 11.1 (41). Since our subjects will have already completed physical therapy without improvement, we hypothesize that the DN and SH groups will marginally improve and that the PRP group will significantly improve on the order of 3 times the improvement of the other groups over the 1 year follow-up period. With 20 subjects, table 2 shows the expected power of our study based on hypothesized changes over time and the pooled SD of the changes in VISA-P scores. To allow for 10% drop out, we will recruit 22 subjects per group. Based on the estimated SD for

N per group	Change in DN	Change in SH	Change in PRP	Pooled SD	Power (%)
20	5.5	5.5	22	10	99.9
20	5.5	5.5	22	15	94.8
20	5.5	5.5	22	20	75.1
20	5.5	5.5	16.5	10	94.8
20	5.5	5.5	16.5	20	64.2
20	5.5	5.5	11	5	94.8

Table 2

the changes in the VISA-P scores reported in the previous study, we are conservatively inflating our pooled SD estimate.

9.0 FDA Considerations

9.1 MRI Hardware/Software: All hardware used to obtain MR images is FDA approved and will be used in accordance with the conditions approved by FDA. The investigational software being used in image acquisition is designed to stay within the current guidelines for MRI safety, established by the FDA. In addition, the investigational software does not meet the definition of a Significant Risk Device as outlined by the FDA under 21 CFR 812.3 as being:

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
- For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

9.2 PRP Preparation and Administration: The proposed project requires that autologous blood be processed at the time of the procedure visit. The Arthrex Double Syringe (ACP – Autologous Conditioned Plasma) System is a commercially available centrifuge system that allows for preparation of platelet-rich plasma (PRP) from a small sample of blood at the patient's point of care. The Arthrex Double Syringe ACP System has received FDA 510K approval (BK070069, Sept 19, 2008) for the purpose of preparing PRP.

Platelet-rich plasma meets the FDA's definition of a biologic, regulated under 21 CFR 607.3, which covers blood and blood products. During the processing of autologous whole blood from the patient, platelets are concentrated, but there are not any non-autologous products added to the PRP which significantly alter the biologic characteristics of the PRP cellular elements. In other words, there are no "activating agents" (e.g., calcium, thrombin) added to the PRP.

9.3 The US imaging hardware and software are FDA approved devices that are being used in a manner that is consistent with these approvals. We are asserting that the Kiio sensor and software are not consistent with the definition of a significant risk device as outlined in section 9.1.

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11.0 Appendix A

Patellar Tendinopathy: Clinical and Biomechanical Assessment Protocol

Equipment

- Instrumented strap (elastic neoprene strap with embedded tapper, accelerometers)
- Cabling (assorted BNCs)
- Signal conditioner (Model 480B21, PCB Piezotronics)
- Function generator (SDG1025, SIGLENT)
- Piezo controller (MDT694B, Thorlabs)
- A/D board (NI USB-6218, National Instruments)
- Computer with LabView collection program (Accelerometer.vi)
- Kiio sensor (and possibly laptop to operate)
- Portable force plate (Bertec, FP4060-05-PT)
- Treadmill

Procedure

1. Preparatory (prior to subject arrival) (**Est 5-10 min**)
    a. Set up collection computer, function generator, piezo controller, signal conditioner, A/D board, force plate
2. Set Up (**Est 3 min**)
    a. Introduction and Brief Description of Tests & Measures
    b. Obtain VAS score
    c. Place instrumented straps over both knees. Secure cables at thigh and waist and run them away from subject and instruct subject to perform a few squats to allow straps to settle into position
        i. Use Coban or Velcro strap on thigh, clip on belt
3. Signal Check (**Est 5 min**)
    a. Record squat trial (subject performs squats for 4 seconds, ~ 2 reps)
        i. Verify signal integrity using Matlab software (i.e. click “run”): wave speeds between 20 and 100 m/s, minimal dropouts
    b. Record passive flexion trial (subject bends knee, open-chain, for 4 seconds)
        i. Verify signal integrity using Matlab software (i.e. click “run”): wave speed does not vary more than 15m/s
    c. If poor signals, shift knee strap so that accelerometers are aligned with mid-patellar tendon. Repeat.
4. Quadriceps Strength (**Est 6 min**)
    a. Seated Isometric Knee Extension using Kiio system to measure force
        i. Position subject at end of mat table
        ii. Adjust Kiio system tether such that tension is present with subject’s knee positioned in 60 degrees of flexion
        iii. Explain to subject that the goal of this task is to kick out as HARD as possible for 3-5 seconds

1. Uninvolved Limb Tested First
    a. Warm Up repetitions (50, 75, 90% of max)
    b. Rest 30 sec
    c. 2 maximal knee extension trials (60 sec rest between trials)
        - Initiate trials by counting down ("3, 2, 1…")
        - Strong verbal encouragement during trial to elicit maximal knee extensor torque ("Kick kick kick/Go Go Go Go!")
2. Repeat procedure with involved limb
    a. VAS score following 2nd rep

5. Vertical Jumps (**Est 8 min**)
    a. Double Leg Countermovement Jump (**Est 3 min**)
        i. Subject positioned with both feet in center of the force plate, feet approximately shoulder width apart
        ii. Subject instructed to place hands on hips and perform countermovement jump beginning from standing position with the goal of maximizing vertical jump height (jump as HIGH as you can)
            1. Warm Up (3-5 submaximal jumps)
            2. Rest 30 sec (turn on tapper)
            3. 3 maximal jump trials (30 sec rest between each trial)
                a. Initiate/Run Collection Program at start of each trial
                b. To constitute a valid trial, subject must land in center of force plate and stabilize for at least 1 second
        iii. VAS score following 3rd rep
    b. Single Leg Countermovement Jump (**Est 5 minutes total**)
        i. Subject positioned with one foot on force plate
        ii. Subject instructed to place hands on hips and perform single leg countermovement jump beginning from standing position with the goal of maximizing vertical jump height (jump as HIGH as you can), and to land on the same leg
            1. Uninvolved Limb Tested First
                a. Warm Up (3-5 submaximal jumps)
                b. Rest 30 sec (turn on tapper)
                c. 3 maximal jump trials (30 sec rest between each trial)
                    i. Initiate/Run Collection Program at start of each trial
                    ii. To constitute a valid trial, subject must land on single leg in center of force plate and stabilize for at least 1 second
            2. Repeat with involved limb
                a. VAS score following 3rd rep

6. Gait (**Est 5 min**)
    a. Walking (3.3 mph) (**Est 2 min**)
        i. Position subject on treadmill (TM); subject instructed to walk normally (20 seconds warmup/set speed)

1. Turn on tapper (button on Piezo Controller)
2. Run Collection Program (8 sec)
3. Repeat 3 times while subject walks continuously
4. Obtain VAS score

b. Running (6.0 mph) (**Est 3 min**)
    i. Position subject on TM, instructed to run normally (30 seconds warmup/set speed)
        1. Turn on tapper (button on Piezo Controller)
        2. Run Collection Program (8 sec)
        3. Repeat 3 times while subject runs continuously
        4. Obtain VAS score
    ii. If subject is able, repeat collection with TM speed of 7.5 mph

7. Record tapper, accelerometer locations (**Est 2 min**)
    a. Subject sits with knees flexed to 90 deg
        i. Sleeve removed, locations of tapper and accelerometers on skin marked
            1. Tapper and accelerometers are strapped tightly enough that they leave slight indentations in skin. Measurements are easy.
    b. Measure distance to each mark from apex of patella and tibial tuberosity

<u>Current Estimated Collection Time</u>:

Prep (5-10 min)
Setup (3 min)
Signal Check (5 min)
Vertical Jump (8 min)
Quad strength (6 min)
Gait (5 min)
Record Tapper/Accel locations (2 min)
Cleanup (5 min)

Estimated Collection Time (with subject): **29 min**

Estimated Total Collection Time (with prep/cleanup): **40-45 min**