Treatment for sacroiliac joint pain using platelet-rich plasma (PRP) regenerative therapy: a randomized controlled trial in comparison with steroid/anesthetic injection with advanced MR analysis.
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Treatment for sacroiliac joint pain using platelet-rich plasma (PRP) regenerative therapy: a randomized controlled trial in comparison with steroid/anesthetic injection with advanced MR analysis.

Low back pain (LBP) is one of the most common causes of disability in the US workforce and one of the costliest to manage, with prevalence increasing up to 170% in the last 15 years. Opioid use for LBP is widespread and long-term, substantially contributing to the current dependence crisis, which has led to an NIH initiative for the development of new LBP therapies. The sacroiliac joint (SIJ) is thought to be the source of LBP in up to 30% of patients. Clinical trials have demonstrated at least moderate treatment effect of steroid and anesthetic injection (SAI) for pain. However, due to poor long-term effectiveness and associated deleterious systemic effects of steroids, other therapies for SIJ pain have emerged. Platelet-rich plasma (PRP) is a therapy in which autologous serum containing growth factors is obtained from whole blood for injection. The proposed mechanism is enhancement of tissue healing. PRP has been used for various spinal pain indications, and a recent meta-analysis concluded up to level III evidence for intradiscal treatment, but level IV for other spine structures (epidural space, facet joints, and sacroiliac joints) due to paucity of trials. For the SIJ, only one clinical trial has been performed which demonstrated significantly greater long-term pain reduction compared to SAI; however, patients were not blinded to procedure type, and inclusion diagnosis was made by physical examination without diagnostic block. Although PRP shows promise, the quality of evidence remains low, warranting more rigorous investigation. We propose to perform a randomized controlled single-blind trial of PRP versus SAI for the treatment of SIJ pain and hypothesize that PRP will demonstrate superior pain and functional outcomes compared to SAI at 3 months, and potentially result in quantifiable joint-related changes by advanced imaging.

Primary Aim: To compare the mean change in pain control, as measured by numeric rating scale, from baseline to 3 months among patients with chronic sacroiliac joint dysfunction with therapeutic platelet-rich plasma (PRP) vs. steroid/anesthetic injection (SAI).
Secondary Aim: To compare mean change in disability in patients with chronic SIJ dysfunction with PRP vs. SAI therapy by Modified Oswestry Disability Questionnaire, Short Form-12 survey, functional testing, and opiate usage assessment at 3 months.
Tertiary/Exploratory Aim: To compare mean intraarticular and periarticular MRI parameters (T1 relaxation time/T2 intensity and periarticular diffusion and perfusion) signal changes in chronic SIJ dysfunction with PRP vs. SAI therapy at 6 months.
Hypothesis: PRP will demonstrate superior pain control and disability outcomes compared to SAI at 3 months, and potentially result in intraarticular chondroprotection and/or anti-inflammatory periarticular changes that will be quantifiable using advanced MRI techniques.

Background and Significance

Prevalence and costliness of low back pain

Low back pain (LBP) is one of the most common causes of US workforce disability, and due to its effect on productivity and resultant lost wages, one of the costliest conditions to manage.[1-4] It is estimated to affect up to two thirds of people in their lifetime and is only increasing in prevalence (up to 170%).[1,5] Likewise, therapies for chronic LBP including opioid use, spinal injections, and surgery have also increased in the last two decades, with opioids the most commonly prescribed medication, used long-term in nearly 76% of cases.[6-9] Because of increasing incidence and recurrence, LBP makes up a substantial amount of the rising healthcare costs over the past two decades, exceeding over $100 billion per year.[1,10] Additionally, long-term opiate usage in LBP has substantially contributed to the opioid crisis.[9] This has led to a translational research initiative from the National Institute of Health (NIH Back Pain Consortium [BACPAC] Research Program) to develop more effective therapies for this prevalent and debilitating condition.[11]

Sacroiliac joint pain

The sacroiliac joint is (SIJ) thought to be the pain generator in up to 30% of cases of LBP.[5] Chronic pain can be separated into mechanical sacroiliitis (joint instability with or without periarticular inflammation) and non-mechanical etiologies (spondyloarthropathies). Instability is related to the angle of the weight-bearing joint, possibly contributing to the slight increased prevalence in females who have a more horizontal joint surface[12], as well as with dysfunction of the regional stabilizing ligaments (iliosacral, iliolumbar, sacrotuberous, sacrospinal ligaments).[13] Pain localization is performed by a combination of history, imaging, physical examination, and diagnostic block.[13] Multi-test physical maneuvers have shown to be promising for localization

in many cases (sensitivity of 78-94%, specificity of 79-85%).[14] However, they have not received reliable consensus[15] and the diagnostic standard remains pain reduction with intra-articular anesthetic injection.[16]

PRP Mechanism of Action

PRP is thought to enhance tissue healing at the site of injection, related to release of growth factors and cytokines within platelets and serum.[17] The PRP mechanism of action is through chondroprotection by platelet-derived growth factor which promotes proteoglycan synthesis and supports chondrocytes,[18] and transforming growth factor which induces chondrogenesis.[18] Additionally, PRP contains multiple anti-inflammatory markers, such as hepatocyte growth factor.[19,20] Platelet released growth factors also stimulate formation of hyaluronic acid, the deficiency of which plays a substantial role in osteoarthritis.[21,22] An *in-vivo* on injured rabbit knees demonstrated marked cartilage regeneration using both leukocyte poor and leukocyte rich PRP.[18] Studies support that PRP is effective not only in cartilage protection and regeneration but also anti-inflammation– both of which play a role in musculoskeletal pain.

PRP Clinical Trials

PRP has been used throughout the musculoskeletal system with positive results,[23-26] with promise particularly seen in the spine.[27-34] A recent meta-analysis of spine PRP trials assigned level III evidence to intradiscal PRP; however, other areas of the spine were assigned level IV evidence due to a paucity of quality clinical trials (epidural space, facet joints, and sacroiliac joints).[31] Specifically in the SIJ, there has been only one clinical trial which demonstrated longer efficacy for pain relief from PRP compared to SAI.[32] Though results were promising, patients were not blinded to the procedure type, and diagnosis of SIJ pain was made only by physical examination without diagnostic SIJ block. Image guidance was also performed with ultrasound which cannot verify intraarticular needle placement.[35] In the investigators clinical trial of PRP SIJ therapy, the investigators will improve on the methodology by optimally screening patients with a diagnostic SIJ block, conducting the trial with patient blinding, and confirming intraarticular needle placement by using CT guidance. The investigators study design will improve the quality of evidence related to the use of PRP for SIJ pain, which is currently limited.[31] This is an area of great importance, as the current treatment of SIJ pain relies heavily on steroids which have known deleterious systemic effects with repeated use including osteoporosis with increased fracture risk, and metabolic changes including blood sugar elevation in diabetics,[35-38], and opioids which can lead to dependence.[9,36-39] PRP SIJ injection with no known significant side effects has great promise to be more cost effective over time when compared to SAI.

Imaging evaluation of PRP related changes

MR imaging studies of PRP show promising results and potential to provide objective imaging markers for regeneration. One MRI study evaluating PRP vs SAI for plantar fasciitis demonstrated decreased thickness of the plantar fascia, and greater decrease in pain by visual analog scale seen with PRP vs. SAI after 6 months, supporting its anti-inflammatory properties.[24] MRI of the knee demonstrated improved cartilage fill-in after PRP compared to a control group after 1 year, supporting not only chondroprotective but also regenerative characteristics of this treatment.[25] A pilot study in rabbit spine demonstrated slower degeneration, and in some cases regenerative changes, of intervertebral discs 45 days after PRP injection when compared to discs that were injected with normal saline.[40] These results correspond with clinical findings in multiple human studies in which intradiscal injection of PRP was found to correlate with decreased pain scores.[27,28,41,42] Because SIJ-dysfunction can have both intraarticular degeneration and periarticular inflammation components, the investigators aim to evaluate both aspects of the SIJ in each of the two groups by MRI, comparing a baseline pre-injection study to a study performed 6 months after therapy – a time period which has been shown to demonstrate PRP changes on prior studies.[24,40]

Preliminary Studies

Prior experience with PRP SIJ injection

The investigators recently began offering PRP to patients as a treatment for sacroiliac joint pain in June of 2018. Since that time, the investigators have offered PRP to four subjects and they have accepted this treatment without reservation. There were no procedural complications or complaints. In three patients who underwent injection >3 months ago, one reported resolution of SIJ pain (0/10 by NRS), one had multifactorial LBP but no further complaints for SIJ related pain, and one continued to have significant pain (>4/10 by NRS) and went on to receive radiofrequency ablation. Due to the short time period since the procedure in the additional subject, further pain outcome data is incomplete at this time.

Advanced MR imaging techniques

The investigators have performed T2-mapping and T1-rho imaging sequences that sensitively evaluate cartilage[44,45] in the SIJ of a healthy volunteer. The investigators technique demonstrated superb delineation of the SI joint space in T1-rho for region of interest analysis and for T2-intensity mapping, with T1-rho demonstrating low relaxation times (expected in normal cartilage) (Figure 1). Intravoxel incoherent motion (IVIM) is a sequence that measures both diffusion and perfusion within soft tissue by using multiple b-values –the lower of which are sensitive to vascular motion and the higher which are sensitive to cellular motion.[46] This sequence is able to measure, and differentiate, both diffusion and perfusion parameters without the usage of intravenous contrast. IVIM has previously been found to differentiate acute inflammation from chronic inflammation along the SIJ in subjects with ankylosing spondylitis.[47] The investigators have used IVIM in prior studies evaluating both diffusion and perfusion changes in swine models after treatment of the facet medial branch with radiofrequency ablation (RFA), allowing quantification of perfusion and diffusion changes in the treatment area.[48] As this sequence has been found to be feasible in evaluating SIJ inflammation (a component of SIJ dysfunction), the investigators will use it to quantitatively measure periarticular inflammation changes after SAI and PRP therapy.

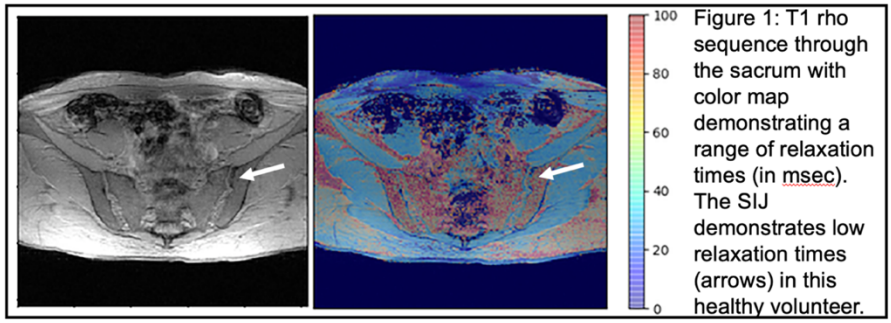

Figure 1: T1 rho sequence through the sacrum with color map demonstrating a range of relaxation times (in msec). The SIJ demonstrates low relaxation times (arrows) in this healthy volunteer.

Experimental Design

Design: After obtaining IRB approval, the investigators will perform a prospective randomized controlled single-blind trial to assess superiority of platelet-rich plasma to steroid/anesthetic in the treatment of chronic SIJ pain.

Inclusion criteria:

- Adult (>18 y/o) males and females referred for therapeutic injection to the investigators spine interventional service with a clinical diagnosis of SIJ pain confirmed by history and at least 3 of 6 provocative physical examination maneuvers localizing pain to the SIJ.
- 50% or greater reduction in pain by a diagnostic anesthetic block[49] using no more than 1.5 cc 2% lidocaine performed under imaging guidance by a pain interventionalist (PM&R, Pain Anesthesia, or Neuroradiology Spine Intervention).
- Baseline pain must be >/=4 by numeric rating scale (NRS)[50], at least 6 weeks in chronicity, and must not be multi-factorial (related to radiculopathy or axial pain localizing elsewhere) by physical examination or confounding medical history (infection, inflammatory spondyloarthropathy, or osseous metastatic disease).

Exclusion criteria:

- SIJ steroid treatment within the prior 6 months.
- Patients with a history of infection currently on antibiotic therapy
- Usage of systemic immunosuppressants
- Pregnancy

Sample Size: Since the SIJ PRP trial paper by Singla et al did not report an estimate of the standard deviation of the visual analog scale results (which are equivalent to NRS but performed visually instead of verbally)[50], a reasonable range of standard deviations between 2 and 3 were considered in the investigators sample size calculation. A study with 20 subjects per study arm will have 80% power to detect a difference of NRS ranging from 1.8 to 2.7 using a 2-sample t-test with a 2-sided 5% type 1 error:

Standard Deviation	NRS Delta
2	1.8
2.5	2.3
3	2.7

The investigators hypothesize detection of this range of deltas is achievable. To mitigate for potential drop-out or loss to follow-up (estimated at 20%), the investigators will enroll 25 subjects per arm. Between the University of Utah and Salt Lake City VA Medical Center, the investigators spine interventional group performed a total of 54 sacroiliac joint SAI on 52 individuals in the past 12 months and 5 PRP injections on 4 individuals in the past 6 months referred in combination from the Anesthesia Pain Service and PM&R at the VA (43 individuals) and Neurosurgery at the University of Utah (9 individuals). Additionally, Dr. McCormick from the PM&R service performs approximately 80 SIJ injections per year at the University of Utah and will be an additional referral partner in the investigators study equaling approximately 136 individuals/year available for recruitment in one

year (272 individuals/2 years). From this referral base the investigators are confident in meeting the minimum goal of enrolling 25 subjects/year for a total of 50 subjects in the two-year study period.
Acquired Clinical Data: age, sex, BMI, history of smoking and diabetes, and current pain medication requirements (specifically initial dosing requirements and time to refill) will be obtained through chart review.
Procedural protocol: Patient randomization will be stratified by site and performed through the RedCap database system which will be available within the procedure room. Equal allocation to 1 of 2 exposure groups will be performed: PRP and SAI. At procedure start 20 mL of blood will be drawn from the patient (no matter which group they are randomized to in order to maintain consistency between procedure types). Following this, a clinical nurse will administer the PROs and functional assessments and then exit the room. The research coordinator will perform the randomization through RedCap, and the assigned injectate (PRP or SAI) will be drawn by the physician and injected into the patient (who is blinded to the injectate type).

- PRP therapy: The SIJ will be localized under CT fluoroscopy. Local lidocaine anesthetic will be provided at the entry site. A 22-gauge Quinke needle will be advanced into the SIJ under CT fluoroscopic guidance. After autologous whole blood centrifugation with the Cascade Autologous Platelet System each sample will be evaluated with a platelet counter to assess integrity of the PRP injectate and specify leukocyte rich vs. poor preparation. Autologous platelet-rich plasma (generally 3-5 cc yield after centrifugation) will be injected into the SIJ after activation with calcium chloride.
- SAI therapy: The SIJ will be localized under CT fluoroscopy. Local lidocaine anesthetic will be injected at the entry site. A 22-gauge Quinke needle will be advanced into the SIJ under CT fluoroscopic guidance. 40 mg depomedrol mixed with 2 mLof 0.25% bupivacaine will then be injected in the SIJ (total of 3 mL).

Approximately 30 minutes following, the clinical nurse blinded to group allocation will re-enter the room and again perform patient assessments. The patient will then be given general post-injection instructions, be asked their preferred method of contact, and be discharged. The patient will remain blinded to the procedure arm throughout the study. A blinded research assistant will remotely contact the patient to obtain NRS and opiate measures at 3 and 7 days, and 2 months post-procedure. A blinded clinical nurse will perform in-person functional and disability assessments and obtain NRS and opiate measures at 1 and 3 months post-procedure.

Primary Aim
Outcomes and their measurements: The primary outcome of pain will be assessed using NRS which will be recorded pre and immediately post treatment in person, at 3 days, 1 week and at 1, 2, and 3 months post-procedure.
Analyses: The investigators will compare the two groups with respect to a mean difference in NRS from baseline to 3 months using a two-sample t-test as the investigators primary endpoint analysis. The investigators will provide 95% confidence intervals to indicate the uncertainty in these estimates. Additional analyses will evaluate the mean difference at 3 days, 1 week, 1 and 2-months post-treatment. A subanalysis will also be performed in subjects who had 80% relief by diagnostic block to determine the effect of the diagnostic cutoff.

Secondary Aim
Outcomes and their measures: The secondary outcomes of disability and quality of life will be analyzed using the Modified Oswestry Disability Questionnaire (MODQ)[52], Short Form 12 (SF-12) Health Survey[53] scores, and opiate usage (by Morphine Equivalent Dose) as reported by the patient and chart review.
Functional outcomes will be analyzed by the following two tests which have been previously validated to assess physical status[54]:

- The “get-up and go test”[55]: The time (in seconds) that it takes a patient to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down is measured.
- The “5 time sit to stand test”[56]: The time (in seconds) it takes the patient to rise from sitting to standing 5 times is measured.

Disability and functional assessments will be performed in-person pre-procedure, immediately post-procedure, as well as 1 and 3 months post procedure. Additionally, reported opiate usage will be assessed at the same time periods as NRS as in the primary aim.
Analyses: The investigators will compare the two groups with respect to a mean difference in survey (SF-12, MODQ) scores from baseline to 3 months using a two-sample t-test as the investigators secondary endpoint analyses. This will also be done to assess the results of the physical functional tests, as well as reported opiate usage. The investigators will provide 95% confidence intervals to indicate the uncertainty in these estimates. A

responder analysis[57] will also be performed with at least a 2-point reduction in NRS at 3 months compared to baseline used as the endpoint, with a separate analysis performed on those who improved by 50%. Responder analyses will also be performed on MODQ and SF-12 results that meet the minimally important clinical change.[58,59] Comparison of proportions will be performed with Fishers' exact test.

Tertiary/Exploratory Aim

Design: This will be an exploratory study to investigate MR imaging biomarkers in SIJ pain and determine whether there are changes in cartilage or periarticular signal with PRP and SAI therapy between baseline and 6 months. Additionally, differences in cartilage or periarticular signal between symptomatic and asymptomatic joint pain within the same individual will be investigated in both baseline and 6 months studies.

Inclusion criteria: Unilateral SIJ pain and all additional criteria from primary aim. This will allow comparison to baseline scan as well as comparison to an asymptomatic joint within the same patient.

Exclusion criteria: MRI contraindications per ACR guidelines and all additional criteria from primary aim.[60]

Sample Size: 5 subjects will be recruited from each exposure group (PRP and SAI) for imaging analysis (10 patients total).

Acquired Clinical Data: See primary and secondary aims.

Advanced MR Imaging Parameters: MRI will be obtained pre-procedure as a baseline (at least one week after diagnostic block to ensure resolution of procedural changes), then again 6 months after SAI or PRP to measure T1 and T2 maps, as well as perfusion/diffusion properties.[24,40]

The following sequences will be obtained with the following parameters:

T2 mapping: TR = 500 ms, ETL = 9, TE = 15, 30, 45, 60, 75 msec; bandwidth = 500 Hz/pixel; spatial resolution 1x1x3 mm^3; acquisition matrix = 256x84x32

T1 rho: 3D FLASH: slice thickness 3 mm, FOV = 256 mm, resolution = 1x1x3 mm^3; averages = 2, imaging; matrix = 256x256x16, 25% slice oversampling; 12 shots per each spin-lock duration; TR/TE = 6/3 ms, group TR = 4000 ms; bandwidth/pixel = 560 Hz/pixel; spin-lock durations : 0, 10, 20, 30, 40, 50 ms; B1 field: 500 Hz (1.18 Gauss); acquisition time = 8:00 min

IVIM: DWI in 3 planes (resolution = 1.8 x 1.8 x 3.3 mm) using the following b-values: 0, 10, 20, 30, 50, 80, 100, 200, 400, and 800 s/mm^2.[47] A STIR sequence will also be performed to evaluate periarticular inflammation.[61]

Post-Processing: Using a home developed processing software, which was developed using Python 3.x programming language, T2 and T1Rho maps are constructed by pixel-by-pixel fitting of the measured T2-weighted images and T1Rho source images to a function "single-exponential + constant" with respect to the echo-times (TE) and spin-lock durations, respectively. Osirix will be used for IVIM post-processing and region of interest (ROI) analysis.

Outcomes and their measurements: T1rho: cartilage relaxation time calculated in msec. T2 mapping: cartilage T2 intensity measured in regions of interest. IVIM: Perfusion parameters calculated by f (perfusion fraction), D* (pseudodiffusion), and fD*. Diffusion parameters calculated by D (tissue diffusion).

Analyses: The investigators will compare the two groups with respect to a mean difference in T1rho relaxation time from baseline to 3 months using a two-sample t-test as the investigators tertiary endpoint analyses. This method of analysis will also be performed for T2 mapping intensity, as well as IVIM parameters as stated above. The investigators will provide 95% confidence intervals to indicate the uncertainty in these estimates. The investigators will compare the mean parameters of the symptomatic joint to the contralateral asymptomatic joint within the same subject using a paired t-test and provide 95% confidence intervals to indicate the uncertainty in these estimates.

References

1. Freburger JK, Holmes GM, Agans RP, et al. The Rising Prevalence of Chronic Low Back Pain(). *Archives of internal medicine.* 2009;169(3):251-258.
2. From the Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults--United States, 1999. *JAMA : the journal of the American Medical Association.* 2001;285(12):1571-1572.
3. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA : the journal of the American Medical Association.* 2003;290(18):2443-2454.

4. Guo HR, Tanaka S, Halperin WE, Cameron LL. Back pain prevalence in US industry and estimates of lost workdays. *American journal of public health.* 1999;89(7):1029-1035.
5. Schwarzer AC, Aprill CN, Bogduk N. The sacroiliac joint in chronic low back pain. *Spine.* 1995;20(1):31-37.
6. Weiner DK, Kim YS, Bonino P, Wang T. Low back pain in older adults: are we utilizing healthcare resources wisely? *Pain medicine (Malden, Mass).* 2006;7(2):143-150.
7. Deyo RA, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. *Spine.* 2005;30(12):1441-1445; discussion 1446-1447.
8. Luo X, Pietrobon R, Hey L. Patterns and trends in opioid use among individuals with back pain in the United States. *Spine.* 2004;29(8):884-890; discussion 891.
9. Shmagel A, Ngo L, Ensrud K, Foley R. Prescription Medication Use Among Community-Based U.S. Adults With Chronic Low Back Pain: A Cross-Sectional Population Based Study. *The journal of pain : official journal of the American Pain Society.* 2018;19(10):1104-1112.
10. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *The Journal of bone and joint surgery American volume.* 2006;88 Suppl 2:21-24.
11. NIH Back Pain Consortium (BACPAC) Research Program. 2019; https://www.niams.nih.gov/grants-funding/funded-research/nih-back-pain-consortium-bacpac-research-program?utm_source=niamsfacebook&utm_medium=social. Accessed 1/10/2019, 2019.
12. Robinson HS, Brox JI, Robinson R, Bjelland E, Solem S, Telje T. The reliability of selected motion- and pain provocation tests for the sacroiliac joint. *Manual therapy.* 2007;12(1):72-79.
13. Ko GD, Mindra S, Lawson GE, Whitmore S, Arseneau L. Case series of ultrasound-guided platelet-rich plasma injections for sacroiliac joint dysfunction. *Journal of back and musculoskeletal rehabilitation.* 2017;30(2):363-370.
14. Laslett M, Aprill CN, McDonald B, Young SB. Diagnosis of sacroiliac joint pain: validity of individual provocation tests and composites of tests. *Manual therapy.* 2005;10(3):207-218.
15. Thawrani DP, Agabegi SS, Asghar F. Diagnosing Sacroiliac Joint Pain. *The Journal of the American Academy of Orthopaedic Surgeons.* 2018.
16. Dreyfuss P, Michaelsen M, Pauza K, McLarty J, Bogduk N. The value of medical history and physical examination in diagnosing sacroiliac joint pain. *Spine.* 1996;21(22):2594-2602.
17. Wu PI, Diaz R, Borg-Stein J. Platelet-Rich Plasma. *Physical medicine and rehabilitation clinics of North America.* 2016;27(4):825-853.
18. Xu Z, Yin W, Zhang Y, et al. Comparative evaluation of leukocyte- and platelet-rich plasma and pure platelet-rich plasma for cartilage regeneration. *Scientific reports.* 2017;7:43301.
19. Moussa M, Lajeunesse D, Hilal G, et al. Platelet rich plasma (PRP) induces chondroprotection via increasing autophagy, anti-inflammatory markers, and decreasing apoptosis in human osteoarthritic cartilage. *Experimental cell research.* 2017;352(1):146-156.
20. Zhang J, Middleton KK, Fu FH, Im HJ, Wang JH. HGF mediates the anti-inflammatory effects of PRP on injured tendons. *PLoS One.* 2013;8(6):e67303.
21. Goldring SR, Goldring MB. The role of cytokines in cartilage matrix degeneration in osteoarthritis. *Clinical orthopaedics and related research.* 2004(427 Suppl):S27-36.
22. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee Osteoarthritis Injection Choices: Platelet-Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). *Clinical medicine insights Arthritis and musculoskeletal disorders.* 2015;8:1-8.
23. Ali M, Oderuth E, Atchia I, Malviya A. The use of platelet-rich plasma in the treatment of greater trochanteric pain syndrome: a systematic literature review. *Journal of hip preservation surgery.* 2018;5(3):209-219.
24. Jimenez-Perez AE, Gonzalez-Arabio D, Diaz AS, Maderuelo JA, Ramos-Pascua LR. Clinical and imaging effects of corticosteroids and platelet-rich plasma for the treatment of chronic plantar fasciitis: A comparative non randomized prospective study. *Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons.* 2018.
25. Krych AJ, Nawabi DH, Farshad-Amacker NA, et al. Bone Marrow Concentrate Improves Early Cartilage Phase Maturation of a Scaffold Plug in the Knee: A Comparative Magnetic Resonance Imaging Analysis to Platelet-Rich Plasma and Control. *The American journal of sports medicine.* 2016;44(1):91-98.
26. Southworth TM, Naveen NB, Tauro TM, Leong NL, Cole BJ. The Use of Platelet-Rich Plasma in Symptomatic Knee Osteoarthritis. *The journal of knee surgery.* 2018.

27. Akeda K, Ohishi K, Masuda K, et al. Intradiscal Injection of Autologous Platelet-Rich Plasma Releasate to Treat Discogenic Low Back Pain: A Preliminary Clinical Trial. *Asian spine journal.* 2017;11(3):380-389.
28. Kirchner F, Anitua E. Intradiscal and intra-articular facet infiltrations with plasma rich in growth factors reduce pain in patients with chronic low back pain. *Journal of craniovertebral junction & spine.* 2016;7(4):250-256.
29. Mohammed S, Yu J. Platelet-rich plasma injections: an emerging therapy for chronic discogenic low back pain. *Journal of spine surgery (Hong Kong).* 2018;4(1):115-122.
30. Monfett M, Harrison J, Boachie-Adjei K, Lutz G. Intradiscal platelet-rich plasma (PRP) injections for discogenic low back pain: an update. *International orthopaedics.* 2016;40(6):1321-1328.
31. Sanapati J, Manchikanti L, Atluri S, et al. Do Regenerative Medicine Therapies Provide Long-Term Relief in Chronic Low Back Pain: A Systematic Review and Metaanalysis. *Pain physician.* 2018;21(6):515-540.
32. Singla V, Batra YK, Bharti N, Goni VG, Marwaha N. Steroid vs. Platelet-Rich Plasma in Ultrasound-Guided Sacroiliac Joint Injection for Chronic Low Back Pain. *Pain practice : the official journal of World Institute of Pain.* 2017;17(6):782-791.
33. Theys T, Van Hoylandt A, Broeckx CE, et al. Plasma-rich fibrin in neurosurgery: a feasibility study. *Acta neurochirurgica.* 2018.
34. Khafagy YW, Abd Elfattah AM, Moneir W, Salem EH. Leukocyte- and platelet-rich fibrin: a new graft material in endoscopic repair of spontaneous CSF leaks. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2018;275(9):2245-2252.
35. Kennedy DJ, Engel A, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J. Fluoroscopically Guided Diagnostic and Therapeutic Intra-Articular Sacroiliac Joint Injections: A Systematic Review. *Pain medicine (Malden, Mass).* 2015;16(8):1500-1518.
36. Carreon LY, Ong KL, Lau E, Kurtz SM, Glassman SD. Risk of Osteoporotic Fracture After Steroid Injections in Patients With Medicare. *American journal of orthopedics (Belle Mead, NJ).* 2017;46(5):E293-e300.
37. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain.* 2018;159(5):876-883.
38. King W, Miller DC, Smith CC. Systemic Effects of Epidural Corticosteroid Injection. *Pain medicine (Malden, Mass).* 2018;19(2):404-405.
39. Liu Y, Carrino JA, Dash AS, et al. Lower spine volumetric bone density in patients with a history of epidural steroid injections. *The Journal of clinical endocrinology and metabolism.* 2018.
40. Gelalis ID, Christoforou G, Charchanti A, et al. Autologous platelet-rich plasma (PRP) effect on intervertebral disc restoration: an experimental rabbit model. *European journal of orthopaedic surgery & traumatology : orthopedie traumatologie.* 2018.
41. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar Intradiskal Platelet-Rich Plasma (PRP) Injections: A Prospective, Double-Blind, Randomized Controlled Study. *PM & R : the journal of injury, function, and rehabilitation.* 2016;8(1):1-10; quiz 10.
42. Levi D, Horn S, Tyszko S, Levin J, Hecht-Leavitt C, Walko E. Intradiscal Platelet-Rich Plasma Injection for Chronic Discogenic Low Back Pain: Preliminary Results from a Prospective Trial. *Pain medicine (Malden, Mass).* 2016;17(6):1010-1022.
43. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. *The American journal of sports medicine.* 2011;39(2):266-271.
44. Albano D, Chianca V, Cuocolo R, et al. T2-mapping of the sacroiliac joints at 1.5 Tesla: a feasibility and reproducibility study. *Skeletal radiology.* 2018.
45. Nozaki T, Kaneko Y, Yu HJ, Kaneshiro K, Schwarzkopf R, Yoshioka H. Comparison of T1rho imaging between spoiled gradient echo (SPGR) and balanced steady state free precession (b-FFE) sequence of knee cartilage at 3T MRI. *European journal of radiology.* 2015;84(7):1299-1305.
46. Le Bihan D, Breton E, Lallemand D, Aubin ML, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology.* 1988;168(2):497-505.
47. Zhao YH, Li SL, Liu ZY, et al. Detection of Active Sacroiliitis with Ankylosing Spondylitis through Intravoxel Incoherent Motion Diffusion-Weighted MR Imaging. *European radiology.* 2015;25(9):2754-2763.

48. Peckham ME, Payne A, Odeen H, Hutchins TA, Miller S, Shah LM. Magnetic resonance guided high intensity focused ultrasound for the treatment of facetogenic pain. American Society of Spine Radiologists; February 14, 2018, 2018; Scottsdale, Arizona.
49. Polly D, Cher D, Whang PG, Frank C, Sembrano J. Does Level of Response to SI Joint Block Predict Response to SI Joint Fusion? *International journal of spine surgery.* 2016;10:4.
50. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* 2003;10(4):390-392.
51. Committee A. ACR Manual on Contrast Media. In: American College of Radiology; 2018.
52. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Physical therapy.* 2001;81(2):776-788.
53. Allen J, Alpass FM, Stephens CV. The sensitivity of the MOS SF-12 and PROMIS(R) global summary scores to adverse health events in an older cohort. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2018;27(8):2207-2215.
54. Marques A, Almeida S, Carvalho J, Cruz J, Oliveira A, Jacome C. Reliability, Validity, and Ability to Identify Fall Status of the Balance Evaluation Systems Test, Mini-Balance Evaluation Systems Test, and Brief-Balance Evaluation Systems Test in Older People Living in the Community. *Archives of physical medicine and rehabilitation.* 2016;97(12):2166-2173.e2161.
55. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. *Archives of physical medicine and rehabilitation.* 1986;67(6):387-389.
56. Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. *The American journal of medicine.* 1985;78(1):77-81.
57. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH task force on research standards for chronic low back pain. *Spine.* 2014;39(14):1128-1143.
58. Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. *Best practice & research Clinical rheumatology.* 2005;19(4):593-607.
59. Ogura T, Ackermann J, Barbieri Mestriner A, Merkely G, Gomoll AH. Minimal Clinically Important Differences and Substantial Clinical Benefit in Patient-Reported Outcome Measures after Autologous Chondrocyte Implantation. *Cartilage.* 2018:1947603518799839.
60. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document on MR safe practices: 2013. *Journal of magnetic resonance imaging : JMRI.* 2013;37(3):501-530.
61. Chan CWS, Tsang HHL, Li PH, et al. Diffusion-weighted imaging versus short tau inversion recovery sequence: Usefulness in detection of active sacroiliitis and early diagnosis of axial spondyloarthritis. *PLoS One.* 2018;13(8):e0201040.

Amendment 1:

What changes are being made? List and number each change, grouping similar changes together.

1. Administrative changes:

a. Fixing previous errors and omissions b. Updating a questionnaire

2. Changes to study design:

a. The investigators are removing the the requirements of "at least 3 of 6 provocative physical examination maneuvers" from the inclusion criteria, and the investigators are adding that performing the maneuvers and collecting the results will be a data point at either the test or study injection visit.

3. Changes to study procedures:

a. The investigators are adding a two week crossover to the study, for patients who do not respond to the arm they initially randomized into. With this, at two weeks the patients will "crossover" and be given the treatment for the other arm, still blinded, and all data collection/follow-ups will restart.

b. The investigators are adding the option of tele-health follow-up to the 1 and 3 month in-person visits.

Describe the reason for each of the changes described above. List and number the reasons according to the list above.

1. Administrative changes are needed to:

a. Fix previous errors and omissions - mainly in the procedure section, mainly needed to clarify some points and omit clinical procedure language that is not relevant

b. Update a questionnaire - SF-12 form was updated to remove irrelevant clinical sections, and add in a scoring rubric and study details. Survey material and language did not change.
2. Changes to study design:
a. The investigators are removing the the requirements of "at least 3 (out of 6) positive maneuvers" from the inclusion criteria, because in current clinical practice the use of the six maneuvers in diagnosing sacroiliac pain is controversial as to its accuracy, with many physicians choosing to not use them at all. The investigators do not want to exclude patients who would otherwise be eligible for the study, based on an outdated technique. However, the investigators are still interested in performing the maneuvers at the test or study injection visit, and collecting that data point, for potential future analysis.
3. Changes to study procedures:
a. The investigators are adding a two week crossover to the study, for patients who do not respond to the arm they initially randomized into and who otherwise could not remain in the study for the required 3 month duration because they need further pain treatment. These patients may still be interested in remaining in the study, but feel unable to continue without further intervention for their pain. This type of crossover is typical in pain studies, and the investigators will adjust the investigators statistical methods accordingly.
b. The investigators are adding the tele-health option to the 1 and 3 month in-person visits in order to maximize patient safety under current COVID-19 suggested social distancing guidelines. The investigators believe this can be done remotely - the two physical examinations can be observed visually and timed by the study team member, and the study team member can read the follow-up surveys aloud to the subject and record their responses.

How does each change described above affect participants? List and number the effects according to the above list.
1. Administrative changes will have no effect on participants.
2. Changes to study design will have no effect on participants.
3. Changes to study procedure: both changes will have no effect on future participants
a: Will affect the one currently enrolled patient - who was already crossed over into the other arm. A deviation report has been filed in conjunction with this amendment.
b: will affect the one currently enrolled patient – the investigators will follow-up with the patient remotely for the patient's 1 and 3 month visit.

Will the modification(s), in the opinion of the local PI, increase or decrease the risk to participants?
Neither

Amendment 2:

What changes are being made? List and number each change, grouping similar changes together.
1. Administrative changes: fixing previous errors and omissions 2. Changes to study design and procedures:
a. The investigator would like to add another inclusion criteria for patients with severe pain (greater or equal to 8 on the NRS scale), where the effect of lidocaine at the test injection may be more limited, so if they experience a clinically meaningful reduction in NRS (at least 2 points) but not necessarily a 50% drop in pain from the NRS scale, they will also qualify for the study
b. The investigators are also amending the SF-12 to include a question regarding the subject's experience with COVID.

Describe the reason for each of the changes described above. List and number the reasons according to the list above.
1. Administrative changes: fixing previous errors and omissions. Primarily, the investigators are explicating the language in the protocol as to who will perform specific duties and follow-up's for better clarity. The investigators are also adding language to the consent forms that was previously omitted, indicating that the 2 in-person follow-ups may be conducted virtually as well.
2. Changes to study design and procedures:
a. The investigators have encountered subjects who due to the severity of their pain (NRS equal to or greater than 8), the test injection of lidocaine may not reduce their pain severity enough to qualify them for the study as under the original inclusion/exclusion criteria. However, the point of the original test injection criteria ("50% or

greater reduction in pain by diagnostic anesthetic block...") is to verify that the pain is indeed originating from the SI joint, and not from another location.
In situations such as the one described above, in cases of severe pain with little NRS reduction after the test block, the pain interventionalist performing the test can verify the pain originates in the SI joint through a combination of factors such as referral and clinical diagnosis of SIJ pain from a back pain specialist (PM&R, Pain Anesthesia, Neurosurgery, Orthopedic Surgery, and Spine Interventional Radiology), patient's medical history, diagnostic maneuvers for localization of pain to the SIJ, as well as clinical judgment.
b. The investigators are also amending the SF-12 to include a question regarding experience with COVID, as some questions are now affected by the COVID-19 pandemic and will help us with analyzing their answer data later.

How does each change described above affect participants? List and number the effects according to the above list.
1. Administrative changes: will have no effect on participants 2. Changes to study design and procedures:
a. Addition of inclusion criteria will have no effect on participants.
b. The addition of an extra question on the SF-12 form will have no effect on participants.

Will the modification(s), in the opinion of the local PI, increase or decrease the risk to participants?
Neither

Amendment 3:

What changes are being made? List and number each change, grouping similar changes together.
1.Administrative Changes: this includes adding a new investigator and correcting previous typos, grammatical errors, and other mistakes/omissions.
2. Changes to study design:
a. The investigators are removing the inclusion criteria of ["In patients with severe pain (>/=8 by NRS) where the effect of lidocaine may be more limited, a clinically meaningful reduction in NRS (at least 2 points) will also qualify for the study"] that was previously added via amendment to the study.
b. The investigators are changing the enrollment goal back to 50.
3. Changes to study procedures:
a. The investigators are removing the two week cross-over arm that was previously added via amendment to the study.
b. The investigators are removing the changes made to the statistical analysis portion that were made following the additions of the two week cross-over arm and the extra pain inclusion criteria.
4. Changes to consent documents - the changes to the consent forms will reflect the above changes listed.

Describe the reason for each of the changes described above. List and number the reasons according to the list above.
1.Administrative Changes – the investigators are adding a study coordinator to the team, and correcting previous typos, grammatical errors, and other mistakes/omissions.
2. Changes to study design:
a. The study team has decided that the addition of the extra pain inclusion criteria was unnecessary.
b. The enrollment goal was changed to 60 following the addition of the two week cross-over arm, to account for the statistical analysis changes that were also made. The cross-over arm is being removed, so the enrollment goal is being changed back to the original goal of 50.
3. Changes to study procedures:
a. The study team has decided that the addition of the cross-over arm was unnecessary and will only delay the trial. Subjects who choose to end the trial and receive a different treatment for their SI pain will be marked as treatment failures.
b. Changes were made to the statistical analysis procedures to account for the additions of the two week cross-over arm and additional pain inclusion criteria to the study. Since the investigators are removing both those previous changes, the investihgators are thus removing the corresponding statistical analysis changes.

4. Changes to consent documents: the changes to the consent documents will reflect the above changes.

How does each change described above affect participants? List and number the effects according to the above list.
1. Administrative Changes will have no effect on participants. 2. Changes to study design:
a. The removal of the severe pain criteria will not affect currently enrolled participants. One participant did qualify for the trial under the severe pain criteria, but was deemed as a treatment failure and already discontinued from the trial.
b. Changing the enrollment goal will not affect currently enrolled participants. 3. Changes to study procedure:
a. The removal of the cross-over arm will not affect currently enrolled participants. Only one participant has crossed over, but was lost to follow-up. All currently enrolled participants who have not yet completed the trial have all passed the two week point and cannot cross-over anymore, so the investigators will not inform them.
b. Changing the statistical analysis procedures will not affect the currently enrolled participants. 4. Changes to consent forms will not affect currently enrolled participants.

Will the modification(s), in the opinion of the local PI, increase or decrease the risk to participants?
Neither