A Double-Blind Randomised Control Trial Investigating the Efficacy of Platelet Rich Plasma versus Placebo for the Treatment of Greater Trochanteric Pain Syndrome

(The HIPPO trial)

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Dedication

I dedicate this work to my wife Alaa and my children Sama and Yamin. Without their love, support, and understanding, I would not have been able to undertake and complete this body of work.

Acknowledgments

I would like to thank Mr. Ajay Malviya and Professor Mike Reed for giving me the opportunity to carry out this work and for their expert advice and guidance. I would like to thank Mr. Ajay Malviya for making this study possible and for believing in me. I would like to thank Dr. Atchia for his guidance and constant encouragement in difficult times. You have provided me with a solid foundation for the future.

My sincere thanks also go to:

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- Gail Waddell and Elizabeth Corbishley, research nurses and friends that brought their passion, attention to detail, and caring attitude to the project.
- The wonderful staff in the R&D department that have been very supportive and looked after me over the years.
- The surgeons and staff of the Department of Trauma and Orthopaedics at Northumbria who hosted the clinical study and made it possible through their support and enthusiasm.

• The participants of this study who gave their time and trust so willingly.

I would like to thank my parents for giving me the tools to make it this far. Finally, my wife, for her unwavering support and patience, I could not have done this without you.

Declaration

This is to certify that the work submitted in this thesis is the result of original research. It has been conducted substantially by me with assistance as outlined below:

The concept of a randomized controlled trial assessing the role of PRP in the treatment of GTPS was conceived by Mr. Ajay Malviya.

The economic evaluation, Study design, the ethical application was conceived by me, Eshan Oderuth, Northumbria healthcare Research and development (R &D) team and designed with the support of Mr. Ajay Malviya.

Data collection, analysis, writing, and general administration were primarily conducted by me with support from Mr. Ajay Malviya.

The statistical planning and analysis were executed with support from Mr. Ajay Malviya.

The study was administered full time by the R &D team and me in the first two years, including recruitment and follow-up of patients and the trial's administrative and clinical governance. In the following years, the R&D team has taken over the recruitment and follow-up of patients.

Supervision of this thesis was undertaken by Prof. Xiao Nong Wang and Mr. Ajay Malviya.

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Statement of Attribution

The role and input of each person contributing to this research are listed below:

Professor. Xiao Nong Wang

Professor. Xiao Nong Wang is a researcher and a lecturer at Newcastle University. She was the university co-supervisor for this Thesis with Mr. Malviya. She also helped me with the drafting and revision of the thesis.

Mr. Ajay Malviya:

Mr. Malviya is a Professor of orthopaedic surgery at Newcastle University and a consultant orthopaedic surgeon at Northumbria NHS Trust. He was the lead university supervisor for this thesis who had responsibility for my day-to-day supervision. He introduced me to the research and development team at North Tyneside General Hospital, and they were able to assist me during the study period. He helped in formulating the study protocol and advancement of the recruitment process. He also helped with the drafting and revision of the thesis and all of the associated publications that derived from this thesis.

Dr. Ismael Atchia:

Dr. Atchia is a consultant rheumatologist at Northumbria NHS Trust. He dedicated a session every week to perform the Platelet-rich plasma injections. He helped formulate the study protocol and advancement of the recruitment process. He also helped with the drafting and revision of the thesis and all of the associated publications that derived from this thesis.

Mr. Eshan Oderuth:

He was the research fellow who proposed this project. He helped formulate the study protocol, obtain ethical approval, and associated publications. Currently, he is a senior orthopaedics trainee at Nottinghamshire.

Ethics Statement

Ethical approval for this study was obtained from the Health Research Authority (HRA). The study was then registered with ClinicalTrials.gov, NCT03479190. Registration was granted on 27 March 2018. Written informed consent was obtained from all subjects before the study. Confidentiality will be respected at all times. All processing of referrals, consent, outcome score sheets, and other physical documentation of patients involved in the study will be conducted within Northumbria Healthcare NHS Foundation Trust, with paperwork kept in secure and locked areas within the research and development department. All work involving data collection and processing using IT systems will be stored on our secure Northumbria NHS Healthcare Trust systems with access and dissemination of these files restricted only to those who require specific access. Within the publication, there will be no patient identifiable data.

Abstract

Introduction: Greater trochanteric pain syndrome (GTPS) is a painful condition that significantly impairs patients' quality of life. The purpose of this clinical trial was to evaluate the effectiveness of ultrasound-guided Leukocyte-rich platelet-rich plasma (LR-PRP) injections in the treatment of GTPS.

Materials and Methods: An ethically approved, adequately powered, double-blinded RCT was conducted to evaluate the clinical outcomes in randomised LR-PRP and Placebo groups using the International Hip Outcome Tool-12 (iHOT12), Visual Analogue Scale (VAS), the modified Harris Hip Score (mHHS), the three-level version of the EuroQol five-dimensional (EQ5D-3L), Minimal Clinically Important Difference (MCID) and the presence or absence of complications.

Results: The final analysis included 78 patients (39 in each group). The iHOT12 and mHHS scores improved significantly from respective baselines in both groups at three-and six-months follow-ups ($P < 0.05$). At the same time, no statistically significant difference was observed between the two groups at both follow-ups ($P > 0.05$). Fourteen patients achieved scores over the iHOT12-MCID in the PRP group and 18 in the placebo group at three months. At six months, fifteen patients achieved over the iHOT12-MCID in the PRP group and 17 in the placebo group. The differences between the groups were not statistically significant at three- and six-months (P 0.482 and P 0.808, respectively). The VAS and EQ5D-3L scores improved from baselines at three and six months in both groups, with no statistically significant difference observed between the two groups ($P > 0.05$). A two-way ANOVA revealed BMI, age and gender had no effect on outcomes. No complications were reported in the two groups.

Conclusions: This superiority trial concluded that both groups achieved statistically significant improvement from baseline; however, there was no significant difference between the two groups. The results did not reject the null hypothesis that LR-PRP is not superior to placebo; hence the routine use of PRP is not justified.

COVID-19 Impact Statement

The health research authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) advised pausing all the trials except the priority1 studies and stopping new screening and recruitment during the Covid-19 pandemic. These decisions were made to reduce the burden on hospitals and keep patients away from hospitals and GP sites where they can catch or transmit the Coronavirus. Add to that; many patients would refuse to come to the hospital and put themself at risk of catching the virus. Subsequently, the recruitment in our study was significantly delayed in 2019, and we had to stop entirely for six months in 2020. These all impacted postponing the submission of my thesis.

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Abbreviations

Abbreviations	Denotations
GTPS	Greater Trochanteric Pain Syndrome
FABER	Flexion, Abduction and External Rotation
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
SWT	Shockwave Therapy
GLoBE	Gluteal La Trobe exercise programme
VAS	Visual Analog Scale
PD-EGF	Platelet-derived Endothelial Growth Factor
PDGF	Platelet-derived Growth Factor
TGF	Transforming Growth Factor
IGF	Insulin-like Growth Factor
VEGF	Vascular Endothelial Growth Factor
BFGF	Basic Fibroblast Growth Factor
PRP	Platelet-Rich Plasma
LR-PRP	leucocyte-rich Platelet-Rich Plasma
LP-PRP	leucocyte-poor Platelet-Rich Plasma
iHOT-12	International Hip Outcome Tool – 12
EQ5D-3L	The Three-level Version of The EuroQol Five-dimensional
mHHS	Modified Harris Hip Score
BMI	Body Mass Index
MCID	Minimal Clinically Important Difference

1. Chapter 1: Introduction

1.1 Greater Trochanteric Pain Syndrome

Greater trochanteric pain syndrome (GTPS), also known as trochanteric bursitis, is a painful condition characterized by pain around the greater trochanter, usually affecting middle-aged women (1). It was first described as trochanteric bursitis in 1958 (2). Further details on the clinical symptoms published in 1978 were pain over the greater trochanter on walking, squatting, or climbing stairs and pain on lying on the affected side or crossing one's legs (3). Few authors described tenderness over the greater trochanter over the insertion of the gluteus tendons (4). GTPS as a term was first used by Karpinski et al. in 1985 instead of trochanteric bursitis as patients did not exhibit typical bursitis signs of swelling, heat, crepitus, or fluctuation (4). This notion has been supported by other studies (5), including a study performed by Bird et al. 2001 evaluated 24 patients using MRI with the clinical picture of GTPS and found that majority of them had gluteus medius tendon pathology with only two patients with trochanteric bursal inflammation (1). Hence, GTPS instead of trochanteric bursitis appears to be the more accurate way of describing the clinical condition, which seems to have multiple facets in its pathology. GTPS has also been associated with low back pain, knee osteoarthritis, and Iliotibial band syndrome. No relation has been found between the occurrence of GTPS and obesity, age or race (5, 6). Raman et al. (7) suggested that GTPS is a commonly misdiagnosed, successfully remediable cause of pain in rheumatoid arthritis (RA) and that specific examination for its presence should be a routine in all patients with RA, especially those with hip pain. Recently Pozzi et al. (8) evaluated the incidence of GTPS in patients who underwent magnetic resonance arthrography of the hip for a suspected femoroacetabular impingement syndrome. They concluded that GTPS was more frequently observed in patients with normal hip morphology than in patients with FAI, particularly in patients under 40 years of age.

GTPS usually settles with conservative treatments such as relative rest and anti-inflammatory medication in most patients (9-11). If traditional measures fail, then progressively more invasive treatment options, including shockwave therapy, corticosteroid injections (CSI), Platelets rich plasma (PRP), and surgery, may be required (12, 13).

1.2 Anatomy

The Greater Trochanter (GT), considered a bony outgrowth or apophysis, is anatomically located in the proximolateral side of the femur, which is just distal to the femoral neck (figure 1).

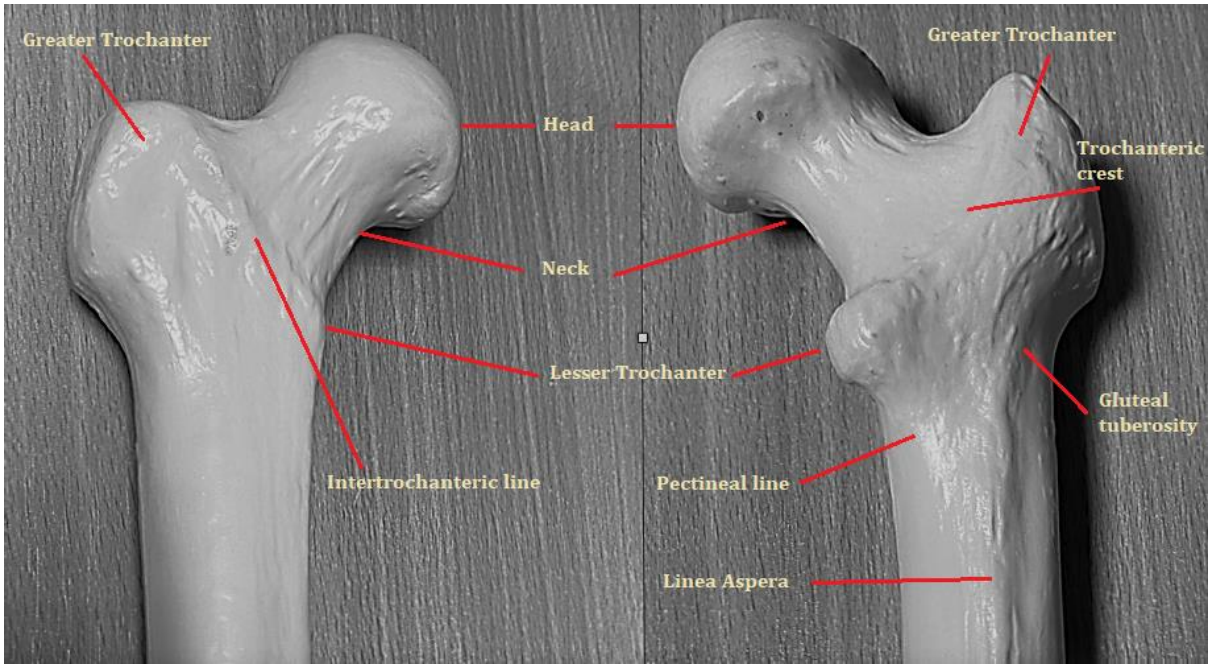

Figure 1: shows the anatomy of the greater trochanter.

The abductor muscles of the hip joint, which include the gluteus medius and gluteus minimus, have their tendons attached to the greater trochanter. Gluteus medius and gluteus minimus muscles originate from the external iliac fossa, with the gluteus medius attaching to the lateral and superolateral facets and the gluteus minimus inserting onto the anterior facet. The medius and minimus muscles are innervated by the superior gluteal nerve which is a purely motor nerve of the lumbosacral plexus that arises from the posterior divisions of L4, L5 and S1. The superior gluteal nerve also supplies the tensor fascia lata muscle which lies over the gluteus medius and gluteus minimus tendons and inserts onto the iliotibial band (14). The gluteus maximus muscle, which is innervated by the inferior gluteal nerve (L5, S1 and S2), increases the tension of the iliotibial band via its iliotibial band attachment and improves the hip joint's passive stability (15). The iliotibial band is also tensioned by the vastus lateralis and the tensor fascia lata and limits hip internal rotation and adduction passively (15). The gluteus medius prevents excessive hip adduction and is commonly considered the pelvis's primary stabilizer (15) (Figure-2).

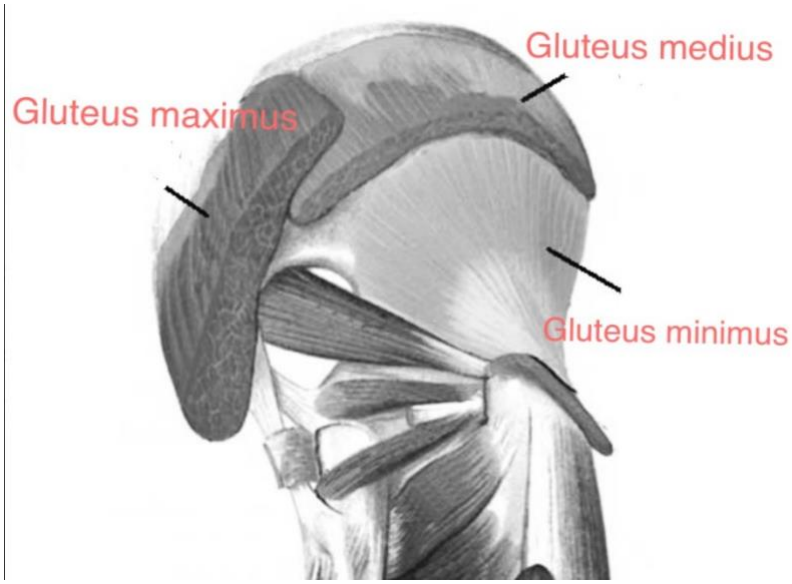

Figure 2: shows the anatomy of the Gluteus muscles.

(The diagram was sourced from https://teachmeanatomy.info/lower-limb/muscles/gluteal-region/)

Bursae are fluid-filled structures that reduce friction between bones and soft tissues (14, 15). The published cadaveric studies describe these bursae' sizes, locations, and numbers (16,17,18). The number of these bursae has been reported to be around six (19). Williams and Cohen, in 2009, highlighted that four of these bursae are consistently present alongside other multiple secondary bursae (9). The three important bursae at the hip include the subgluteus maximus, the subgluteus minimus, and the subgluteus medius bursa (14). The gluteus medius and minimus bursae are innervated by the superior gluteal nerve, while the gluteus maximus bursa is innervated by the inferior gluteal nerve.

On the other hand, the hip joint is supplied by the rami articulares of the Obturator, Femoral, and Sciatic nerves (20). The anatomists have recently discovered a branch of the femoral nerve that supplies the periosteum and bursa of the Greater Trochanter (21, 22). This discovery could be used to improve pain management via interventional denervation of the Greater Trochanter or anatomically guided injections of corticosteroids and local anaesthetics (21, 22).

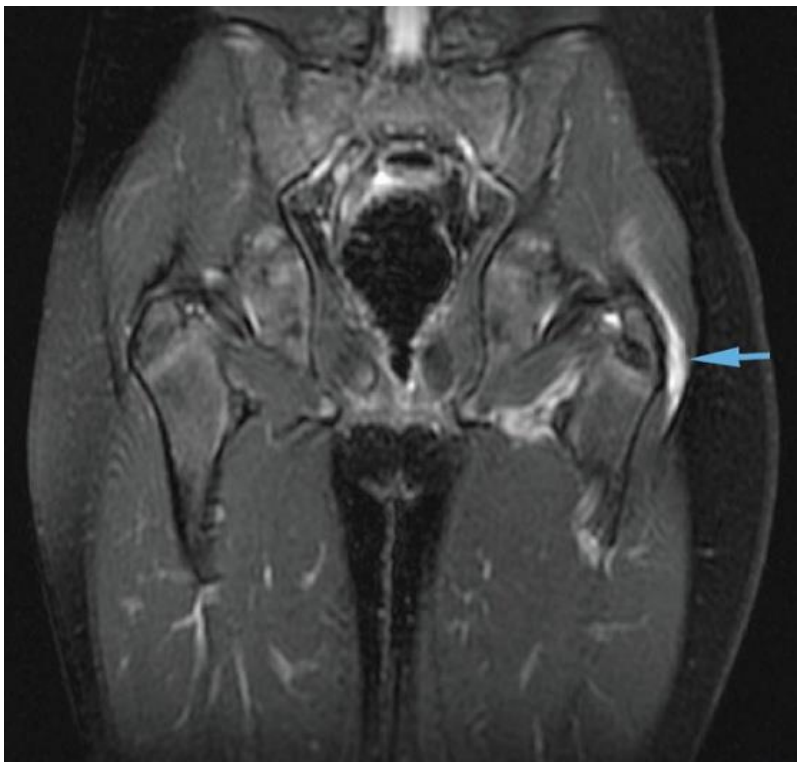

Figure 3: shows an inflamed bursa on MRI scan.

Pfirrmann et al. (14) studied the anatomy around the greater trochanter with magnetic resonance (MR) imaging, bursography, and MR Bursography. They concluded that the bony surface of the Greater Trochanter consists of four facets: anterior, lateral, posterior, and supero-posterior. The Gluteus Medius muscle attaches to the supero-posterior and lateral facets. The Gluteus Minimus muscle attaches to the anterior facet. The trochanteric bursa covered the posterior facet and the lateral insertion of the Gluteus Medius muscle. The Sub-gluteus Medius bursa was located in the superior part of the lateral facet, underneath the Gluteus Medius tendon. The Sub-gluteus Minimus bursa lies in the area of the anterior facet, underneath the Gluteus Minimus tendon, medial and cranial to its insertion, and extends medially, covering the distal anterior part of the hip joint capsule. The trochanteric bursa is delineated with fat on both sides and can be seen on transverse unenhanced T1-weighted images as a fine line curving around the posterior part of the trochanter (figure 3). Westacott et al. (23) conducted a systematic review to assess the accuracy of magnetic resonance imaging and ultrasonography in diagnosing gluteal tendon tears in patients with persistent lateral hip pain or Greater Trochanteric Pain Syndrome (GTPS). He found that MRI had a sensitivity of 33-100%, specificity of 92-100%, a positive predictive value of 71-100%, and a negative predictive value of 50%. False positives were common. The high signal

located superior to the trochanter had a stronger association with tears. Ultrasonography had a 79-100% sensitivity and a 95-100% positive predictive value. They suggested that ultrasonography may prove to be the investigation of choice, despite being an operator-dependent procedure. Blankenbaker et al. (24) conducted a study to determine whether the MR findings of peri-trochanteric fluid or hip abductor tendon pathology correlate with GTPS. They retrospectively reviewed MR examinations of 256 consecutive hips for T2 peri-trochanteric signal and abductor tendon abnormalities without knowing the clinical symptoms. They concluded that patients with trochanteric pain syndrome always have peri trochanteric T2 abnormalities and are significantly more likely to have abductor tendinopathy on magnetic resonance imaging. However, although the absence of peri trochanteric T2 MR abnormalities makes GTPS unlikely, detecting these abnormalities on MRI is a poor predictor of GTPS as these changes are present in a high percentage of patients without trochanteric pain.

1.3 Aetiology and Pathomechanics

Tendinopathy is a degeneration of the collagen protein that forms the tendon. Tendinopathies, as well as tendonitis, are often due to overuse of a tendon or sudden stress on a tendon. Add to that, aging and lack of muscle tone can also participate in the progression of tendinopathy. Tendinopathy and tears of the gluteus medius and minimus tendons can be possible causes of greater trochanteric pain syndrome. Add to that, GTPS is thought to develop from friction of the ITB over the greater trochanter, leading to regional microtrauma with overuse. The exact mechanism of tendinopathy is still unknown; however, it is thought to be multifactorial. These factors include overuse of tendons, mechanical overload, incomplete or failed healing, and compression of the tendon at the enthesis is another possible cause of insertional tendinopathies (25, 26). A combination of high tensile loads and excessive compression is thought to be the most detrimental factors (25). As anti-inflammatory medications are largely unsuccessful in the treatment of this condition, and with the increase in histopathological data showing degenerative changes but little inflammation, the inflammatory hypothesis in overuse tendon injury became decreasingly popular (27). The term “tendonitis” became increasingly replaced by “tendinosis” (27), but a definitive diagnosis of either should only be made following histopathological confirmation (27).

However, it became evident that tendon biopsies from operated patients were likely to represent the end stage of a pathological continuum (28), probably demonstrating a different histopathological picture to that which would be seen in the initial stages of injury. This was supported by evidence from human and animal biopsies that showed that both peritendinitis and a failed healing response, wrongly labelled “tendinosis,” could be present concurrently (27).

In tendinopathic lesions, the parallel orientation of collagen fibres is lost, with a decrease in collagen fibre diameter and in the overall density of collagen. Collagen micro tears may also occur and may be surrounded by erythrocytes, fibrin, and fibronectin deposits. Normally, collagen fibres in tendons are tightly bundled in a parallel fashion. In tendinopathic samples, there is unequal and irregular crimping, loosening, and increased waviness of collagen fibres, with an increase in type III (reparative) collagen (27). Vascularity is typically increased, and blood vessels are randomly oriented, sometimes perpendicular to collagen fibres. Inflammatory lesions and granulation tissue are infrequent and, when found, are associated with partial rupture: therefore, tenocytes are abnormally plentiful in some areas (28).

Tendinopathies are common in elite and recreational athletes and are traditionally considered overuse injuries, involving excessive tensile loading and subsequent breakdown of the loaded tendon (27). Although acute traumatic conditions such as ligament and muscle tears receive much attention in the lay press, tendinopathies account for much of the lost time in practice and competition (27).

Biopsy studies have shown that classic inflammatory changes are not frequently seen in chronic tendon conditions and that histopathology features in tendinopathic tendons are clearly different from normal tendons according to Domb et al. (26), up to 25% of middle-aged females and 10% of middle-aged males have gluteus medius tears. Tears can be acute, but degenerative tears are far more common, with the gluteus medius tendon being most frequently affected. These tears at the gluteus medius tendon insertion can be complete, intra-substance, or partial, with partial tears occurring most frequently (29, 30). When the hip abductors are weaker than normal, particularly gluteus medius, increased adduction on the hip is found to cause increased compression of the gluteus medius and minimus tendons at the greater trochanter. With the increased adduction, the iliotibial band exerts higher compressive forces on the gluteal tendons, amplifying the compression (30). Furthermore, higher degrees of hip flexion may also increase the compression of the gluteus medius and

minimus tendons due to increased tension in the iliotibial band. This compression would explain the occurrence of pain with prolonged sitting (25).

Kummer in 1993 suggested that pelvic control in a single leg stance position was mainly controlled by the abductors (70%) while the iliotibial band tensioners (gluteus maximus, tensor fascia Lata, and vastus lateralis) accounted for the remaining 30% (31). It has also been shown that people with gluteal tendinopathy commonly develop gluteus medius and minimus atrophy and hypertrophy of the tensor fascia Lata. The changes of muscle bulk alongside the weakness significantly impact the balance of the abductor mechanism and increase the compression of the gluteal tendons (31). It is postulated that females are more susceptible to GTPS due to pelvic biomechanics, activity levels, and hormonal effects (14). Some authors have suggested that females have a more petite gluteus medius tendon insertion, resulting in a smaller area that could dissipate tensile load. Add to that, it makes the moment arm shorter, causing reduced mechanical efficiency (32).

1.4 Diagnosis of greater trochanteric pain syndrome

1.4.1 Clinical diagnosis

No single test can be used alone to diagnose greater trochanteric pain syndrome, and available tests have limited validity when used alone. A combination of tests, on the other hand, can increase diagnostic accuracy (33). GTPS, when diagnosed based on clinical features, and medical history, the evaluation must include the following:

- Subjective assessment to collect necessary details, such as medical history and clinical features.
- Hip examination: It is often characterised by the 'jump' sign where palpation of the greater trochanter causes the patient to nearly jump off the bed (33).
- Specific tests to confirm or rule out the suspected diagnosis of GTPS, such as FABER, greater trochanter palpation, examination of resisted external derotation, and resisted abduction (33). These tests are detailed below:

1-Trendelenburg test:

This test is used to examine the function of the hip abductor muscle and to decide whether the hip abductor muscle is damaged or torn. The reduction in height of the pelvis on the contralateral side shows a weakness of the stance leg's hip abductors, indicating a positive result (34). In this test, the patient is asked to stand on one leg without leaning to one side the patient can hold onto something if balance is an issue. The clinician observes the patient

to see if the pelvis stays level during the single-leg stance. A positive Trendelenburg test is indicated if during unilateral weight bearing the pelvis drops toward the unsupported side, which can be due to pain, gluteal muscle weakness, or a hip deformity (figure 4).

Figure 4: shows the Trendelenburg test.

2-**FABER Test:**

FABER or Patrick's test includes flexion, abduction, and external rotation and helps diagnose GTPS and hip OA, as illustrated in (figure 5). These three movements combined result in a clinical pain provocation test to assist in diagnosing pathologies at the hip, lumbar, and

sacroiliac region. The test evaluates the hip joint as the forces being transferred through the joint. The position of flexion, abduction, and external rotation, when combined with overpressure, stresses the femoral-acetabular joint and produces pain if irritated. Hence it helps rule out intra-articular pathologies (35).

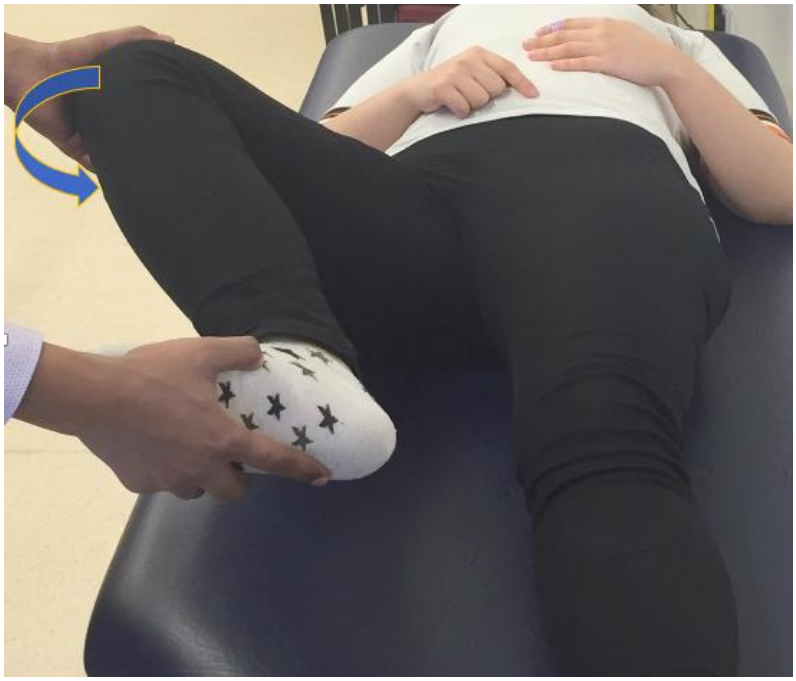

Figure 5: shows the FABER or Patrick's test.

3-Noble's and Ober's tests for iliotibial band assessment:

Noble's test can help differentiate the iliotibial tightness from other causes of lateral knee pain, including bicipital or popliteal tendinopathy, lateral collateral ligament strain, knee Osteoarthritis, and lateral meniscal abnormality (35). Traditionally, the Ober's test was utilised to determine whether or not an individual has TFL or ITB. In Ober's test the patient is lying on the good side, close to the edge of the couch on the unaffected leg with hip and knee flexed to 90°. The examiner stands behind the patient, stabilizes the patient's pelvis with one hand, and with the other hand, holds the medial side of the affected knee (figure 6). The examiner flexes the affected knee to a 5° angle, then fully abducts the tested leg. The examiner then allows the force of gravity to adduct the tested leg (without rotating) until the hip cannot adduct any further. If the thigh movement is less than 10 degrees, the result is considered positive (35). If the affected leg remains abducted and does not lower, the test is deemed to be positive. Gautam et al (36) described a new test for estimating iliotibial

band contracture as Ober's test was deemed unreliable and cannot determine the degree of contracture. In Gautam's test, the patient is placed in a prone position on a flat surface. The examiner stands on the side opposite to the limb being assessed and holds the leg near the ankle with one hand, placing it in maximum abduction at the hip. With the other hand, pressure is applied to the affected buttock to flatten the pelvis and correct any flexion deformity at the hip. The latter is maintained in neutral rotation with the knee in 90° of flexion. The hip is then gradually adducted until a firm endpoint is reached, with pressure maintained on the buttock to prevent the pelvis from lifting. The angle of abduction of the thigh in relation to the vertical axis of the body is then a quantitative assessment of the contracture of the iliotibial band.

Figure 6: shows the Ober's test.

4-Renne's Test:

This test can be used separately or combined with Noble's Compression Test to determine Iliotibial band syndrome (ITB) (35). In this test, the examiner asks the patient to put his hand on the examiner's shoulder for balance, and slowly squat one-legged to about 75° flexion and then rise back up. First, the examiner will palpate the ITB just above the lateral femoral epicondyle, then have the patient squat and stand up a second time while the examiner is applying firm pressure. This test should reproduce the patient's symptoms and help rule out GTPS.

5-Single-leg stance (SLS) test (30 seconds):

In this test, the patients stand on one leg for 30 seconds with their fingers on the wall and eyes open. When the patients raise their foot off the floor, the 30 seconds begins. On SLS 30 seconds, tender palpation of greater trochanter pain suggests GTPS. Keep the spot, according to Grimaldi and Fearon, before symptoms reappear (35, 37).

6-Resisted External derotation test and modified external derotation test:

During this test, the patient's hip is given a flexion up to 90 degrees with outward rotation in neutral adduction/abduction. External rotation is slightly reduced to minimize tendon compression. The patient is asked to deliberately give rotation to the leg to neutral against the examiner's resistance. With absolute hip abduction, the adjusted test is conducted the same way (35, 37). This position usually is intolerable for patients with Greater Trochanteric pain syndrome. The test result is deemed positive when the usual pain is reproduced. If the effect is negative, the test can be performed in the prone position with the hip held in extension and the knee flexed at 90 degrees (figure 7). The patient normally points to the trochanteric area and it is tender on deep palpation.

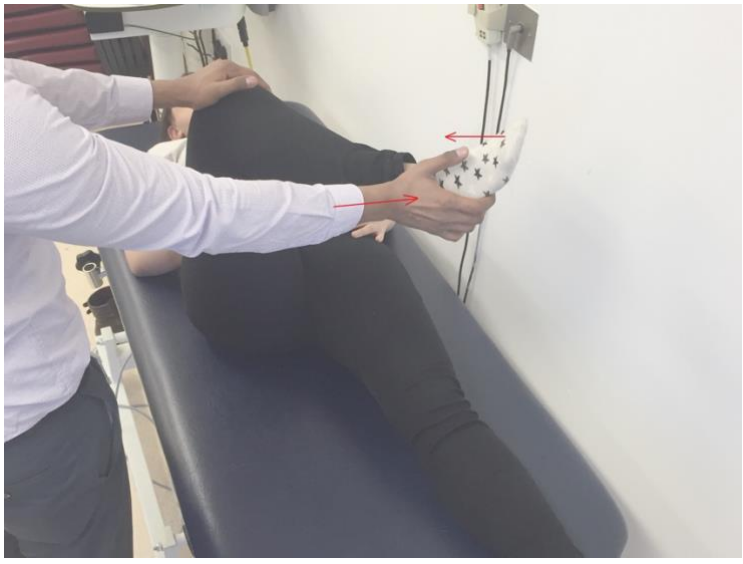

Figure 7: shows the Resisted external derotation test.

7-Resisted abduction test:

This test is 73% sensitive and 87% specific for Gluteus Medius pathology. During this test, the examining limb is passively abducted to 45°. Against the examiner's resistance, the patient retains his position. The opposition is applied 1cm above the lateral malleolus (35, 38).

8-Resisted internal rotation test:

This test is 88% accurate in diagnosing Gluteus Medius tears, with a sensitivity of 92% and a specificity of 85%. During this test, the patient is supinely positioned with the examining limb in 90 degrees flexion of hip and knee and 10 degrees external hip rotation. Against the examiner's pressure, the patient performs active hip rotation. The test is considered positive if the patient feels pain, weakness, or discomfort (39, 40).

1.4.2 Radiological Diagnosis

The plain x-ray findings are usually non-conclusive with symptomatic patients of GTPS. X-rays are considered the first-line test in the differential diagnosis of other causes of the symptoms, including femoroacetabular impingement, OA, fractures, avulsion, and stress injuries (41). Calcification next to the greater trochanter are observed in up to 40% of GTPS patients. These are generally insertional tendinopathic calcific deposits rather than bursal calcification. Chronic GTPS patients can develop trochanteric exostoses or osteophytes (41). Ultrasound is a simple, responsive, affordable, radiation-free, and safe diagnostic study for peri-trochanteric anomalies with a high positive predictive value (42). The combination of modern software and high-frequency probes are very successful in assessing the gluteal tendons. This combination can be considered as an outstanding first or second-line imaging test. In tendinopathy, the fibrillary architecture loss and thickening of gluteal tendons, can be easily detected (42). Ultrasonography can show tendon hypo-echogenicity or increased vascularity, which are associated with tendinopathy. Hypo-echogenic tissues reflect relatively few of the US waves and appear dark grey on the scan. Intratendinous hypoechoic or anechoic foci or tendinous contour detects partial-thickness tears, while a 'bald' facet shows a full-thickness tear (42). An increase in colour Doppler flow is a sign of inflammatory neovascularity; however, it is not common. The deep and anterior parts of the gluteus medius tendon are deemed to be more prone to tendinopathy and partial tears. Ultrasound facilitates image-guided aspiration and injection of calcific gluteal tendinopathy, which is more reliably diagnosed than MRI. In the case of bursitis, distension of fluid in the

trochanteric bursa induces a crescent-like anechoic or hypoechoic collection deep in the gluteus maximus tendon. Dynamic ultrasound can be used to correlate the audible 'snap' with the snapping ITB movement from a posterior to the anterior location around the greater trochanter during hip flexion (42).

MRI (Magnetic Resonance Imaging) with High-resolution Multiplanar visualisation can be used to determine the greater trochanter facetal anatomy and insertion of a tendon (43). The fluid inside the trochanteric bursae is determined more accurately and can appreciate various trochanteric bursae anatomy. The axial and coronal planes are more accurate for evaluating the gluteus minimus and gluteus medius tendon as well as lateral attachments of obturator internus and externus, and piriformis. In contrast, the sagittal and coronal planes are best to assess the gluteus medius tendon superolateral attachment. In para-tendinopathy, T2-weighted signal hyperintensity surrounds the normal and an intact hypointense tendon, which is consistent with fluid distension of paratendinous soft tissue (43). Tendinopathy most commonly affects the gluteus medius tendon, which is described as thickening of the tendon or intra-substance T2-weighted signal hyperintensity within the intact tendon. Secondary characteristics of gluteal tendinopathy include calcification at the tendon attachment and greater trochanter bony cortical irregularity.

We may also differentiate between partial and full-thickness tendon tears with MRI. A partial-thickness tear involves the absence of intact tendon fibres in a focal/partial field. The deep and superficial surface of the tendon, a longitudinal split or intra-substance defect filled with fluid or granulation tissue, may be affected (43). Similar to ultrasound, total tendon discontinuity and a 'bald' insertional facet define a full-thickness tendon tear on MRI. In the elderly female population, a full-thickness and partial-width tendon tear are less common, and the avulsion of the tendon with a small bony fragment is more common (42). A tendon tear is also followed by more than 2 cm lengthening between the gluteus medius insertion and musculotendinous junction. A noticeable lengthening of the tendon occurs due to atrophy in contrast to the normal contralateral side. At the anterior and lateral facets junction, tears affecting the gluteus minimus and neighbouring third anterior fibres of the gluteus medius tendon are common.

When researchers compared the results of MRI in GTPS to intraoperative pathological findings, they discovered that MRI is a very sensitive tool of diagnosis (43). On the other hand, symptomatic patients have had similar MRI abnormalities, suggesting that these

findings aren't fully specific. In diagnosing tears in the gluteus minimus and medius tendons, ultrasound is more sensitive, having a positive predictive value of 1.0 (41, 42). According to a comparison study between MRI and plain x-ray in patients with GTPS, irregularities of more than 2 mm in greater trochanter surface observed on plain x-ray were related with gluteal tendon abnormalities and peri-tendinous oedema observed on MRI. Since MRI is expensive and rare in GTPS, it is usually reserved for patients who have failed to respond to conservative measures and have been referred to a specialist (44).

1.5 Treatment

Currently, the treatment ladder for GTPS consists of conservative measures such as physiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs) (45). Most patients will settle with conservative management; however, if this fails, then more invasive treatment options include shockwave therapy and corticosteroid injections. These second-line treatments are essential in preventing the need for surgery as a last resort (46, 47, 48).

1.5.1 Physiotherapy

The initial approach to treat Greater trochanteric pain syndrome includes a range of conservative interventions such as physiotherapy. The physiotherapist can combine exercises with local corticosteroid injection, PRP injection, shockwave therapy (SWT), activity modification, anti-inflammatory medications, and weight reduction (49). Only a few studies discussed the use of physiotherapy as a treatment for GTPS (49-52).

The physiotherapist usually prescribes a home exercise regimen for the patient, emphasizing the importance of stretching the iliotibial band, tensor fasciae lata, spine external rotators, quadriceps, and hip flexors. Regular face-to-face follow-up sessions usually accompany this to assess progression and compliance with the exercise regimen. Also, the physiotherapist should carefully control the stretching exercises to avoid the exacerbation of GTPS. Gradual involvement in sporting events should be part of the physiotherapy program. To prevent a recurrence of GTPS, patients should continue the exercise program at home (52).

Exercise should be recommended from the beginning of tendinopathy therapy, with four main key objectives. These objectives include load management, reducing compressive forces, Gluteal muscle strengthening, and managing the co-morbidities. Gradual loading is generally required in gluteal tendinopathy to recondition the tendon and make it load tolerant. During the early recovery phase, incremental tensile loading exercises should be started (37). Strengthening would be important for patients with gluteal tendon tear to

achieve optimum function and increase the tensile strength of the healing tissue. Gluteus medius has been found to activate better in weight-bearing positions than in non-weight-bearing positions (37). Strengthening the hip abductors, as well as the central and lumbopelvic stabilisers, is recommended (37).

External coxa saltans patients may have a problem due to increased stress or imbalances, requiring neuromuscular control modifications. This is achieved by performing conditioning with or without motor control exercises. Patients can do these exercises with a fair amount of effort and few repetitions. It's a good sign that the tendon is responding to exercise if night pain in gluteal tendinopathy patients improves. It might be a warning that the patient is carrying too much weight if their night pain gets worse (37).

Ganderton et al. (2018) (51) recruited 94 post-menopausal women with GTPS. They were split into two groups, with each receiving instruction on modifying their activities and reducing those that are thought to cause tendon compression. The Gluteal La Trobe exercise programme (GLoBE) was also used in one group, whereas a fake exercise intervention was used in the other. From baseline through the 12- and 52-week time points, both groups improved considerably in all metrics (save the sports component of one questionnaire). There were no changes between the groups who received either sham workouts or the GLoBE glute and kinetic chain loading programme. Responders with a global rating of change of plus five or higher were subjected to a responder analysis. There were differences between the groups in this subgroup (approximately half of each group), with the GLoBE intervention doing better in most outcome measures at both the 12- and 52-week time points. It is also worth noting that by the 52-week mark, nearly half of the trial participants had not improved in terms of pain.

Mellor et al. (52) compared education and exercise with corticosteroid injection (CSI) and a 'wait and see' group. Participants were 35 to 70 years old and had been suffering from lateral hip discomfort for at least three months, with a pain level of at least four out of ten and a clinical diagnosis of GT based on clinical testing and MRI data. A total of 204 people were studied, with 167 of them being women and an average age of 54.8 years. The education plus exercise group received 14 physiotherapy sessions over eight weeks, with a progressive rehab programme to improve gluteal musculotendinous unit load capacity and education focused on avoiding painful compressive movements. The corticosteroid group

received one ultrasound-guided injection, while the 'wait and see' received one consultation with a physiotherapist who discussed GT, risk factors, continued activity, and prognosis.

Global rating of change in hip condition (on an 11-point numerical scale ranging from "very much better" to "very much worse") and hip pain severity were the primary end measures in this study (the average amount on an 11-point scale from 0 to 10 with no pain at 0 and 10 being the worst pain). The VISA-G questionnaire, the patient-specific function scale, and Hip Abductor Muscle Strength tests were used as secondary end measures. Education and exercise performed better than steroid injections and a wait-and-see approach for gluteal tendinopathy. At the 8-week mark, education and exercise had a global rating of the change success rate of 77.3 percent, which was higher than both the CSI (58.5%) and the wait-and-see groups (29.4%). At eight weeks, the education and exercise group had much lower hip pain intensity, casting doubt on the commonly held belief that CSI is superior for pain alleviation in the short term. The global evaluation of change in the education and exercise group remained much higher than the other groups at 52 weeks, with a success rate of 78.6 percent compared to 58.3 percent and 51.9 percent for the CSI and wait and see groups, respectively. At this point, the steroid injection group's success rate did not differ significantly from the 'wait and see' technique. It is worth noting that over half of the gluteal tendinopathy patients in this trial had a successful outcome in terms of global rating of change after a year without treatment, even though both education and exercise and the CSI group reported decreased pain at this time. Also, worth noting is that, while education and exercise had a higher global rating of change than the injection, there was no significant difference in pain severity after one year (although both groups remained better than the waiting list). Education and exercise appear to be superior to the CSI group in secondary outcomes at eight weeks. At 52 weeks, the education and exercise group had less frequent pain but no other differences in secondary outcomes from the CSI group.

Transcutaneous electrical nerve stimulation (TENS) cross-frictions and low-level laser have not been assessed properly for GTPS. Ice and heat have been suggested for pain management, but there is limited supporting evidence and there are no studies proving the effectiveness of ultrasound (45, 46, 53).

1.5.2 Infiltration

Corticosteroid injection is an established second-line treatment for GTPS that is efficacious but not necessarily long-term, as reported by a randomised study comparing steroids to

other treatment modalities (47). This notion has been supported by numerous reviews of GTPS management (47, 48). Infiltration of corticosteroids and local anaesthetic into the region of the bursa and tendon insertions of the lateral hip can relieve pain in 60–100% of cases when conservative treatment fails (54, 55). Corticosteroids Infiltration has been used in the treatment of GTPS since the 1960s (56). This method seems to be successful in the short term (54, 55, 56), and several authors consider this strategy a valuable alternative for treating GTPS (57-61).

A randomised clinical trial (62) found that infiltrating patients with GTPS with corticosteroids and lidocaine was successful and had a long-term effect. A lack of prompt response to corticosteroid infiltration, on the other hand, should prompt the clinician to consider another diagnosis. While bursitis is not the cause of GTPS, most patients experience some relief in the medium term after corticosteroids and a local anaesthetic are injected into the trochanteric bursa (63). In 49–100% of cases, using corticosteroid infiltration as the primary treatment, symptoms are resolved, and the patient may return to prior activities, with no need for multimodal conservative therapy (63). The majority of patients only need one infiltration, but up to 33% need a second, and some need as many as five (63). Many of the studies used a combination of corticosteroids and local anaesthetics, except for one, which used only methylprednisolone or triamcinolone. A single infiltration was given in three studies that used the visual analog scale (VAS); the authors found a mean improvement of 2.8 (63). Ege Rasmussen and Fan (54) investigated 36 GTPS patients who had a corticosteroid infiltration and found that 24 of them had outstanding outcomes after one or two infiltrations. The patients' health improved in the remaining cases, though nine had a relapse over the next two years. According to researchers, corticosteroid infiltration was associated with a lower percentage of chronic pain and was predictive of improvement at five years. The patient's reaction to the local infiltration also assists in the diagnosis (64). Other factors (e.g., the involvement of other bursae, tendinitis, incorrect diagnosis, improper needle placement during infiltration, or recurrence of symptoms) may explain the lack of response to the infiltration (65).

1.5.3 Low-energy extracorporeal Shock wave therapy (SWT)

Shock wave therapy has been utilised effectively since the late 1980s for the treatment of different musculoskeletal pathologies, including Achilles tendinopathy, plantar fasciopathy, shoulder calcific-tendinitis, and elbow epicondylitis (66). The theories of action of Shock

wave therapy are not yet fully understood. Many ways have been described in explaining Shock wave effects. These include healing stimulation, possibly by stimulating cellular activity and increasing blood flow (66). Add to that neovascularisation, direct suppressive effects on nociceptors, and a hyperstimulation mechanism that would hinder the gate-control system. Although extracorporeal shock wave therapy has been clinically applied to treat tendinopathy for more than ten years, relatively few research studies were conducted to see how it affects the tendon at the cellular level. Researchers are working nowadays to understand the cellular and biochemical mechanisms by which SWT can enhance tendon repair (67). Initially, based on earlier studies, authors advocated that high-energy shock wave treatment can bring about fibrinoid necrosis, paratenon fibrosis, and inflammatory cell infiltration in normal tendons, as well as an impaired tensile strength of tendons (68). More contemporary studies have shown that shock wave treatment can prosper the number of new vessels at the normal tendon-bone junction (69). This occurs through the release of growth factors and some other active substances (70).

Mani-Babu et al in their systematic review reported variable outcomes for this treatment modality. Recent clinical trials reported improved results in the tendinopathy group (71) and in particular for GTPS. There are different treatment protocols for Shock wave therapy based on energy density, frequency of shockwaves, and the number of sessions (71). Some authors highlighted that low-energy shock wave therapy is an effective treatment for chronic GTPS, and its effect can last more than 12 months (71). Furthermore, Furia et al in a cohort study reported significant improvement with repetitive low-energy shock wave therapy compared to CSI at four months (72).

Nevertheless, the published evidence on the uses of shock wave therapy in Greater trochanteric pain syndrome is limited and of moderate methodological quality. The published studies are heterogeneous, showing many variables, including wave type (focal or radial), intensity per shock wave, frequency of the shock waves, kind of shock wave therapy generator, and the overall treatment protocol. Hence comparison of results is therefore tricky.

1.5.4 Foot orthotics

The main idea of using foot orthotics in treating GTPS is to address any biomechanical faults in the legs or feet that can precipitate any inflammation or tendinopathy (73). The only study that was published about foot orthotics was by Ferrari et al. (74). They conducted cohort-

controlled research with 68 participants involved to assess the effect of customised foot orthotics versus corticosteroid injections for trochanteric bursitis. After four months, most of the orthotic group (90%) and less than half of the injection group (40%) reported recovery. Ferrari et al.'s study concluded that for patients with acute or subacute GTPS, adding custom-made foot orthotics to local corticosteroid injection appears to improve the short- and long-term outcome, with fewer recurrences. This study, however, has a number of limitations. First, it was not a randomized controlled study. There could be a number of factors that affected the observed outcomes, including subject characteristics not measured, producing a selection bias. The author was involved in the care of the subjects. It is possible that the primary care physicians learned of the subject's use of orthotics, and this may have influenced how they treated the subjects, thus affecting outcomes. It is also possible that there was a selection bias caused by practitioner style and treatments between the 2 groups because the subjects were from 2 clinics. At the same time, the author was involved in the clinical care in all subjects as was, in some cases, the same primary care physician.

1.5.5 Platelet Rich Plasma (PRP)

What is PRP?

The platelet is a small, anucleated cell that originally derives from the hematopoietic lineage via the megakaryocyte. The production of platelets from megakaryocytes is a systematic and regulated process that is thought to occur either in the bone marrow or, as has been shown more recently, the lung (75). Due in large part to the extreme shear forces, the platelet is exposed to in the vessel as well as the limitations imposed on the platelet due to the absence of a nucleus; the lifespan of the platelet is limited to between 5 to 7 days following formation and separation from the megakaryocyte. While several labs have recently demonstrated that it is possible for the platelet to split into several smaller functional platelets under certain experimental conditions by utilizing the transcription machinery within the platelet, this process has rarely been observed outside of controlled conditions in the lab, and its importance in normal physiology of the vessel remains unclear (76). During its normal life cycle, platelets decrease in size such that young platelets are measurably larger than older platelets. At the end of their life in the vessel or following full activation of the platelet and incorporation into a forming clot in the vessel, they are removed from the vessel by neutrophils and macrophages and transported to the spleen for removal from the body.

PRP is an autologous blood product postulated to promote healing in damaged or inflamed tissues, including muscles, ligaments, bones, and tendons (77). Platelets contain a variety of elements, including growth factors and cytokines which are involved in tissue healing. These include PD-EGF, PDGF, TGF, IGF, VEGF and bFGF (platelet-derived endothelial growth factor, platelet-derived growth factor, transforming growth factor, insulin-like growth factor, vascular endothelial growth factor and basic fibroblast growth factor, respectively (77). These growth factors are present in the processes of tissue injury, inflammation, and repair. Therefore, the theory is: the higher the concentration of platelets, the more growth factors there will be present to promote the healing process when administered directly to the area of interest. (77). PRP has been applied in other fields of medicine, including regenerative therapies in oral and maxillofacial surgery (78-79). Over the past decade or so, there have been numerous studies of PRP's efficacy in treating inflammatory musculoskeletal conditions similar in pathology to GTPS with such as lateral epicondylitis, patellar tendinitis, rotator cuff pathology, Achilles tendinopathy, and plantar fasciopathy. Several authors have collectively reviewed this with reports of mixed efficacy compared to standard treatments for these conditions, with the most promise shown in plantar fasciopathy and patellar tendinitis (80-83). These reviews all mention the lack of evidence to fully support or reject PRP's efficacy in these conditions, except for Achilles tendinopathy, where PRP showed no difference compared with placebo in a randomised study. PRP's healing or regenerative properties have shown promise in other areas of orthopaedics, such as cartilage pathology (80-83).

The RCT by Boesen et al (84) included 40 males with an acute Achilles tendon rupture 38 of which was followed for 12 months. Outcomes included the self-reported Achilles tendon Total Rupture Score (ATRS) as well as heel-rise work, heel-rise height, tendon elongation, calf circumference, and ankle dorsiflexion range of motion. The mean ATRS score improved in both groups at all-time points ($P < .001$), but there was no difference between the groups at any time points (12 months: 90.1 points in PRP group and 88.8 points in placebo group). No differences in all functional outcomes at any time points were seen between the groups. At 12 months, the injured leg did not reach normal functional values compared with the uninjured leg. Boesen et al concluded that the use of PRP in non-surgically treated Achilles tendon injuries did not result in any superior clinical and functional improvement. Furthermore Vos et al (85) conducted an RCT comparing eccentric exercise with PRP versus eccentric exercise with saline injection (placebo). They concluded that PRP injection compared with a saline injection did not result in greater improvement in pain and activity.

Principles and Methods of Preparation of Platelet-Rich Plasma:

The main process of preparing PRP is known as differential centrifugation. In this process, acceleration force is adjusted to sediment certain cellular constituents based on different specific gravity (86, 87). Within this process, researchers commonly use two different methods, which are the PRP and the buffy-coat methods.

In the PRP method, researchers perform initial centrifugation to separate red blood cells (RBC), then second centrifugation is done to concentrate platelets suspended in the smallest final plasma volume (figure 8).

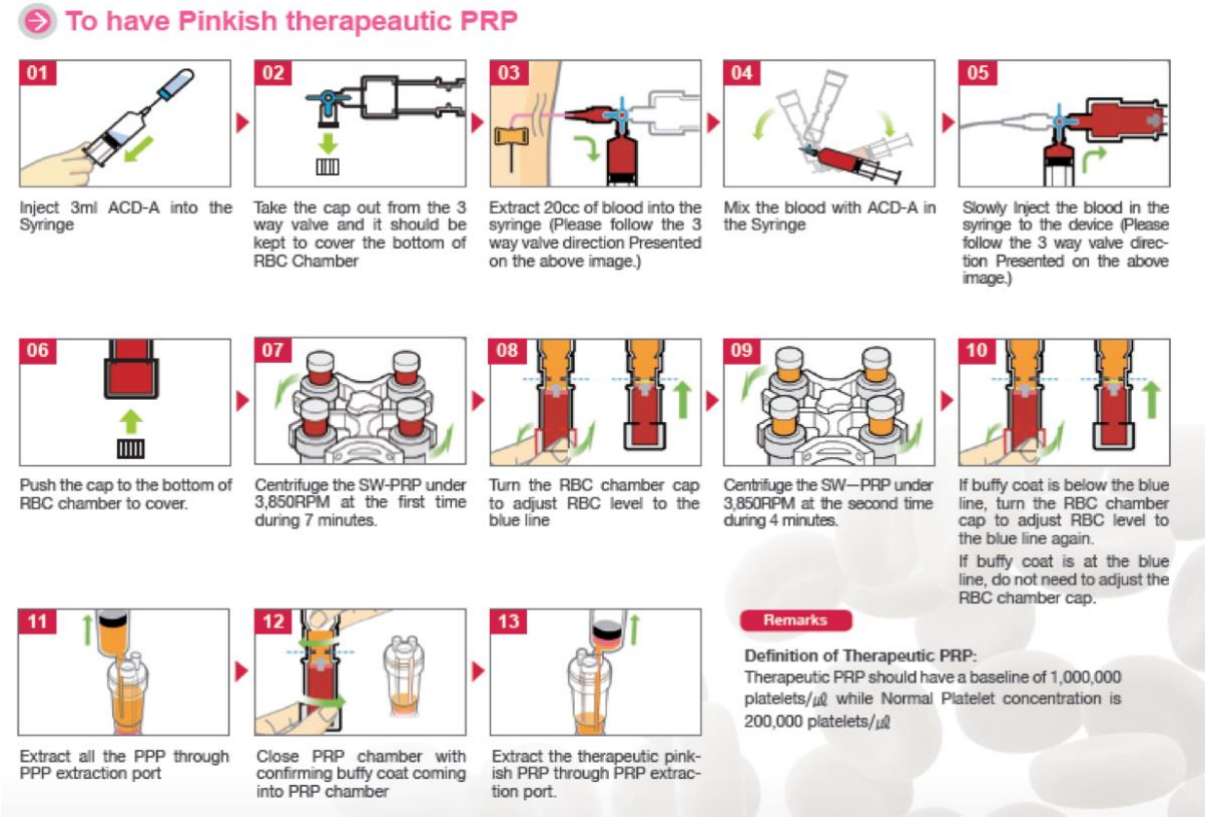

Figure 8: shows the PRP preparation steps using the NTL Biologica system.

This figure describes a double centrifugation process of PRP. Whole blood is first collected in Syringes that contain Acid-citrate-dextrose anticoagulant (ACDA). The first spin step is conducted at a steady acceleration to separate RBCs from the remaining whole blood volume. Following this, the entire blood splits up into three layers: an upper layer that mainly contains platelets and white blood cells, a thin intermediate layer that is known as the buffy coat and that is rich in white blood cells, and a bottom layer that consists mainly of red blood cells. In order to obtain a leucocyte-rich PRP (LR-PRP), the upper layer, the whole

layer of buffy coat and a few RBCs are transferred. The second spin is then performed to allow the formation of soft pellets (erythrocyte-platelet) at the bottom of the tube. The top part of the fluid that is composed chiefly of leucocyte -poor platelet rich plasma (LP-PRP) is extracted. Pellets are uniformed in the lower third to formulate the Platelet-Rich Plasma. In the buffy coat method, whole blood is centrifuged at a 'high speed' with subsequent buffy coat collection.

The term "activation" refers to 2 key processes that are initiated during PRP preparation: (1) degranulation of platelets to release GFs from α-granules and (2) fibrinogen cleavage to initiate matrix formation, a clotting process which allows the formation of a platelet gel, and therefore to confine the secretion of molecules to the chosen site (88). An activation step before PRP administration is included in many of the protocols used, commonly by adding thrombin and/or calcium chloride (CaCl2), but some physicians prefer to inject PRP in its resting form, relying on the spontaneous platelet activation occurring after exposure to the native collagen present in the connective tissues (89). Currently, there is a lack of evidence on the most suitable method for PRP activation, and the choice of strategy to activate it is mainly based on practical reasons rather than supported by studies on the effects of the different procedures on the final platelet releasate. The definition of the differences among activation methods might allow PRP preparations to be optimized, by identifying the most suitable strategy for each specific pathology, in order to obtain a customized PRP for the various clinical indications. There is no strong published evidence on whether or not platelets must be previously activated before their application and with which agonist. Some researchers used thrombin or calcium to activate platelets. On the other hand, others used platelets without being previously activated, advocating that better results are achieved (84, 85).

-The difference between Leukocyte rich and Leukocyte poor PRP:

One critical variable that needs addressing is the PRP type. As PRP has become very popular over the last two decades, many papers have been published and many questions raised concerning the heterogeneity of results (90). The majority of the published systematic reviews highlighted the need for a standardised protocol (91). The use of leukocyte-rich platelet-rich plasma or leukocyte-poor platelet-rich plasma is not well described in these articles, and there is no explicit agreement on which type is more effective and for which pathology.

Zhou et al. (90) isolated tendon stem cells from patellar tendons of rabbits. These cells were treated with leukocyte-rich platelet-rich plasma or leukocyte-poor platelet-rich plasma. Then they measured cell proliferation, progenitor cell marker expression, inflammatory gene expression, and protein anabolism and catabolism. Both types of PRP induced similar trophoblast stem cells differentiation into active tenocytes (90). However, while leukocyte-rich platelet-rich plasma encouraged mainly catabolic and inflammatory effects in differentiated tenocytes, leukocyte-poor platelet-rich plasma-induced predominantly anabolic changes. Zhou et al. (90) suggested that leukocyte-rich platelet-rich plasma may exert detrimental changes because of its catabolic activity. In contrast, the use of leukocyte-poor platelet-rich plasma in acute injuries may result in excessive scarring due to the strong potential of encouraging extravagant anabolic activity. Assirelli et al. (91) conducted an *in vitro* study during which leukocyte-rich platelet-rich plasma or leukocyte-poor platelet-rich plasma were applied to synovial fibroblasts isolated from patients with osteoarthritis intra-operatively (91). Leukocyte rich platelet-rich plasma induced a higher increase in the pro-inflammatory factors interleukin-1b, interleukin-8 and fibroblast growth factor-2, and a significant decrease in anticatabolic mediators in cartilage such as hepatocyte growth factor and tissue inhibitor of metalloproteinase-4. *In vitro* studies show that leukocyte-rich platelet-rich plasma creates a more significant inflammatory response than leukocyte-poor platelet-rich plasma (91).

Another *in vivo* study using healthy rabbit tendons reported that leukocyte-rich platelet-rich plasma induces a more significant acute inflammatory response than leukocyte-poor platelet-rich plasma at five but not 14 days after injection in healthy rabbit tendons (92).

In another study using a chronic tendinopathy model induced by a local injection of collagenase in the Achilles tendon of rabbits, authors evaluated the effect of both types of PRPs on healing outcomes four weeks after the intra-tendon injection of either leukocyte-rich platelet-rich plasma or leukocyte-poor platelet-rich plasma (93). The study showed that leukocyte-rich platelet-rich plasma stimulated better histological structures with large collagen fibril diameters than leukocyte-poor platelet-rich plasma. Compared with the leukocyte-poor PRP group, higher gene expression and more protein synthesis of collagen I ($P = .0160$ and $P = .0309$, respectively) and CD163 ($P < .0001$ and $P = .0411$, respectively) were found in the leukocyte-rich PRP group. Considering TEM and biomechanical testing, the leukocyte-rich PRP group demonstrated more mature collagen fibres ($P < .0001$), a larger

fibre diameter (P = .0005), a higher failure load (P = .00417), and higher tensile stress (P < .0001) than the Leukocyte-poor PRP group.

However, when to use each type of PRP treatment depends on the healing stage and the type of injury. A recent literature review by Le et al. (94) concluded that using the leukocyte-rich platelet-rich plasma in treating tendinopathy has a better outcome compared to leukocyte-poor which works better in osteoarthritis. Again Fitzpatrick et al. (95) conducted a meta-analysis to assess the effectiveness of PRP in treating tendinopathy. They concluded that there is good published evidence supporting a single ultrasound-guided injection of leukocyte-rich platelet-rich plasma in tendinopathy.

The safety profile of PRP:

There are very few papers that describe adverse events when using PRP (96-100). Bielecki et al. (101) suggested that mixing allografts and L-PRP gel when treating large bone cysts is ineffective and can cause unknown local reactions between the graft and PRP, leading to complete bone graft destruction. The patient who developed this complication had his bone graft surgery 8 months before the PRP injection. The patient exhibited a decrease of bone mineral density on radiographs and Dexa examination at 8 weeks following the PRP. The radiographs showed soap-bubbles appearances. At 12 weeks incomplete sub-trochanteric fracture was seen on the CT scan and was treated non-operatively by non-bearing. On the other hand, recent research has confirmed the osteoinductive properties of L-PRP gel *in vitro* (102, 103). Driver et al. (104) conducted a multi-centre trial to examine the safety and efficacy of autologous platelet-rich plasma gel for treating non-healing diabetic foot ulcers in 129 cases. The study revealed an increase in the blood urea nitrogen in the control group, and an increase in either the thrombin time or the activated partial thromboplastin time was noted in both treatment groups. Senet et al. (105), in the trial on the local biological effect of autologous platelets used as adjuvant therapy for chronic venous leg ulcers, reported that two patients with dermatitis (one in each treatment group), one patient developed an infection in an existing ulcer, and one had thrombophlebitis (both in the PRP group). Overall, all studies agreed that there were no treatment-related severe complications.

Ultrasound guided injection:

Ultrasound-guided operations have a low risk of complications. However, conducting these procedures requires a steep learning curve that includes visualising the needle and needle tip

and trainees become competent at variable rates (106). The transducer is usually held in one hand while the needle is advanced with the other. Other institutions may employ a team method, with the sonographer holding the transducer and locating the target while the operator advances the needle under the sonographer's supervision. Regardless of the technique employed, the most crucial safety recommendation is to constantly visualise the needle tip before pushing it toward the target. Unintended consequences of neurovascular damage can be avoided if the location of the needle tip is monitored instantaneously. The selection of the appropriate transducer is the first step in the ultrasound-guided injection process. Most musculoskeletal injections are directed at superficial components that can be visualised with a high-frequency linear transducer. On the other hand, injections around the hip are frequently directed at deeper regions that can be better viewed with a lower-frequency curved transducer (106-110).

1.5.6 Dry Needling

Dry needling or fenestration, when used by physicians and physical therapists, is a relatively new treatment modality (111). It classically refers to needling muscles. Tendon dry needling (percutaneous needle tenotomy) involves repeatedly fenestration of the affected tendon, which is thought to disrupt the chronic degenerative process and encourage localized bleeding and fibroblastic proliferation. This procedure has also been called dry needling to emphasize that the procedure does not involve the injection of any substance, and therefore, placing the needle into the tendon may be the primary reason that the tendon improves and not a specific substance used in prolotherapy and autologous whole-blood for example (112). Trigger-point dry needling is an invasive procedure where a fine needle or acupuncture needle is inserted into the skin and muscle. It is aimed at myofascial trigger points which are hyperirritable spots located in the taut band of the skeletal muscle and can be palpable as a nodule. Trigger point dry needling can be carried out at the superficial or deep tissue level. Trigger points are thought to be due to an excessive release of acetylcholine from selected motor endplates. They can be divided into Active and Latent myofascial trigger points and also deep and superficial based on the targeted tissue. Dry needling has been shown to immediately increase pressure pain threshold and range of motion, decrease muscle tone, and decrease pain in patients with musculoskeletal conditions. It has been hypothesised that it can elicit a local twitch response which can lead to alteration in the length and tension of muscle fibres and stimulate mechanoreceptors like A Beta fibres (113, 114).

A systematic review and meta-analysis with level 1a evidence concluded that dry needling applied by a physical therapist has very low to moderate quality evidence for superiority over no treatment or sham dry needling in reducing pain and improving pressure pain threshold in patients with musculoskeletal pain in the immediate to 12-week follow-up period (115).

1.5.7 Surgical treatment

When surgery is indicated due to failed non-operative strategies, open Z-plasty of the iliotibial band at the level of the greater trochanter has been the traditional procedure. Craig et al (13) studied the outcome of Z-lengthening in fifteen patients (17 hips) with refractory GTPS. Fourteen patients were women. The average age was 60 years and average duration of symptoms was 4.7 years. At mean follow up of 47 months, eight patients reported excellent results with complete resolution of symptoms, eight had good results with symptoms improved and one had a poor result. One patient required secondary repair of a tear in the tendon of gluteus minimus, with a subsequent excellent result. The mean Harris Hip Score improved from 46 to 82.

Sayed-Noor et al (116) assessed the results of distal ITB lengthening in 12 females with refractory GTP after total hip replacement. The procedure was done under local anaesthesia on an outpatient basis. The patients were followed up 3-4 months postoperatively by phone interview and at 1-3 years by EQ-5D questionnaire and clinical examination including tenderness evaluation with algometer. All patients improved significantly (EQ-5D = 0.26 preoperatively vs. 0.67 postoperatively; $P < 0.005$) except one patient who experienced no change in GTP symptoms. No postoperative complications were reported.

Other treatment options include bursectomy and longitudinal debridement of the ITB. There are no studies of high quality, but publications suggest high success rates of all the treatment options (11). Endoscopic release of the ITB and bursectomy at the level of the greater trochanter has been established as a procedure over the last decade. Fox et al (117) reported the results of arthroscopic bursectomy in 27 patients with recurrent lateral hip pain despite at least 2 steroid injections. Minimum follow-up was 1 year, and the cases of 22 patients were reviewed after 5 years. Twenty-three of the 27 patients had good or excellent results immediately following the procedure and experienced no complications. At 1 year, only 1 patient had experienced symptom recurrence, and at 5 years, only 2 patients had had recurrence. All patients except 1 were satisfied with their outcome.

Crutchfield et al's (118) systematic review looked at the results of open versus arthroscopic trochanteric bursectomy in 502 hips. The fourteen distinct Patient Reported Outcome scores that were reported by the included studies improved significantly from baseline to final mean follow-up for both approaches, demonstrating statistically significant patient benefit in a variety of hip arthroscopy settings ($P > 0.05$). The complication rates of all procedures ranged from 0%-33% and failure to improve pain ranged from 0%-8%. Patient satisfaction with surgery was high at 95% and 82% reported a willingness to undergo the same surgery again. No significant mean differences were found between the open and arthroscopic techniques. Crutchfield et al concluded both approaches are both safe and effective

procedures in treating refractory lateral hip pain. No significant differences in Patient Reported Outcome scores, pain, total complications, severity of complications, and total failures were seen between technique outcomes.

Chapter 2: LITERATURE REVIEW

A systematic review of the available literature was initially conducted to review the published evidence and assess the feasibility of the trial. The review was first registered with PROSPERO International prospective register of systematic reviews and given the registration number (CRD42017080662) (119). Our initial review was published in the Journal of Hip Preservation Surgery in August 2018 (120). For the thesis purpose and as more evidence has been published, the systematic review has been updated. Three new studies were published recently, and these have been incorporated in the initial review.

2.1 Literature review Methodology

2.1.1 Search

A search of NICE healthcare database advanced search (HDAS) (121) via OpenAthens (122) was conducted. The search involved PubMed, MEDLINE, CINAHL, EMBASE, and AMED databases. The search was conducted from the database year of inception to October 2021 with the keywords: “Greater Trochanteric Pain Syndrome” or “GTPS” or “Gluteus Medius” or “Trochanteric Bursitis” and “Platelet Rich Plasma.”

Broad search keywords were used rather than specific terms to ensure no articles were missed. There was no language limit, and all the relevant published articles or abstracts were included. The guidance of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was employed (123).

Abstracts from the search were reviewed for relevant articles by two authors (MA and EO). If a decision regarding relevance could not be made from reviewing the title and abstract alone, then the full-text article was reviewed. All the references listed in the relevant articles were also reviewed for any other papers not found in the initial search. Studies were included if they reported clinical, functional, and imaging outcomes of GTPS patients treated

with PRP. Due to a lack of studies, we did not set a minimum follow-up period. Case reports, study protocols, literature reviews, animal studies, and technical notes were all excluded. Also, we have excluded articles not written in the English language.

Once relevant articles were identified, data were extracted using a standardised form for each of the following: Author, year of publication, study design, sample size, demographics, diagnostic test, injection technique, outcome measures, and follow-up frequency. Lower quality non-randomised studies accompanied RCTs. Published conference abstracts were also included due to the paucity of evidence available but reported separately to full-text articles. Due to the heterogeneity of the included data, a meta-analysis could not be conducted; therefore, all data were reported descriptively.

2.1.2 Quality assessment

This review utilised the Cochrane Risk of Bias Tool (124) to assess the quality of the included randomized controlled trials. Bias is evaluated as a judgment (high, low, or unclear) for individual components from five domains: selection, performance, attrition, reporting, and others. Selection bias includes the random sequence generation and allocation concealment, while Performance bias includes blinding the participants and personnel. The attrition bias includes the incomplete outcome data, while the reporting bias includes selective reporting. Other bias involves any essential concerns about bias not addressed above.

The non-RCT studies were assessed using the Methodological index for non-randomized studies (MINORS) score (125). MINORS is a validated instrument designed to assess the methodological quality of non-randomized surgical studies, whether comparative or non-comparative. It has 12 domains for which non-comparative studies use the first eight domains. These domains are described in table 1. The items were scored 0 if not reported, 1 when inadequately reported, and 2 when reported and adequate. The global ideal score was 16 for non-comparative studies and 24 for comparative studies. The investigators discussed scores where a more than two-point difference was recorded until an agreement was reached.

Methodological items
1. A clearly stated aim
2. Inclusion of consecutive patients

3. Prospective collection of data
4. Endpoints appropriate to the aim of the study
5. Unbiased assessment of the study endpoint
6. Follow-up period appropriate to the aim of the study
7. Loss to follow up less than 5%
8. Prospective calculation of the study size

Additional criteria in the case of comparative study

9. An adequate control group
10. Contemporary groups
11. Baseline equivalence of groups
12. Adequate statistical analyses

Table 1: shows the domains of the Methodological index for non-randomized studies (MINORS) score.

2.2 Literature Review Results

2.2.1 Search results

The search threads used in the Nice HDAS database resulted in 89 articles. After excluding all duplicates, titles and abstracts were individually screened to exclude non relevant articles. Reviews, operative technique and case reports were then excluded as shown in figure 9.

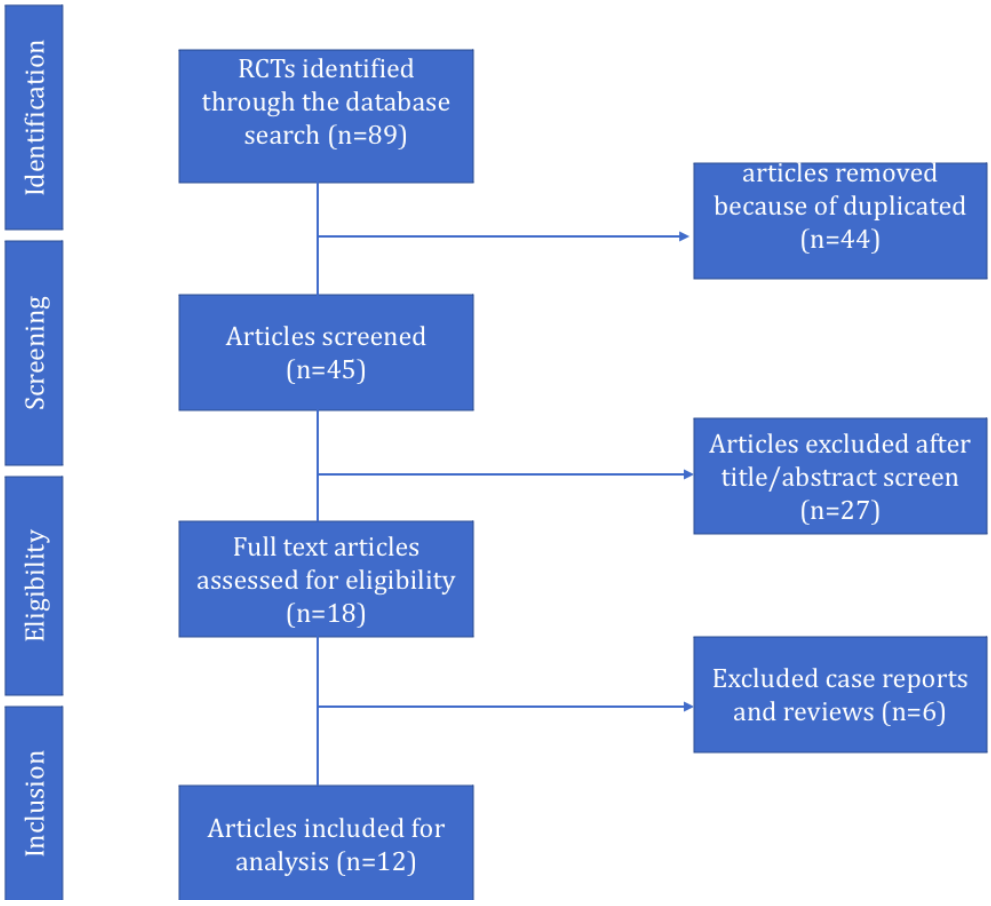

Figure 9: shows the flow chart of the literature search.

2.2.2 Summary of Studies

In total, eight full articles and four conference abstracts were included in this review. The full articles include six randomised controlled trials (126-131) and two case series (132, 133). The two RCT reports by Fitzpatrick et al. used the same cohort. The first paper reported outcomes at three months, and the second paper reported results at two years follow-up. We also identified four additional studies from published conference abstracts, including one RCT (and three case series (134-137).

The full-text articles included 178 patients given PRP injections, with sample sizes ranging from 10 to 40 patients, with a mean age ranging from 48 to 60 years, and the majority of the patients were female (Table 2).

Author-Year	Type of study	Control group	No of Hips in the PRP group	Male: Female	Mean age (years)	Diagnostic test	Duration of symptoms	Mean FU	Outcome measures	Methodology assessment
Begkas et al. 2020 (126)	RCT	Steroid injection	12	06:18	48.7	US/MRI	Over 12 weeks	24 weeks	VAS HHS	Cochrane ROB: Low
Thompson et al. 2019 (127)	RCT	Placebo	24	02:22	54.3	Clinical +/- Pain relief following injection of 2mls 1% Xylocaine at the focal tender point	Over 3 months	12 months	Numeric Rating Scale (NRS), Likert Scale of progress, adherence to exercise, medication use, health professional consultation rates	Cochrane ROB: Low
Fitzpatrick et al 2019 (128)	RCT	Steroid injection	40	06:34	60.3	US/MRI	14 months	2 years	mHHS PASS	Cochrane ROB: Low
Fitzpatrick et al 2018 (129)	RCT	Steroid injection	40	06:34	60.3	US/MRI	14 months	12 weeks	mHHS, PASS	Cochrane ROB: Low
Ribeiro *et al* 2016 (130)	RCT	Steroid injection	10	3:7	49.8	MRI	Minimum 3 months	2 months	FEPS, HHS, WOMAC	Cochrane ROB: Low
Jacobson *et al* 2016 (131)	RCT	Fenestration	15	1:14	53	US	Minimum 3 months	3 months	Pain score estimate	Cochrane ROB: Low
Mautner *et al* 2013 (132)	Case series	N/A	16	Not reported	48	MRI	18 months	15 months	VAS, improvement of symptoms	MINORS score: 6/16
Lee *et al* 2016 (133)	case series	N/A	21	4:17	48	US	Minimum 3 months	19.7 months	mHHS, HOS-ADL, HOS-Sport, iHOT-33	MINORS score: 13/16

Table 2: shows the description of the included articles.

The conference abstracts included 147 hips, with sample sizes ranging from 10 to 85 patients, with a mean age ranging from 60 to 76.2 years, and the majority of the patients were female (Table 3).

Author-Year	Type of study	Control	No of Hips in the PRP group	Male/Female	Mean age	Diagnostic test	Duration of symptoms	Mean FU	Outcome measures
Blucher *et al* 2015 (134)	Case series	N/A	85	1:4	60	MRI/US	Minimum 3 months	Not reported	EQ-5D, VAS, HOOS
Monto 2014 (135)	RCT	Steroid injection	20	5:15	66	MRI/US	11 months	12 months	HHS, WOMAC
Rajeev *et al* 2016 (136)	Case series	N/A	32	12:20	76.2	Not reported	Minimum 6 months	12 months	HHS, VAS
LaSalle *et al* 2013 (137)	Case series	N/A	10	1:9	64.7	MRI	12 weeks	10.2 months	VAS, NASS, FRI

Table 3: shows the description of the included abstracts

2.2.3 Quality assessment and risk of bias results

Based on the Cochrane Risk of Bias tool, all the randomised clinical trials have low risk of bias as detailed in figure 10.

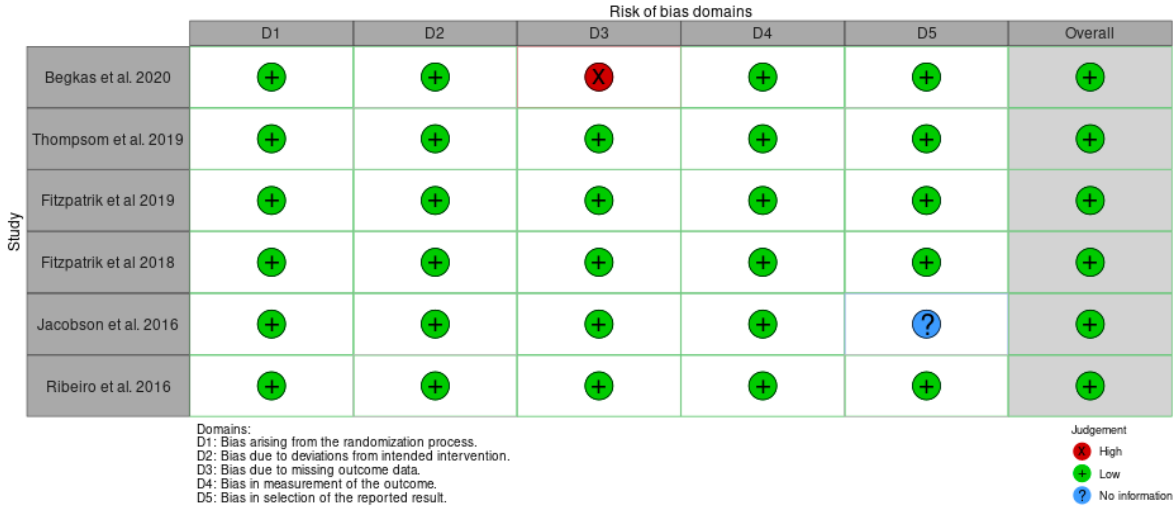

Figure 10: shows risk of bias using the Cochrane risk of bias tool.

For the two case-series, the MINORS scoring system was used to assess study quality. Lee et al.'s study was found to be of good quality (133). On the contrary, Mautner et al.'s study (132) has poor quality based on the MINORS score, detailed in table 4.

	1. clearly stated aim	2. Inclusion of consecutive patients	3. Prospective collection of data	4. Endpoints appropriate to the aim of the study	5. Unbiased assessment of the study endpoint	6. Follow-up period appropriate to the aim of the study	7. Loss to follow up less than 5%	8. Prospective calculation of the study size	9. An adequate control group	10. Contemporary groups	11. Baseline equivalence of groups	12. Adequate statistical analyses	score
Mautner *et al* 2013	2	1	0	1	0	1	1	0	N/A	N/A	N/A	N/A	6/16
Lee *et al*. 2016	2	2	2	2	1	1	2	1	N/A	N/A	N/A	N/A	13/16

Table 4: shows MINORS scores of the case series.

2.2.4 Diagnostic methods used by authors

Most authors diagnosed GTPS using either ultrasound or MRI except for Thompson et al. Thompson et al. (127) diagnosed GTPS clinically, and in borderline cases, they used a trial injection rapid-acting local anaesthetic at the focal tender point. This is considered confirmatory when patients report complete pain relief within 10 minutes and last less than two hours.

In all studies, patients had more than three months duration of symptoms and had failed conservative management. The mean follow-up ranged from 2 months to 19.7 months. The conference abstracts used MRI and Ultrasound as diagnostic modalities except in one study by Rajeev et al. (136). Patients had more than twelve weeks duration of symptoms and failed conservative management. The mean follow-up was reported in three studies to range between 10.2 months to 12 months.

2.2.5 Outcome measures

The full-text articles used a variety of outcome measures, including a pain score, Harris Hip Score (HHS), Western Ontario McMaster Index (WOMAC), Facial Expressions Pain Scale (FEPS), Visual Analogue Scale(VAS), modified Harris Hip Score (mHHS), Hip Outcome Score–Activities of Daily Living subscale (HOS-ADL), Hip Outcome Score–Sport-Specific sub-scale (HOS-Sport), the International Hip Outcome Tool–33 (iHOT-33), the Patient Acceptable Symptom State (PASS), Numeric Rating Scale (NRS), Likert Scale of progress, adherence to exercise, medication use and health professional consultation rates.

The outcome measures utilised in the conference abstracts included the HHS, WOMAC, VAS, EuroQol EQ-5D (general health-related quality of life measure: EQ-5D), North American Spine Society patient satisfaction index (NASS), Hip Disability, and Osteoarthritis Outcome Scores (HOOS), and Functional Rating Index (FRI).

2.2.6 PRP Injection preparation systems

Authors utilised different PRP systems in their studies. Each system requires a specific volume of blood to generate a particular volume of PRP. These systems include the GPS III by Zimmer Biomet, Magellan by ISTO Biologics, Harvest Technology by Lakewood, Fanem Excelsa II by FANEM, ACP double-syringe system by Arthrex and SW-PRP system by NTL Biologica (table 5). The PRP preparation, drawn blood and PRP volumes were poorly documented in all conference abstracts (Table 6).

Author Year	Volume of blood drawn	Volume of PRP	PRP preparation	Injection technique	Complications	PRP System
Begkas et al. 2020 (126)	40mls	4mls	Centrifuged at 3850 rpm for seven minutes. Red blood cell fluid centrifuged for further four minutes at 3850.	Local anaesthetic was administered. US-guided, the most painful point was identified by palpation.	None	SW-PRP (NTL Biologica)
Thompson et al. 2019 (127)	55mls	5	0.3ml of 8.4% sodium bicarbonate for buffering was added to PRP	2mls into the focal tender point, and the remaining 3–4mls injected in three areas around it.	Not reported	GPS III kit (Zimmer Biomet)
Fitzpatrick et al 2018-2019 (128, 129)	55mls	6-7mls	Centrifuged for 15 minutes. 9.3x platelet increase over baseline and 5x white blood cell increase over baseline. used straight away	No buffering agent was added. Local anaesthetic was used, and then 6 to 7 mL was injected into the affected area of the tendon in 5 to 6 passes using US.	Pain	GPS III kit (Zimmer Biomet)

Ribeiro *et al* 2016 (130)	60mls	3-4mls	Centrifuged for 15 minutes, platelet concentration of PRP was 9.23x106 U/µL. used straight away	US-guided, injected into the bursa and around it, according to the size of the affected area	NONE	Fanem Excelsa II
Jacobson *et al* 2016 (131)	60mls	7-10mls	Centrifuged at up to 2650 rpm for approximately 14 minutes. leukocyte-rich sample, concentration 4 to 6 times, used straight away	US guided, needle was inserted into the deepest aspect of the tendon abnormality, and the PRP was injected as the needle was withdrawn through the abnormal tendon segment	NONE	Harvest Tech
Mautner *et al* 2013 (132)	Variable	Variable	Not reported	US guided Did not mention site of injection	NONE	Not reported
Lee *et al* 2016 (133)	25mls	4mls	Leukocyte-rich, used straight away	US guided, into the hypoechoic and tender regions overlying the greater trochanter. A needle tenotomy technique followed, consisting of 6 to 9 needle passes through the hypoechoic regions of the gluteus medius tendon.	NONE	Magellan

Table 5: shows PRP technique and complications reported in full articles.

Author-Year	**amount of blood drawn**	**Amount of PRP**	**Injection technique**	**complications**	**PRP System**
Blucher *et al* 2015 (134)	Not Reported	Not Reported	Blind	Not Reported	Not Reported
Monto 2014 (135)	Not Reported	Not Reported	US guided	Not Reported	Not Reported

Rajeev *et al* 2016 (136)	Not Reported	Not Reported	Blind	Not Reported	Arthrex ACP
LaSalle *et al* 2013 (137)	Not Reported	Not Reported	US guided	Not Reported	Not Reported

Table 6: shows PRP technique and complications reported in conference abstracts.

2.2.7 Results summary of Full Articles

Begkas et al. (126), in their recently published paper, aimed to compare the efficacy of US-guided PRP injections with corticosteroid injections in the treatment of GTPS. A total of 24 patients were selected and randomly allocated to a single PRP or steroid injection. Clinical results in both groups were measured and compared with the Visual Analogue Scale (VAS) of pain, Harris Hip Score (HHS), and the presence of complications at 4, 12, and 24 weeks after injection. Outcome scores improved in both groups compared to their baseline scores, but patients in the PRP group had a statistically significant ($p < 0.05$) decrease in VAS score and a significantly increased HHS at the last follow-up (24 weeks post-injection). In their series, there were no complications reported. The study concluded that patients with GTPS show better and longer-lasting clinical results when treated with US-guided PRP injections compared to those with CSI.

Thompson et al., in 2019 (127), conducted a study to see whether a single platelet-rich plasma injection could benefit people suffering from chronic Greater Trochanteric Pain Syndrome. Participants with chronic lateral hip pain were randomly assigned to either a PRP injection (intervention group) or a saline injection (control group), and they were all given the same eccentric exercise. The Brief Pain Inventory (BPI), health professional appointment rate, drug use, a Likert scale of performance, and Expectation of Improvement Scale were assessed monthly for six months, with a one-year follow-up. No difference was found in any outcomes between the two groups during any follow-up stage (all $p>0.39$). They concluded that a single PRP injection resulted in no noticeable improvement in GTPS compared to a placebo injection. One of the exciting points in Thompson et al.'s study is that they analysed one millilitre of whole blood from the pre-centrifuge sample and 1ml of the PRP component for platelet counts. This has increased from $254.9 \pm 55.3 \times 10^9$/L pre-centrifuge to $1232.3 \pm 637.8 \times 10^9$/L Post-centrifuge. Add to that, fixed effect parameters (age, BMI, duration, month and treatment) for the model without interaction highlighted that average

pain decreases significantly with duration (P=0.008) and time point increases with body mass index (P=0.007).

Fitzpatrick et al.'s (2018) double-blind RCT compared the effect of single ultrasound-guided leukocyte-rich PRP injections with corticosteroids to treat gluteal tendinopathy (129). Each arm included 40 patients with a mean age of 60 years and a mean duration of symptoms of 14 months. Follow-up period intervals were 2, 6, and 12 weeks. PRP demonstrated a significant advantage compared to corticosteroid groups over 12 weeks (mean mHHS 74.05 +/- 13.92 vs 67.13 +/- 16.04 respectively, p =0.048). There were no significant differences between the groups at 2 weeks (mean mHHS, PRP: 65.23 +/- 11.60 vs corticosteroid: 66.95 +/- 15.14) or 6 weeks (PRP: 68.79 +/- 13.33 vs corticosteroid: 69.51 +/- 14.78). When considering the MCID, 82% in the PRP group achieved improvement compared to 56.7% in the corticosteroid group (p = 0.016). Fitzpatrick et al. in 2019 (128) conducted further analysis of their data at two years follow-up to assess whether there would be a sustained long-term difference in the mHHS (128). They found that the improvement after LR-PRP injection is sustained at two years, while the symptomatic relief from a corticosteroid injection is maximal at six weeks and not maintained beyond 24 weeks.

Ribeiro et al.'s (130) double-blind, randomised prospective comparative study compared the efficacy of ultrasound-guided PRP injections against corticosteroid (Triamcinolone) in 20 hips with GTPS. Outcomes were assessed at baseline, 10, 30, and 60 days using the FEPS, HHS, and WOMAC questionnaires. The inter-group analysis demonstrated no significant differences between the two treatment arms at any time point with any of the outcome measures. Intra-group comparisons demonstrated significant improvements in the HHS in the corticosteroid group at 10 and 60 days (pre – 10 days: mean difference 20.8, p = 0.03; pre – 60 days: mean difference 22.3, p = 002) and at each follow up period for the FEPS (pre – 10 days: mean difference 2.1, p = 0.004; pre – 30 days: mean difference -2.1, p = 0.004; pre – 60 days: mean difference 2.9, p = 0.0001. The PRP group showed no statistical improvement in any of the outcome measures up to two months.

In Jacobson et al.'s study (131), 30 patients were randomised equally to compare the efficacy of ultrasound-guided PRP injection against percutaneous tendon fenestration for treatment of GTPS. The fenestration group received 20-30 passes of the needle, and the PRP group received a maximum of 10 passes. Patients answered a series of questions using a scale of 0 – 10 about hip symptoms, including the level of pain, pain interfering with general activity, pain interfering with walking, pain interfering with climbing stairs, and pain

interfering with sleep. Pain scores were recorded at baseline, week 1, week 2, and 3 months after treatment. The fenestration group demonstrated mean pain scores of 32.4 (SD 10.2, range 8-49) at baseline, 16.8 (SD 11.5, range 0-34) at one week, and 15.2 (SD 10.8, range 0-34) at two weeks. The PRP group demonstrated mean pain scores of 31.4 (SD 7.3, range 11-41) at baseline, 25.5 (SD 8.8, range 9-40.5) at one week, and 19.4 (SD 10.3, range 4-42) at two weeks. The authors reported significant pain score improvements comparing baseline with 1- and 2-weeks follow-up ($p<0.001$) with no difference between the groups ($p=0.162$). At three months, 71% and 79% improvements in the fenestration and PRP groups, respectively, with significant improvements in pain scores in both groups. No significant difference between the treatments was identified ($p >.99$).

Mautner et al. (132) evaluated the efficacy of ultrasound-guided PRP injections in a retrospective cross-sectional study for chronic tendinopathies refractory to conventional treatments in 180 patients. Their main outcome measures were perceived improvement in symptoms at least six months after treatment, VAS, functional pain, and overall patient satisfaction. Mean follow-up for all patients, including those with gluteus tendinopathy, was 15 months (+/- 6 months) following PRP injection. The study included 16 patients with gluteus medius tendinopathy out of the 180 patients. The remaining patients had a variety of tendinopathies affecting other tendons such as patella, Achilles, lateral epicondyle, rotator cuff, and others. Although the study did not report specific outcome measure values separately for gluteus medius tendinopathy, they found that 81% of patients with gluteus medius tendinopathy had moderate improvement to complete resolution of symptoms at a mean follow-up of 15 months. The authors presented their main comparative results by combining the VAS scores of all 180 patients. Sixty percent of the 180 patients received only one injection, 30% received two injections, and 10% received three or more injections. Seventy five percent had a perceived decrease in VAS, from 7.0 1.8 to 1.8 2.0 (5.2, SD 2.7, 95% confidence interval 5.65 to 4.86, *P* .001). Ninety-five percent had no pain at rest, and 68% reported no pain during activities. Eighty-five percent were satisfied with PRP injection.

Lee et al. (133) reported a prospective case series evaluating the efficacy of US-guided PRP injections with needle tenotomy in GTPS. Their injection method consisted of PRP injection into the tendon followed by needle tenotomy (6-9 passes). The 21 patients included in this series had symptoms longer than three months, and their symptoms were refractory to other treatments. All participants were assessed at baseline and post-injection with four outcome measures: mHHS, HOS-ADL, HOS-Sport, and iHOT-33. The mean follow-up was 19.7

months (range 12.1-32.3 months). The mean improvements from baseline to post-injection follow-up were 56.73 (range 35.20 – 73.70) to 74.17 (range 42.90 – 95.70) for mHHS, 68.93 (range 20.59 – 100.00) to 84.14 (range 48.53 – 100.00) for HOS-ADL, 45.54 (5.56 – 94.40) to 66.72 (range 28.13 – 100.00) for HOS-Sport and 34.06 (range 6.45 – 74.06) to 66.33 (range 19.60 – 94.60) for iHOT-33. The improvements in all outcome measures were clinically and statistically significant (P< .001).

2.2.8 Results of Conference abstracts

The conference abstracts were included in our initial review in order to evaluate all the published evidence as there were few full articles. The conference abstracts one randomised trial and three case series, which were non-peer-reviewed, and presented limited data but were included in this review to assist when making inferences and drawing conclusions. We generally found that information about PRP preparation, amount of injected PRP and complications following injections were not included.

Blucher et al. (134) reported their prospective single-surgeon case series of 85 patients with recalcitrant GTPS to assess whether PRP injections improved their symptoms and evaluate PRP effects on quality of life and daily activities. Gluteal tendinopathy and trochanteric bursitis were proven radiologically with either MRI or ultrasound. However, they did not report the relative proportions of either. Pain scores (0-10), EQ-5D Health Domain, HOOS, Utility and VAS scores were collected at baseline and following PRP injection. The duration of symptoms ranged from 3-120 months. Twenty percent of patients reported moderate and 78% severe symptoms. Pain scores improved from 8.1 at baseline to 4.6 post-injection ($p<0.0001$). Sixty-nine percent of patients reported successful outcomes. Both EQ-5D Utility and EQ-5D VAS scores improved after the PRP injection, and the proportion of reported level II (some problems) and III (extreme problems) decreased significantly for each of the EQ-5D dimensions at the final follow up ($p<0.001$). HOOS scores increased significantly ($p<0.01$) in all groups after treatment.

Monto R (135) compared US-guided PRP injection with a cortisone injection in treating severe cases of GTPS. Forty patients who had failed a minimum of 6 months of conservative treatment were randomised into a two-arm blinded study. The results in group 1 (cortisone) demonstrated an improvement from a mean baseline HSS of 52 (range 43-54) to 75 (range 62- 84) at three months post-injection but worsened to 68 (range 54-84) at six months and 59 (range 53-77) at 12 months. The trend was similar with the WOMAC scores, with a

baseline of 58 (54-66), 83 (range 61-87) at three months, 68 (range 54-84) at six months, and 63 (range 58-79) at 12 months. Group 2 (PRP) demonstrated sustained improvements from a mean baseline HSS of 51 (range 49-53) to 84 (range 77-92) at three months and 87 (range 82- 92) at six months and 87 (range 81-92) at 12 months. This was reflected in the WOMAC scores with improvements from a mean baseline of 59 (range 55-61) to 91 (range 80-97) at three months, 90 (range 83-97) at six months, and 89 (range 83-96) at 12 months. They reported a statistical significance of $p = 0.001$.

Rajeev et al. (136) prospectively assessed the outcomes of PRP injection in a thirty-two patient case series with severe GTPS following total hip replacement. Patients had a minimum of 6 months of conservative treatment. Using HHS and VAS, patients were evaluated at baseline, three months, six months and one year following PRP injection. The pre-treatment HHS was 54 (range 48-60), and VAS was 7.8 (7-8). The post-treatment HHS initially improved to 78 (62-84) and VAS of 4.5 (3-5) at three months. The HHS after six months were 72 (64-80) and VAS 5.4 (5-6). The HHS dropped to 68 (54-74) at one year, and VAS deteriorated to 6.7 (5-8).

LaSalle et al.'s (137) abstract retrospectively reported the efficacy of US-guided PRP injections in patients with radiologically (MRI) proven gluteus medius or minimus tears, tendinosis or degeneration. Ten patients had more than 12 weeks of unsuccessful conservative treatment. The main outcome measures included VAS, FRI, and NASS. The mean duration of pain was 46 months (range 8 – 120 months), and the mean follow-up was 10.2 months (range 6 – 26 months). The mean VAS was 8.10 (SD 1.7) at baseline and 3.8 (SD 2.7) post-injection ($p = .002$). Overall patient satisfaction was 80% (as measured by NASS). Two patients reported no improvement. Of the eight patients who reported improvement, their mean FRI score was 62.4 (out of 100) at baseline and 21.3 six months post-injection ($p = .001$). The average VAS scores among these eight patients were 8.7 (SD 1.1) at baseline and 2.7 (SD 2.1) post-injection.

2.3 Systematic Review Discussion

The application of platelet-rich plasma in the management of musculoskeletal conditions has become more prevalent in recent years. The use of PRP in treating tendinopathies has been widely investigated, including testing cultures of equine and human tendon cells, which show an increase in the types of expression of collagen genes in tendon cell cultures when mixed with PRP (138-140). Multiple reviews have been summarising the available evidence

and comparing the outcomes of PRP injections with other therapeutic modalities. Arirachakaran et al. (141) performed a systematic review and meta-analysis of randomized controlled trials to compare relevant clinical outcomes between the use of PRP, Autologous blood, and Corticosteroids injection in the treatment of lateral epicondylitis. They concluded that PRP injection could improve pain and has a lower risk of complications. Considering the application of PRP in the treatment of patellar and Achilles tendinopathy, a systematic review of the literature was performed by Di Matteo et al. in 2015 (89). Twenty-two studies were included and analysed. All the papers concerning patellar tendinopathy reported positive outcomes for PRP, which proved to be superior to other traditional approaches such as shock-wave therapy and dry needling. In the case of Achilles tendinopathy, despite the only RCT available showing no significant clinical difference between PRP and saline solution, there were encouraging findings reported by the case series.

Our review illustrates a growing interest in the use of PRP in musculoskeletal (MSK) conditions over the past few years. We identified a small number of RCTs and non-comparative studies reporting the use of PRP in GTPS. All of the full-text articles' studies used US guidance for their injections, but all used differing PRP systems with differing injection volumes, spinning protocols, and reported compositions of PRP. Three studies reported using leukocyte-rich PRP. This review highlights the interesting conclusions from the included articles to shed light on whether this is an efficacious method of treating this condition.

The different PRP preparations and the possibility of exerting different therapeutic effects have been previously investigated *in vitro*. However, the role of leukocytes in PRP has not yet been defined under tendinopathy conditions *in vivo* (142). Yan et al. (142) compared the effects of the intra-tendinous injection of leukocyte-poor PRP (Lp-PRP) versus leukocyte-rich PRP (Lr-PRP) in a rabbit chronic tendinopathy model *in vivo*. They concluded that Lp-PRP is superior to Lr-PRP as it improves tendon healing and is a preferable option for the clinical treatment of tendinopathy. Another study by Zhou et al. (90) found that while LR-PRP and LP-PRP appear to be safe in inducing the differentiation of tendon stem cells into active tenocytes, Lr-PRP may be disadvantageous the healing of injured tendons because it produces catabolic and inflammatory effects on tendon cells. Conversely, using LP-PRP to heal acute tendon injuries may give rise to excessive scar tissue due to the strong potential of LP-PRP to cause disproportionate cellular anabolic effects.

Summarising the full published papers in our review, three RCTs concluded that patients with chronic gluteal tendinopathy achieve better clinical outcomes when treated with PRP injection than corticosteroid, whereas the other RCTs found no significant differences. Fitzpatrick et al.'s studies (128, 129) were deemed high quality with the Cochrane risk of bias tool. The study was blinded, with a relatively large sample size and reporting of their trial design methodology was robust. At 12 weeks, 39 out of 40 in the PRP group were available for analysis. Recently, Fitzpatrick et al. reported the two-year follow-up results showing that the PRP group had better and longer-lasting clinical results. Compared to Ribeiro et al.'s study (130), slightly more (30 patients) were randomised by Jacobson et al. (131) to compare PRP injection with fenestration. Although the study showed a comparable improvement in the two groups, the authors only measured pain scores and recorded no functional outcomes.

Ribeiro et al.'s (130) study was rated as a high-quality randomised trial based on the Cochrane ROB tool. Although the study was randomised and double-blinded, the limitations of this study were the small sample size (20 patients) and short duration of follow-up (2 months). Furthermore, the study did not demonstrate the longevity of treatment as the mean follow-up was three months.

The two case-series reported improvements in treating gluteal tendinopathy. Lee et al.'s case series (133) was a high-quality study based on the MINORS score. The study showed statistically significant improvement with values that exceeded the minimum clinically important difference (MCID). The criticisms of this study were the small sample size, no comparative group, and the non-consistency of the post-injection therapy program among patients. There was little information on the PRP composition.

Conversely, Mautner et al.'s (132) case series was a poor-quality study based on MINORS score. Although the study was multi-centred, it was retrospective, over-ridden with heterogeneity, and the PRP injection methodology was non-uniform. Furthermore, patients had both needle tenotomy and PRP injection; hence the relative effects could not be distinguished. Furthermore, they did not present specific outcome measure values with significance for gluteus medius tendinopathy, forcing us to draw conclusions based on a percentage.

With regard to the published abstracts, there is a lack of valuable study information compared to the full published articles; therefore, the conclusions provided are of low quality, and clinical value as the experiments cannot be replicated.

All of the abstracts reported good outcomes in treating GTPS with PRP. The randomised study by Monto et al. demonstrated PRP to be superior compared to corticosteroid (135). Although the study was randomised with a modest sample size compared to other reviewed articles, the randomisation process and study design could not be evaluated without a full-text article. The main limitation shared by the non-randomised studies outside of being non-peer-reviewed was a lack of a control group. Blucher et al.'s (134) study's strengths include large sample size and prospectively collected data. Although the study reported promising results and good outcomes in subjective and objective scoring, it did not report the follow-up period. Rajeev et al.'s (136) prospective case series did not report the significance of their results or intra-group comparisons. Furthermore, as GTPS may have been secondary to surgery or distortion of biomechanics, the judgment on the efficacy in this study might not be accurate; therefore, conclusions are difficult to draw from this article. Lasalle et al.'s study was limited by a small sample size of 10 patients (137).

2.4 Systematic review summary

Our review highlights the lack of adequately powered studies providing high-quality evidence, especially when the global pathology of GTPS is considered. The pathology often may be in the gluteus medius and minimus tendon but not exclusively the bursa; therefore, the injection site needs to be considered. Only Ribeiro et al conducted a quality check for their PRP injections. Ribeiro et al collected 1ml aliquot in all cases to determine the final platelet concentration in the sample (Fanem Excelsa II, 206 BL, São Paulo, Brazil). The final volume of PRP preparation was 4 ml, to which 0.1ml of 10% calcium gluconate was added. The mean platelet concentration of PRP was 9.23x106 U/µL.

In most of the studies, improvements were observed during the first three months after injection. Significant improvements were reported when patients were followed up to 12 months post-treatment. There are, however, conflicting results between the randomised studies as to whether PRP is superior to corticosteroid. Furthermore, the use of different PRP systems, concentrations, and volumes provides heterogeneity when trying to provide comparisons. Varying outcome measures were used to assess pain and functional outcomes with short follow-up and small sample sizes. Considering these factors, PRP seems a viable alternative treatment with the current evidence in patients with GTPS refractory to conservative measures. However, due to the limitations in these studies, the definitive role of PRP in managing GTPS is open for debate. This review has prompted us to investigate

further the role of PRP in the management of GTPS via a large-sample and high-quality randomised clinical trial to provide evidence of the duration and efficacy of this treatment.

Chapter 3: Study Protocol and Methodology

3.1 Aims of the project

The aims of this trial are:

1. To test the hypothesis that PRP is effective in treating GTPS in patients who have failed conservative management.
2. To assess the duration of the PRP effect.

3.2 Null Hypothesis

This is a superiority trial and the null hypotheses are:

- PRP is not more efficacious than the placebo (Normal Saline) in the treatment of Greater Trochanteric Pain Syndrome.

- BMI and Age have no effect on the outcomes of the treatment.

3.3 Trial design

The trial is a two-arm single-centre double-blind, randomised controlled trial. The study includes a two-way comparison between PRP and placebo normal saline injections for treating GTPS. The trial design was established based on our local experiences with using PRP in patients with GTPS and the results of our systematic review, comparing PRP versus other non-operative treatments in patients with severe GTPS.

We conducted a very productive and informative focus group meeting with patients who have had personal experiences with PRP injections and GTPS. We discussed our proposed study and what they thought about it and their own experiences. The key points we took from the meeting were:

1. Patients suffering with GTPS for a number of years that has not responded to initial treatments including steroid injections suffer a great burden due to pain and disability. They welcomed the idea of a trial investigating the effects of PRP.

2. They found steroid injections ineffectual

3. Compared to steroid injections, they described PRP injections as “perfectly bearable” especially with the local anaesthetic

4. Placebo: they understood that comparing PRP with normal saline would allow us to ascertain if PRP worked in the first place. But they were concerned about the length of time that one would have to endure a burden if they received the normal saline. They suggested that at the 6 month follow up that the participant should be offered PRP definitively as a second treatment if they did not want to receive their blinded allocated treatment again. They thought that this would offer reassurance to the participant and make entering the study with placebo as a possible treatment less of a burden for them. This should definitely be made clear at the initial meeting with participants.

5. They found the process of coming to theatre and having their blood taken and receiving PRP ok. They were sore for up to a week afterwards but logically thought that this was reasonable and expected after having an injection.

6. They suggested waiting for up to a week after the initial meeting with participants for them to make a decision on whether to enter the study was reasonable.

7. Randomisation and blinding: All patients understood the randomisation process and the reasons for being randomised/blinded. They accepted this as part of a study protocol given that patients reviewed at 6 months could receive PRP if they absolutely wanted to. They accepted our method of blinding using a sheet to obscure the line of sight to the participant’s hip and accepted that blood needed to be taken from every participant to maintain the blind.

8. They agreed with the 3, 6 and 12 month follow up periods.

9. Participants receiving a summary of the outcome of the study is a good idea.

10. They were equivocal regarding whether the treatments should take place in theatre or in a clinic setting.

11. Patient information sheet: they were general happy with the information sheet besides a couple of areas of jargon/misunderstanding that we have rectified as a result.

Participants were identified and referred for inclusion in the study by their primary care provider (GP, Orthopaedic surgeon, Rheumatologist and physiotherapist). Participants were invited for a first interview where eligibility was assessed, further information about the study was given, and written consent for inclusion was taken. Potential participants were permitted to reschedule another interview appointment if they needed more time to decide whether they wished to participate.

The diagnostic criteria for GTPS were clinical and radiological diagnosis with MRI or US if MRI is contraindicated. The final diagnosis was made by Mr. Malviya (hip preservation surgeon). Only patients with gluteus tendinopathy were included in this trial (no tear). Participants were then allocated randomly to either the treatment arm of PRP or normal saline injection. Eligible patients were older than 18 years and had a history of more than three months of gluteal tendinopathy with symptoms including lateral hip pain, pain with activity (eg, walking and stair climbing), and pain lying on the affected side at night and with clinical signs on examination including tenderness over the greater trochanter. Radiological confirmation of the diagnosis of tendinopathy (no tear) was made with ultrasound and magnetic resonance imaging.

Participants received their treatment under sterile conditions in the outpatient department under ultrasound guidance by a consultant rheumatologist, Dr. Ismael Atchia. The participants were contacted by phone a week after receiving the treatment to monitor for any adverse events. Participants and outcome assessors were both blinded. Participants were then reviewed at baseline, 3 and 6 months with patient-reported outcome measures (PROMs) completed at each of these reviews.

At the six-month follow-up, participants were given the option of a repeat injection of their original treatment arm, or if they specifically requested PRP, we referred them to Mr. Asaad (orthopaedic surgeon at Northumbria) while maintaining the blind of their initial treatment. This was a critical ethical discussion point in our focus group meeting engaging patient and public involvement in that expecting participants to potentially continue with placebo for a further six months while in pain would place a significant burden on them.

The trial was expected to last approximately four years, allowing 1.5-2 years for recruitment, with the remaining time used to complete the follow-up period until the last patient recruited (figure 11). The recruitment was significantly delayed during the COVID-19 pandemic. The health research authority (HRA) and Medicines and Healthcare products

Regulatory Agency (MHRA) advised pausing all the trials except the priority1 studies and stopping new screening and recruitment. Priority 1 studies are the studies we must endeavour to maintain such as open studies in which recruited patients would be at risk of harm if the study is paused, or studies of Covid-19. These studies should continue for patients who have already been recruited. These decisions were made in order to reduce the burden on hospitals and keep patients away from hospitals and GP sites where they can catch or transmit the Coronavirus (143). Add to that, many patients would refuse to come to the hospital and put them self at risk of catching the virus. A study by Mirza et al. published during the pandemic concluded that patients are less willing to participate in observational and interventional rheumatology research studies while COVID-19 is present in the community (144).

Provision of a centrifuge and PRP kits have been secured from NTL Biologica. Funding support was from the Research and Development Office, North Tyneside General Hospital.

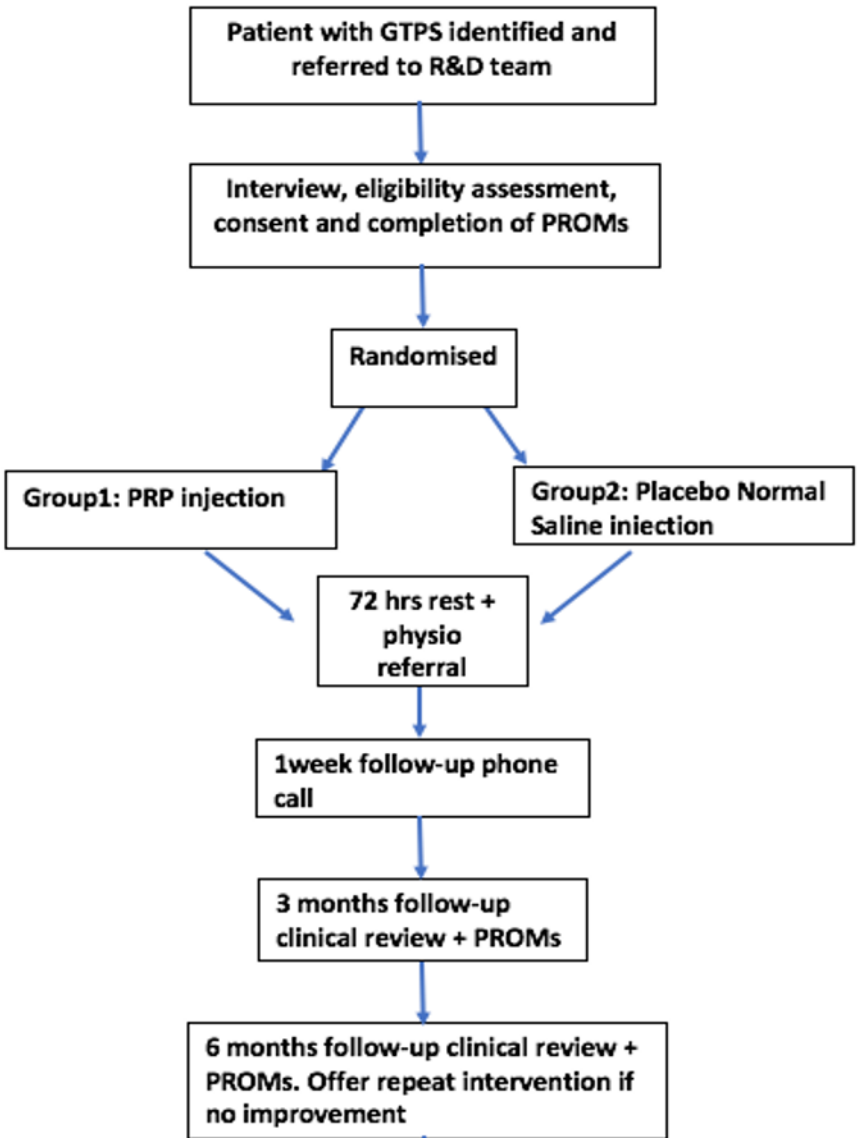

Figure 11: Trial Flow Diagram.

The feasibility and scientific quality of the trial were peer-reviewed and approved by the Principal Investigator and Research and Development team at the Northumbria Healthcare NHS foundation trust. The ethical approval has been granted by Health Research Authority (HRA) England, and the trial is listed with the number 198415. The initial version of the study protocol was published in the 2018 Trials journal, which is a high impact, peer-reviewed, and PubMed indexed journal specialised in clinical trials and trials protocols (145). Add to that, this trial was also registered in clinicaltrials.gov for more publicity (ClinicalTrials.gov Identifier: NCT03479190) (146).

3.4 Outcome measures

3.4.1 Primary outcome measure

Our primary Patient-reported outcome measure (PROMS) is the International Hip Outcome Tool – 12 (iHOT-12). The iHOT score was developed by Mohtadi et al. (147) to assess patients' ability to return to an active lifestyle through obtaining subjective measures of symptoms besides considering the emotional and social health status. The iHOT-12 score was developed to examine the younger population (between 18-60 years of age) presenting with a variety of hip pathologies. Initially, the score contained 33 questions, and it was named iHOT-33 until modified by Griffin et al. in 2012 to contain only 12 questions (148) and become iHOT-12 which has been validated and popularised as an effective and reliable assessment and easier to obtain. The lowest score is 0 which represent poorest function and the highest is 100. The scores will be collected at baseline, 3 and 6 months and compared within and between the PRP and normal saline arms.

3.4.2 Secondary outcome measures

These include the Visual Analogue Scale for pain (VAS), the three-level version of the EuroQol five-dimensional (EQ5D-3L) and the Modified Harris Hip Score (mHHS). These scores will be collected at baseline, 3 and 6 months will be compared within and between the PRP and normal saline arms.

The VAS is a subjective measure of acute and chronic pain that has been proven to be accurate. It features a straight line with a spoken description of each extreme "no pain" and "worst pain" on its limits, as well as a continuous scale for subjective magnitude estimation. The line is usually 10 cm long horizontal, and scores are recorded by making a handwritten mark (149). The lowest score is 0 which represent no pain, and the highest score is 10 which represent the worst pain.

The mHHS was created to assess the results of hip surgery and evaluate various hip disabilities and the outcomes of their treatment methods. The mHHS consists of four domains which are covered by ten questions. These domains include pain, function, absence of deformity, and range of motion. It has proven to be a valid test when compared to Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Short Form 36 (sf-36) scores (150). The lowest score is 0 which represent poorest function and the highest is 100.

The EQ5D-3L is a simple self-reported generic measure of current health. It consists of a two-page questionnaire that contains five domains that may have one of the three-level answers and a visual analog scale (VAS) on which patients can mark their current health state from 0% to 100%. The five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) have three levels of functioning each (no problems, some problems, and unable to/extreme problems) (151). The highest score is 1.00 which represent best outcome while

3.4.3 Demographics and Body mass index (BMI)

We recorded patients' genders and ages and assessed if they had any impact on the outcome scores. Based on the literature search, we classified patients into three groups. The youth group from 18–47 years old, the middle-aged group 48–63 years old, and the elderly group included 64 years old and above.

BMI is a statistical index that utilises a person's weight and height to measure body fat in males and females of any age. BMI is calculated by dividing a person's weight in kilogrammes by their height in metres squared (BMI= weight (in kg)/ height2 (in m2)). Instead of using standard height vs. weight charts, the National Institute of Health (NIH) now utilises BMI to decide if a person is underweight, average weight, overweight, or obese. It is well known that individual differences can exist, and BMI alone is insufficient to designate a person as obese or malnourished. In certain populations, such as professional athletes and bodybuilders, an elevated BMI may not instantly relate to their health state due to their increased muscle mass and weight. NIH as well as the World Health Organization (WHO) use these BMI classifications for White, Hispanic, and Black people (152, 153). Because the cut-offs underestimate the risk of obesity among Asian and South Asian populations, their classification differs slightly. Furthermore, BMI facilitates comparisons between children of the same sex and age in the paediatric population. A BMI of less than the fifth percentile in children is considered underweight, while a BMI of more than the 95th percentile is considered obese (154). In adult population, BMI is classified as follow:

1. Severely underweight - BMI less than 16.5kg/m^2
2. Underweight - BMI under 18.5 kg/m^2
3. Average weight - BMI greater than or equal to 18.5 to 24.9 kg/m^2
4. Overweight – BMI greater than or equal to 25 to 29.9 kg/m^2
5. Obesity – BMI greater than or equal to 30 kg/m^2:

- Obesity class I – BMI 30 to 34.9 kg/m^2
- Obesity class II – BMI 35 to 39.9 kg/m^2
- Obesity class III – BMI greater than or equal to 40 kg/m^2 (also referred to as severe, extreme, or massive obesity)

We classified patients in our trial based on this classification and analysed the effect of treatment on each group. We used the NHS BMI calculator which calculates the BMI based on height, weight, age, sex, ethnic group and activity level.

3.4.4 Measure of Harm and Adverse Events

Participants were monitored for adverse events at each follow-up. One week after their treatment, each participant will receive a phone call to monitor early adverse events.

Expected Adverse Events:

1. Pain: localised inflammation at the injection site can present as pain, swelling and irritation. This reaction can be to the needle or the PRP/Placebo that was injected, or both. This reaction can appear immediately, or it may take hours after the injection. Usually, this reaction is benign and resolves spontaneously; however, it rarely may require anti-inflammatory medications (155). We expect all our patients to have pain from the injection however severe pain in less than 10%
2. Infection: very rarely, intramuscular injections cause serious infectious complications such as abscesses which may progress to bacteraemia and generalized sepsis. These complications appear a few days after the injection (156). We estimated less than 1% infection risk.
3. Nerve injury: nerve damage following an injection is extremely rare. Injury can result from direct needle trauma, chemical irritation, toxic action of the injected solution, and neuritis. When a needle causes nerve damage, most patients experience immediate agony after the injection (157). We estimated less than 1% risk of nerve injury.
4. Haematoma or bleeding: injections can injure the local blood vessels, and patients subsequently end up with a haematoma which will resolve most of the time spontaneously. If the patient is on anti-coagulant, these haematomas can progress in size and become more symptomatic (158). We estimated less than 5% risk of developing haematomas.

3.4.5 Minimal Clinically Important Difference

Several patient-reported outcome measures have been created during the last three decades to directly involve and improve the participation of patients in the evaluation of the benefit of therapy received. The standardisation of patient-reported outcome measures has increased our ability as researchers to identify treatment options that are more effective when applied to homogeneous groups. The creation of the minimal clinically important difference score (MCID) is occurring in tandem with the improvement of patient-reported outcome measures (PROMs). Jaeschke et al (159) were the first to coin the term MCID in 1989. They contended that, while statistically significant changes frequently happened during the use of tools that monitored change following an intervention, the significant improvements in certain circumstances had little therapeutic importance. As a result, their operational definition of the MCID was "the smallest difference in score in the domain of interest that patients perceive as beneficial and that, in the absence of bothersome side effects and high cost, would mandate a change in the patient's management." This definition was relying on a tiny amount of patient-reported change, and anything significant enough to affect patient management. Based on published evidence (160-164), the iHOT12 MCID value was determined to be 13 while mHHS MCID is 8 and VAS MCID is 0.99. With regard to the EQ-5D-3L, The TTO MCID is 0.310 and VAS MCID is 23. We calculated these values and compared them between the two groups to assess for any statistically significant differences.

3.5 Power and sample size

The power calculation was done by William Gray, a statistician at Northumbria NHS Foundation Trust. The primary outcome of interest was the change from baseline to 3 month and 6 month follow-up for the 12 items International Hip Outcome Tool (iHOT-12), comparing the PRP and placebo groups. The study was run as a superiority trial. The cut-off for statistical significance was set at 5% and desired power at 90%, with two-tailed tests applied. The change from baseline data is also assumed to be parametric in nature, and t-tests will be applied to the data to assess statistical significance.

The minimally clinically important difference (MCID) for the iHOT-12 has been reported as 13 (from 100) (160, 162). Although there is little previous data on which to base a sample size calculation, Monto et al. (135) compared the change from baseline to 12-month follow-up in a group of 40 patients with hip bursitis with steroids and PRP as the interventions being compared. In the PRP group, Harris Hip scores increased from 51.7 to 87.4, while in the steroid

group, scores increased from 50.5 to 58.8 at 12 months. Our sample size calculation was based on these figures since the Harris Hip score is also scored from 100.

We conservatively assume that change in iHOT score from baseline in the placebo group will be no more than the steroid group of Monto et al. and estimate a maximal change of 10. We also estimate that the change in the iHOT score from baseline in the PRP group will be no less than 27. Based on these figures, a minimal sample size at follow-up of 66 (33 in each group) will be required.

Pilot data obtained by our team suggest that the refusal to participate rate should be no more than 25% and the dropout rate no more than 35% over 12 months.

Refusal rates tend to be low in this patient group, given the chronic nature of the condition and the fact that patients will only be approached once conservative management has failed.

3.6 Eligibility

The recruitment source was from their primary care provider (GP, orthopaedic surgeon, rheumatologist or physiotherapist). Following the first interview and consent to enter the trial, eligibility checks (Table 7) are repeated for each participant on the day they attended for treatment to ensure that participants are not randomised in error. The participants received confirmation of their inclusion in the trial, which was also recorded in their medical notes and their GPs were informed. The inclusion criteria were set to include adult patients with capacity who are suffering from chronic GTPS. Also, to be included, patients should have a confirmed diagnosis with an MRI scan or US if MRI is contraindicated. We excluded patients with spine and other hip pathologies, which can give symptoms similar to GTPS. Patients with deformities or who had surgeries around the hip that can change the anatomy were also excluded. Add to that, patients with a high risk of bleeding or developing blood clots.

Inclusion criteria:
1. Over 18 years of age
2. Symptoms consistent with GTPS present for at least 6 months
3. Radiological diagnosis of GTPS using MRI, or ultrasound scan if MRI contraindicated
4. Failed conservative management in any other care setting

5. Patient is willing and able to provide written informed consent.
EXclusion criteria:
1. Lacks capacity to provide consent
2. Has hip joint osteoarthritis demonstrated on a plain radiograph, requiring treatment
3. Presence of confounding pathologies on the hip MRI
4. Any extensive surgery or deformity of the hip demonstrated on x-ray
5. Presence of systemic disorders – coagulopathy, active infection, immune system disorders, peripheral neuropathy, malignancy, unresolved fractures
6. Had any surgical treatment specifically targeted at GTPS e.g. bursectomy/ilio-tibial band lengthening
7. Pregnancy
8. Anti-coagulant therapy e.g., warfarin, rivaroxaban, apixaban, dabigatran
9. Haemoglobin < 10 g/dl or platelets < 150,000/ul
10. Unable to safely stop anti-platelet/NSAID medications e.g., recent cardiac stenting
11. Has lumbar-sacral spine pathology or a recent history of acute hip trauma
12. Has a recent history of acute sciatica
13. Is not able to attend or comply with treatment or follow up scheduling
14. Participates in any other clinical trial

Table 7: shows Inclusion and exclusion criteria.

3.7 Post randomisation withdrawal and exclusions

Participants were allowed to withdraw from the trial at any time without giving reasons and without their current or future care being adversely affected. Should any participants have any serious adverse events or if any further safety issues become apparent at our monitoring meetings or at any time during the study, then that participant and others may be excluded on safety and ethical grounds. All excluded patients were offered follow-up under our care just the same as all other continuing participants. We attempted to reduce the “lost to follow-up” by collecting PROM scores for these patients at the trial follow-up periods when they allowed us to; however, they remained outside the remit of the study.

3.8 Ethical approval and Consent

The trial received full ethical approval from Health Research Authority England on 23 October 2017: registration number 198415. The study was also approved by Northumbria Healthcare NHS Foundation Trust. Any modifications to the protocol were submitted for

further ethical approval and approved changes were documented on the ClinicalTrials.gov registry. The trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social Care, 2005. Written informed consent was obtained from all participants in the trial. Copies of the consent forms are kept in the trial site files and the patients' medical notes. Participants were free to withdraw from the study at any time without giving a reason. All the information collected during this trial are confidential and held in accordance with NHS Data Protection guidelines and Good Clinical Practice guidelines. Confidentiality will only be breached if patients disclose to us information which may indicate that there is a risk of harm to themselves or others. All participants attended a first interview meeting with our research team following a referral from their primary care provider (GP, Orthopaedic Surgeon, Rheumatologist or physiotherapist). They should already have received the trial information sheet. We explained the purpose and nature of the trial again and assessed their eligibility. They were given up to a week to decide whether they wished to be entered into the trial. A second interview was rescheduled if necessary. Written consent to enter the trial was taken. Once the participant has consented, their baseline PROMs will be assessed and recorded.

3.9 Recruitment

Participant recruitment started in March 2018 and finished in November 2021. The recruitment source is from their primary care provider (General Practitioner, Orthopaedic Surgeon, Rheumatologist or physiotherapist). Following the first interview and consent to enter the trial, eligibility checks were repeated for each participant on the day they attended for treatment to ensure that participants were not randomised in error. The participant received confirmation of their inclusion in the trial, which was also recorded in their medical notes and their GPs were informed. In order to enhance our recruitment, we circulated emails within the orthopaedics department asking all hip specialists to discuss the trial with their patients if they have GTPS. In addition, we displayed posters in all the clinic rooms in the outpatient departments of Northumbria Healthcare NHS Foundation trust. Furthermore, a website was created to facilitate the referrals and improve the recruitment process (166). This website gives information about the trial and our team and has links to online referrals.

3.10 Treatment allocation

Participants were enrolled by our research team, led by Mr. Ajay Malviya. They were allocated their treatment randomly. The allocation sequence was generated using a computer-generated randomiser. The results of this randomisation were kept in a secured separate Excel file. The participant was allocated to either the PRP or normal saline arm of the trial. All injections were performed by a consultant rheumatologist (Dr. Atchia) and sometimes by a musculoskeletal consultant radiologist (Dr. Rahul Dharmadikari) who does not have any direct links with the trial otherwise. The allocation sequence was hidden from the principal investigator and outcome assessors. Their allocation was recorded on a separate database to which the principal investigator/outcome assessors had no access. Only the treatment administrators had access to this, so they knew what treatment they were issuing. They and a dedicated research nurse were guardians of this allocation sequence database to ensure that the patients, principal investigator, and outcomes assessors do not have access. Allocation was revealed after the trial ended and data analysis has commenced.

3.11 Blinding

All participants were blinded to the treatment allocation. All preparation of the treatments was performed in another room, and the patient had a screen between them and their hip, preventing them from seeing what treatment they were being given (Figure 12). The treatment administrator was not blinded. Outcome assessors were blinded.

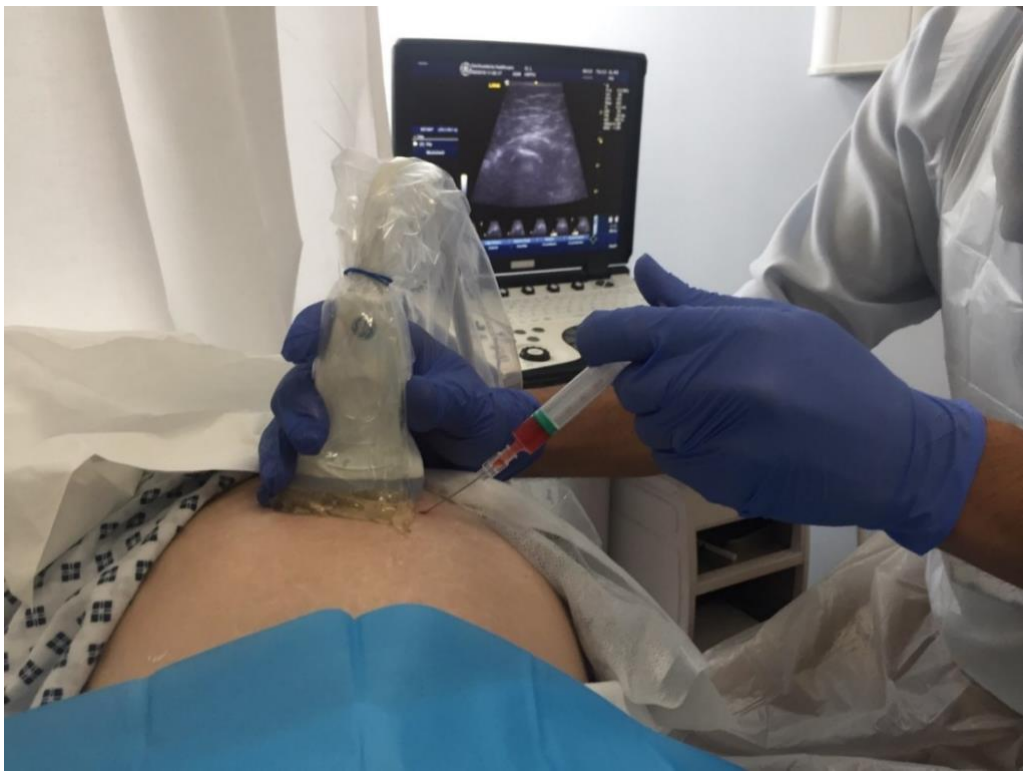

Figure 12: shows Dr. Atchia performing an ultrasound guided PRP injection.

3.12 Trial treatment

3.12.1 Injection Preparation:

Participants were randomised into two groups:

1. Test: Platelet Rich Plasma
2. Placebo: 4mls of normal 0.9% saline.

All participants attended the hospital as a day case. As per Northumbria Healthcare NHS Foundation Trust policies, written consent should be taken for these procedures; hence the consent was made generic to cover both treatment arms. All participants had 40mls of blood drawn from the antecubital vein using the aseptic technique. This blood was then taken to another room for 20mins to simulate the centrifuge time for the PRP preparation regardless of which treatment they were receiving. During these 20 minutes, our research nurse gets the patient ready for the injection. Dr. Atchia screens the hip using ultrasound and marks the injection site. Extensive cleaning of the area using alcohol and Chlorhexidine was done, followed by sterile drapes. All injections were performed in a lateral position (figure 12).

Three millilitres of Anticoagulant Citrate Dextrose Solution (ACD) were injected into the syringe to prepare the PRP. The ACD solution has the advantage of chelating calcium in the

blood, preventing coagulation, and lowering the pH of the blood to 6.5. At this pH, platelets do not aggregate. Twenty millilitres of blood were then extracted into the syringe. The blood was mixed with the ACDA and then injected into the PRP device. Another 20mls was obtained using the same steps. The two devices were centrifuged under 3,850 revolutions per minute for 7 minutes, and this was followed by a 4 minutes second cycle using the SW-PRP system provided by NTL Biologica (figure 13). The PRP was then extracted and passed to another sterile syringe through a 3-way valve to maintain sterility (figure 14). The end-result PRP using this system will have a baseline of 1,000,000 platelet/ µl. The quality check was guaranteed by the NTL Biologica and in our study we did not conduct quality control checks.

Figure 13: shows the SW-PRP system provided by NTL Biologica.

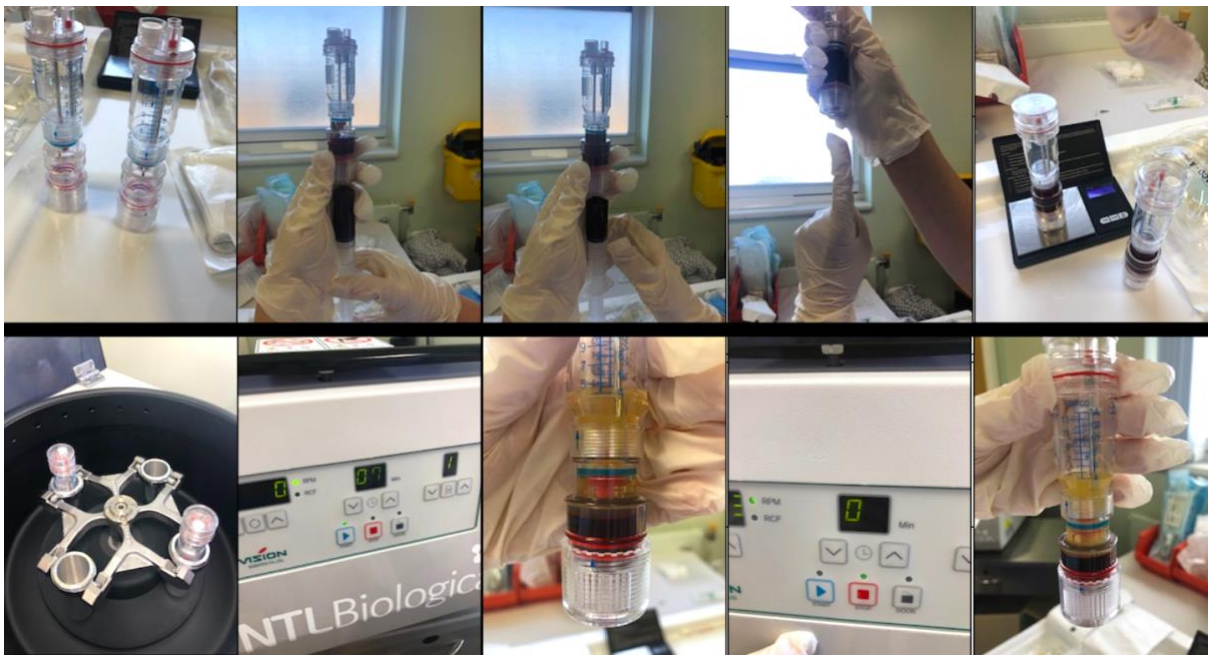

Figure 14: shows the steps of the PRP preparation.

The procedure took place in sterile conditions in the outpatient department to minimise the risk of infection. Patients, before the injection, had a curtain obscuring their hip and treatment area from their line of sight. They had local anaesthetic infiltrated superficially and deep in the greater trochanter area. Our consultant Rheumatologist, Dr. Atchia, injected either PRP or normal saline under ultrasound guidance into the trochanteric bursa and abductor tendons. All these measures were made to maintain the participant blind. All participants were then advised to rest for 72 hours before starting physiotherapy.

3.12.2 Injection technique

The operator utilises a sterile transducer cover and gel with a standard sterile approach for ultrasound-guided injections. Local anaesthesia is initially delivered to the skin surface and deeper subcutaneous tissues with 25 to 30-gauge needles to a depth of roughly 1.5 inches. 22-gauge needles are preferred to avoid needle clogging when delivering PRP. Standard 22-gauge 3.5-inch spinal needles are typically used, although longer needles may be required depending on the patient's body habitus. A diagnostic ultrasound examination of the symptomatic hip using a high frequency 12–5 MHz linear transducer is conducted prior to the injection. The patient is in a lateral decubitus position, with the problematic hip raised and the hips and knees moderately flexed in a comfortable position. Imaging the bony greater trochanter, the gluteus medius tendon insertion on the lateral facet of the greater trochanter, and the subgluteus medius and greater trochanteric bursae are all part of the routine

diagnostic examination. Gray-scale and power Doppler images of the femur are obtained longitudinally and transversely to the long axis. The patient's point of maximal tenderness over the gluteus medius insertion on the greater trochanter is located and marked along the posterior aspect of the transducer with the transducer in the transverse plane perpendicular to the long axis of the femur. Treatment is then delivered, and the injection site is dressed.

3.12.3 Patients flow during the COVID-19 pandemic

Patients were contacted to make an appointment and during the phone call patient were given safety instructions. Patients were again contacted 5 days before their appointment to discuss any symptoms. If symptoms were present the patient were given a future appointment. On Day of appointment, clinic room was set up as per protocol for COVID-19 and personal protective equipment were worn by all staff. We checked patients' temperature, those with temperature above 37.5 were sent home and a future appointment was given.

3.13 Physiotherapy programme

The home exercise program we followed was focusing on three main types of exercise. These types include stretching, strengthening and balance exercises. The stretching exercises used included Iliotibial Band (ITB) stretches, Piriformis stretches, prone lumbar extension, supine lumbar rotation and Cat stretches. We also advised specific strengthening exercises for the muscles around the hip, such as Side-lying leg lift, Clam and Gluteal kickback. The last set of exercises was made to improve balance and coordination and better activate the hip and lower back muscles. In addition to these rehabilitation exercises, the program encourages patients to progress back to regular physical activity to maximise health gains. The physiotherapy program leaflet was self-explanatory and made very easy to follow. When patients felt that they would need help with these exercises, they were referred to our physiotherapy department, which was already made aware of the trial and the physiotherapy program we created.

3.14 Data management

The data collected from the trial were entered into a trial database. The database was agreed upon and set up by our IT technician, statistician, and principal investigator using Microsoft Excel. The database will be stored securely on our computer systems in the hospital.

The database will be frozen during the interim analysis to ensure that data collected after this point is not included in the interim report. Access to the data is limited to those directly involved in the trial and part of the research team. The data is anonymised from identifiable participant data and will only contain demographic details. Identifiable participant data is held on a separate database in our secure computer network in the hospital. Each participant has a unique participant code, so their outcome data can be matched with their personal identifiable data if required.

In a locked cabinet, all physical data is stored in the Research and Development Office, North Tyneside General Hospital. The office is secured by a code-operated lock and is only accessible by the research team. All computer data is stored on our secure password-protected Trust computers. Archiving of data will be performed in accordance with the Research and Development Department, Northumbria Healthcare NHS Foundation Trust guidance. A data monitoring committee will be formed and convened for this trial.

3.15 Statistical analysis plan

The Test group (PRP) Alone: The difference between the follow-up scores with baseline will be assessed (eg, baseline vs. three months, baseline vs. 6 months). A significant difference will be a “p-value” of less than 0.05. The Placebo Group (Normal Saline) Alone: This will be analysed the same as the test group described above. **Test vs. Placebo:** For all outcome measures, the differential change at each follow-up time point will be compared between the trial arms and a significance value calculated. Statistical tests will be performed to ensure that BMI and age differences have not had a significant association with a particular result.

Data has been analysed using standard statistical software (SPSS and Excel) and online calculators such as MedCalc (167). In the first instance, data has been analysed using simple descriptive statistics to compare the two groups regarding demographics, clinical characteristics at baseline, and outcomes. The primary outcome of interest will be the change from baseline to 6-month follow-ups for the 12-item International Hip Outcome Tool (iHOT-12), comparing the PRP and placebo groups. The iHOT-12 data are expected to be parametric, so an unpaired t-test is used to compare the difference in change from baseline in the two groups. Since randomisation was stratified, we have looked to adjust for the possible confounding influence of differences in baseline characteristics (e.g., age, sex

distribution, using multivariable methods (e.g., logistic regression). The significance level for all inferential tests has been set at 5%.

In a secondary analysis, we have investigated changes in visual analogue pain score and modified Harris Hip score in the two groups as for the primary outcome. In sub-group analysis, we have investigated the data based on specific previous treatment, patients who required more than one treatment, and patients with the highest baseline pain levels.

3.16 Trial organisation and oversight

A trial steering committee has been formed from members of the research team, including the Principal Investigator and Trial coordinator from the research and development team, and a member of our patient focus group. All issues relating to the management and conduct of the trial have been reviewed and addressed in regular meetings organised by the research and development team. All indemnity, compensation, and insurance issues are detailed in the Sponsorship Agreement between our Research and Development team at North Tyneside General Hospital and Northumbria Healthcare NHS Foundation Trust.

Chapter 4: RESULTS

Eighty-one patients were recruited and randomly assigned to the PRP treatment group (n = 41) and the Placebo group (n = 40). One patient has opted out from the placebo group and two from the PRP group; hence data has been collected for 78 patients. Those three patients opted out after receiving the injection and were no longer interested in participating in the trial. Thirty-nine patients in each group. All the 78 cases were followed up periodically between 2018 and 2021. There were no statistically significant differences between the two groups' demographics, including age, gender and BMI. The following are the collected observations and analysed data.

4.1 Demographics

4.1.1 Age

The mean age of the patients in the PRP group was 59.26 years old, and the Placebo group was 58.51 years old (table 8). There was no statistically significant difference between the two groups (*P* 0.736). The majority of the patients were in the middle age group (48 to 63 years old) (figure 15). Few patients were in the youth group, and there were nine elderly patients in each group. The BMIs were comparable between these age groups in the PRP and the placebo group (table 9).

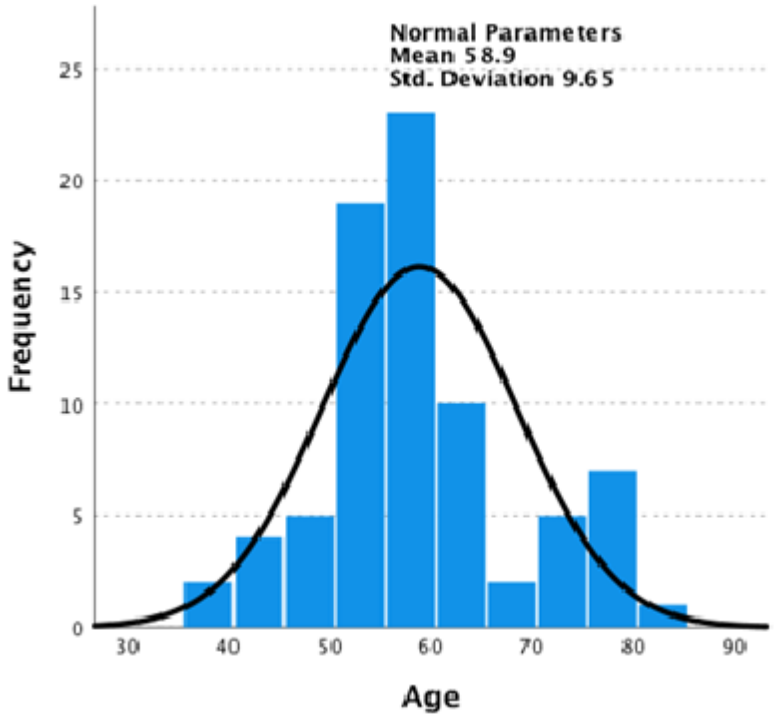

Figure 15: shows age distribution using one-sample Kolmogorov-Smirnov Normal Test.

Intervention	Mean Age (SD)	Minimum age	Maximum age
PRP (N 39)	59.26 (10.42)	37	80
Placebo (N 39)	58.51 (8.93)	40	85
P value (95% CI) (Fisher's Exact test)	0.736 (-3.635 to 5.122)		

Table 8: shows that the mean age of the two groups is not significantly different.

Age group (years)	PRP Number of patients (percentage)	Placebo Number of patients (percentage)	BMI PRP group	BMI placebo group
18–47 (youth)	4 (10.25%)	3 (7.69%)	29.5 (1.69)	28.7 (4.67)
48–63 (middle age)	26 (66.67%)	27 (69.23%)	27.45 (6.56)	28.72 (3.31)
≥ 64 (elderly)	9 (23.08%)	9 (23.08%)	28.26 (6.06)	26.79 (1.15)
Chi-Square test (P value)	0.922		0.696	0.265

Table 9: shows patients' distribution according to age and relations to BMI.

4.1.2 Gender

The Majority of the patients were females. There was no statistically significant difference between the two groups (table 10 and figure 16).

Intervention	Number of Males (%)	Number of Females

PRP	2 (5.13%)	37 (94.7%)
Placebo	4 (10.26%)	35 (89.74%)
P value (Fisher's exact test)	0.675	

Table 10: shows patients' distribution according to gender.

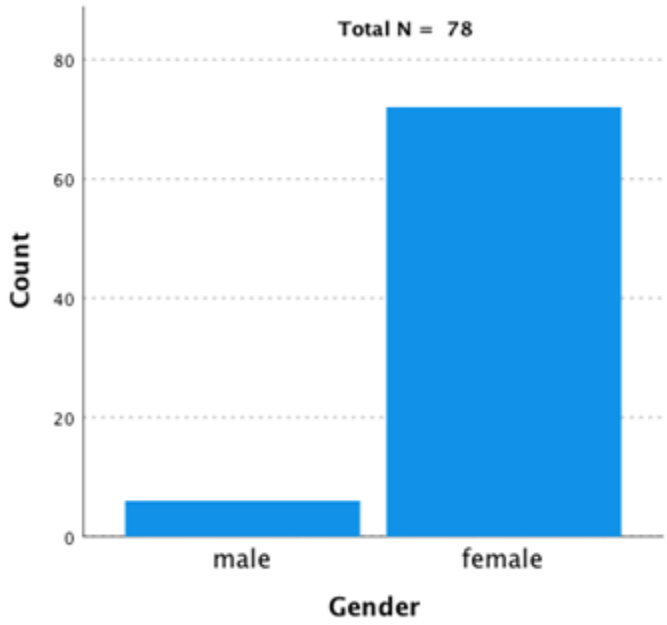

Figure 16: Bichart shows gender distribution.

4.1.3 BMI

The mean BMI for all participants was 28.06 (figure 17). The BMIs were comparable between the two groups with no statistically significant differences (table 11). Again, dividing patients into low and high BMI did not reveal any statistical difference (table 12).

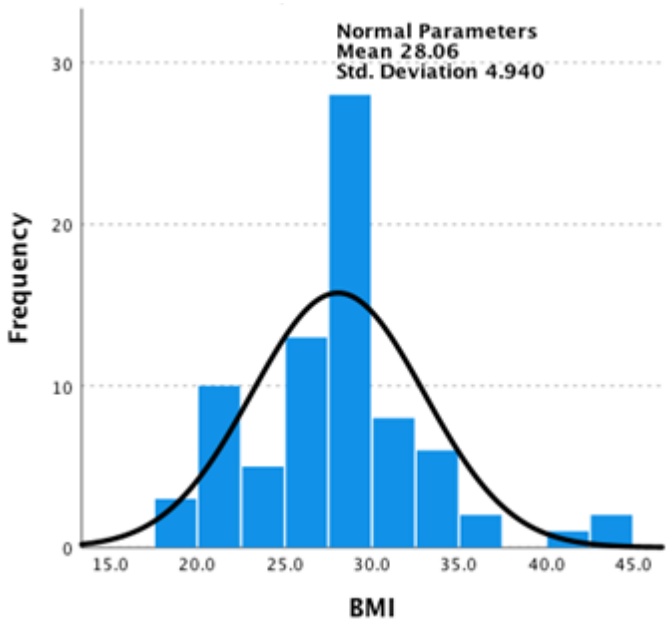

Figure 17: shows BMI distribution using one-sample Kolmogorov-Smirnov Normal Test.

BMI	PRP (SD)	Placebo (SD)	Chi-Square test (P value)
Mean	27.85 (6.15)	28.27 (3.19)	
minimum	17.5	21.2	0.468
maximum	43.8	35.9	

Table 11: compares the mean Body Mass Index (BMI) between the two groups.

BMI Classification	PRP number of patients (%)	Placebo number of patients (%)	P value (Fisher's Exact Test)
Up to 24.9	12 (30.77%)	6 (15.38%)	0.112
25 and above (obese and overweight)	27 (69.23%)	33 (84.62%)	

Table 12: shows patients' distribution according to BMI.

4.2 The Outcome scores

4.2.1 International Hip Outcome Tool 12-items (iHOT12)

The iHOT12 data was normalised hence parametric tests were used for analysis (table 13). The Boxplot revealed one outlier in the placebo group (figure 18). This was winsorized as suggested by the statistician.

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	intervention	Statistic	df	Sig.	Statistic	df	Sig.
iHOT12 Baseline	PRP	0.079	38	0.200	0.978	38	0.645
	Placebo	0.128	39	0.104	0.949	39	0.076

Table 13: Kolmogorov-Smirnov test shows normalised data.

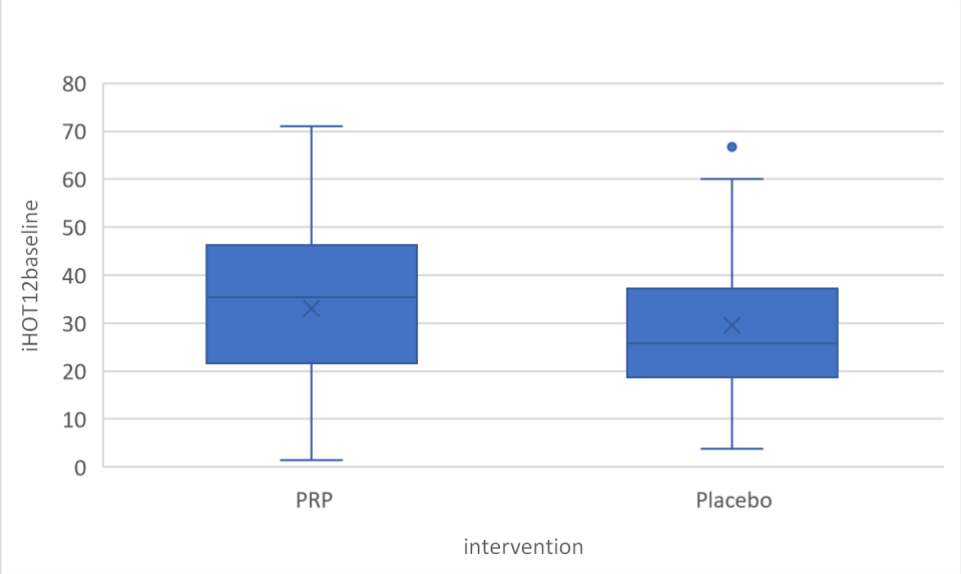

Figure 18: Boxplot of iHOT12 scores at baseline shows one outlier in the Placebo group.

The mean baseline iHOT12 score of the PRP group was 33.04 (SD±17.15). The mean score increased to 44.61 (SD±26.82) at the three-month follow-up. The change of score mean was 12.61. At the six-month follow-up, the mean score declined to 41.19 (SD±26.65). The change of scores mean at from six months was 9.51 (Table 14).

The mean baseline iHOT12 score of the Placebo group was 29.78 (SD±16.14). The mean score increased to 48.49 (SD±29.48) at the three-month follow-up and the change of score

mean was 17.65. At the six-month follow-up subsequently, the mean score slightly declined to 45.91 (SD±30.85) and the change of score mean was 16.93 (figure 19).

Groups		Baseline iHOT12 (Patients Number)	3 months iHOT12 (Patients Number)	Change of score from Baseline mean	6 months iHOT12 (Patients Number)	Change of score from Baseline mean
PRP	Mean	33.04 (38)	44.61(36)	12.61	41.19(36)	9.51
	SD	17.15	26.82		26.65	
Placebo	Mean	29.50 (39)	48.49 (37)	17.65	45.91 (35)	16.93
	SD	16.14	29.48		30.85	

Table 14: compares the iHOT12 scores between the PRP and the placebo groups.

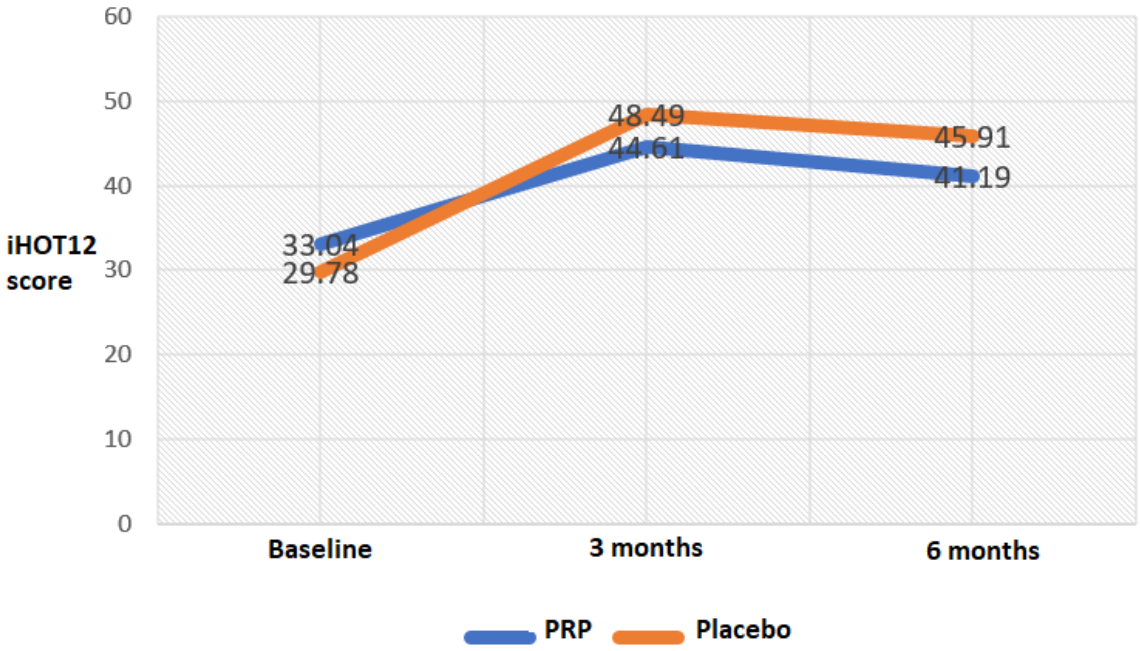

Figure 19: shows changes of the iHOT12 mean scores during the follow-up period.

To compare the mean baseline score with the three-months mean score and baseline with the six-months mean score, a paired T test was conducted. The mean scores significantly improved at three- and six-months follow-ups in the two groups (P value < 0.05) (Table 15).

Independent T test was then conducted to check for any significant difference between the two groups at baseline, three- and six-months follow-ups. Add to that we compared the mean change of scores at three and six months. The independent T test showed no statistically significant difference at all time points (P value > 0.05) (table 16).

Intervention		Paired Differences							
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Upper	Lower	t	df	Sig. (2-tailed)
PRP	iHOT12 Baseline Vs Three months	13.17	21.53	3.58	20.46	5.89	3.67	35	.001
	iHOT12 Baseline Vs Six months	8.89	17.11	2.93	14.86	2.91	3.02	33	.005
Placebo	iHOT12 Baseline Vs Three months	18.35	25.26	4.15	26.78	9.93	4.41	36	.001
	iHOT12 Baseline Vs Six months	16.95	28.90	4.88	26.88	7.02	3.47	34	.001

Table 15: shows iHOT12 statistically significant improvement achieved by both groups based on the Paired T test.

iHOT12 Scores PRP vs Placebo		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Baseline score	Equal variances assumed	.440	.509	.934	75	.354	3.54	3.79	-4.01	11.10
	Equal variances not assumed			.933	74.437	.354	3.54	3.79	-4.02	11.11
Three months	Equal variances assumed	.758	.387	-.588	71	.558	-3.88	6.60	-17.04	9.28
	Equal variances not assumed			-.589	70.686	.558	-3.88	6.59	-17.03	9.26
Three months Change of scores	Equal variances assumed	1.822	.181	-.970	71	.335	-5.04	5.20	-15.42	5.32
	Equal variances not assumed			-.973	69.061	.334	-5.04	5.18	-15.40	5.30
Six months	Equal variances assumed	1.676	.200	-.679	67	.499	-4.72	6.95	-18.59	9.14
	Equal variances not assumed			-.681	66.108	.498	-4.72	6.93	-18.56	9.12
Six months Change of scores	Equal variances assumed	8.666	.004	-1.323	65	.191	-7.42	5.61	-18.64	3.78
	Equal variances not assumed			-1.332	55.163	.188	-7.42849	5.57733	-18.60498	3.74

Table 16: shows no significant difference between the two groups' iHOT12 scores using the Independent T test.

MCID:

The minimally clinical important change was set at 13 based on previously published evidence as detailed in the methods section previously. In our series the mean change in scores at three months was 12.6 in the PRP group and 17.6 in the placebo group. Fourteen patients have achieved 13 or more MCID in the PRP group and 18 in the placebo group at three months. Comparing the two groups the difference is not statistically significant (P value using the Fisher's Exact test was 0.482). The mean change in scores at six months was 9.5 in the PRP group and 16.93 in the placebo group. Fifteen patients have achieved 13 or more MCID in the PRP group and 17 in the placebo group at six months. Comparing the two groups the difference is not statistically significant (P value using the Fisher's Exact test was 0.808).

4.2.2 Visual analogue Scale (VAS)

The test of normality revealed that the baseline VAS scores were not normally distributed (Table 17). Hence the data was analysed using non-parametric tests. The Boxplot showed no outliers in the two groups at baseline (figure 20).

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	intervention	Statistic	df	Sig.	Statistic	df	Sig.
VAS Baseline	PRP	0.167	39	0.008	0.935	39	0.026
	Placebo	0.193	39	0.001	0.942	39	0.043

Table 17: Kolmogorov-Smirnov test shows a non-normalised data.

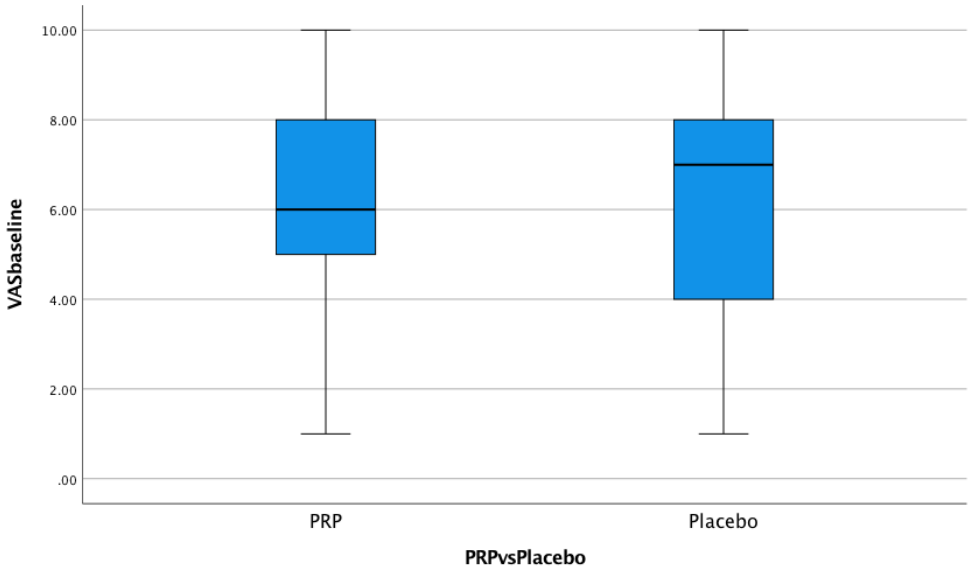

Figure 20: The VAS Boxplot shows no outliers.

The mean VAS score of the PRP group at baseline was 6 (SD±2.32). The mean score decreased to 5.03 (SD±3.02) at the three-month follow-up. The change of score mean was 1.23. At the six-month follow-up, the mean score increased to 5.43 (SD±3.07). The change of score mean at six months was 0.65 (Table 18).

The mean VAS score of the placebo group at baseline was 6.38 (SD±2.36). The mean score decreased to 4.83 (SD±2.86) at the three-month follow-up. The change of score mean was 1.62. At the six-month follow-up, the mean score increased to 5.5 (SD±3.10) (Table 18). The change of score mean was 0.84.

Groups		Baseline VAS (Patients Number)	3 months VAS (Patients Number)	Change of score from Baseline	6 months VAS (Patients Number)	Change of score from Baseline
PRP	Mean	6 (39)	5.03 (37)	-1.23	5.43 (36)	-0.65
	SD	2.32	3.02		3.07	
Placebo	Mean	6.38 (39)	4.83 (38)	-1.62	5.5 (37)	-0.84
	SD	2.36	2.86		3.10	

Table 18: compares the VAS scores between the PRP and the placebo groups.

The independent Mann-Whitney U Test showed no statistically significant difference between the two groups at baseline (P 0.436), three-months (P 0.827) and six-months follow-ups (P 0.920) (figures 21-23). The VAS scores improved at three month and six months follow compared to baseline (figure 24). The Wilcoxon Signed Rank Test showed the Placebo group significantly improved at three months (P 0.010) while the improvement achieved by the PRP group was insignificant (P 0.095). The same test showed no significant difference between baseline and the six months follow-up in both PRP and placebo groups (P 0.184 and 0.333 respectively) (table 19).

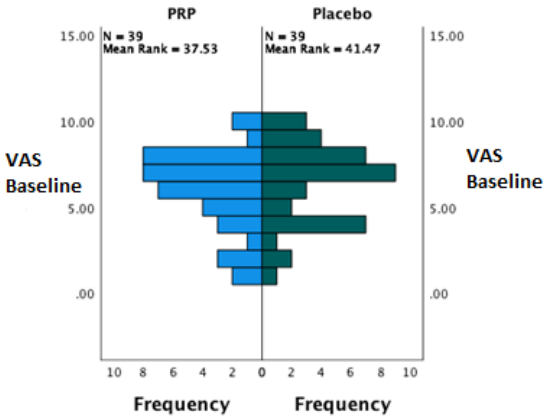

Figure 21: shows the VAS Independent-Samples Mann-Whitney U test at baseline

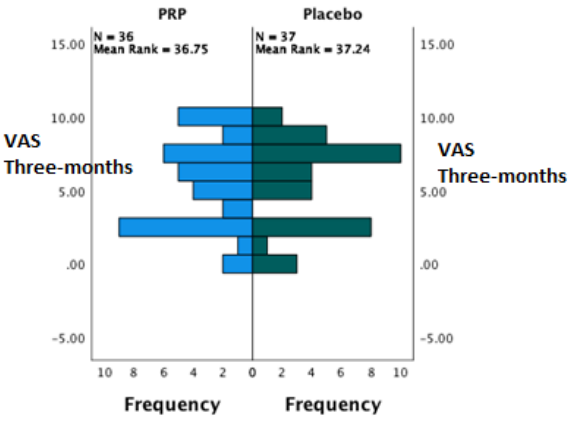

Figure 22: shows the VAS Independent-Samples Mann-Whitney U test at three months

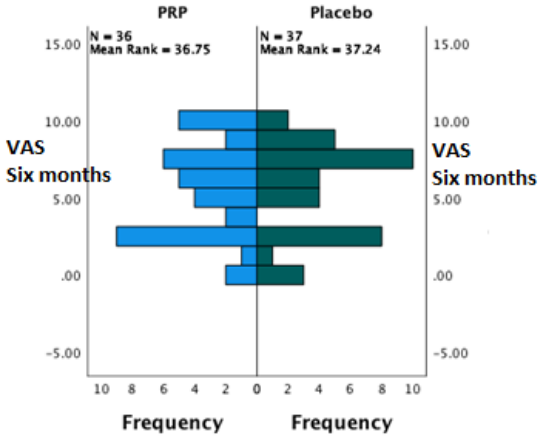

Figure 23: shows the VAS Independent-Samples Mann-Whitney U test at six months

In addition, there were no significant differences when compared the mean change of scores at three and six months (P 0.579 and P 0.794 respectively).

Age and BMI had no effect on scores in the two groups (P 0.889 and P 0.545 respectively).

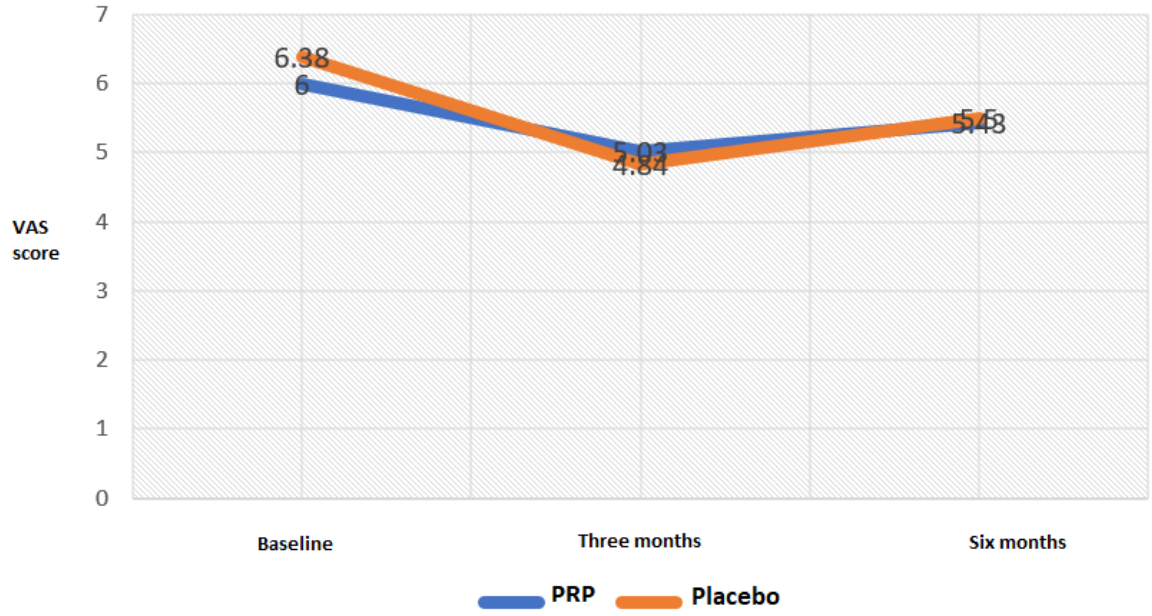

Figure 24: shows changes of the VAS mean scores during the follow-up period.

Related-Samples Wilcoxon Signed Rank Test		VAS Baseline vs three months	VAS Baseline vs six months
PRP	Total N	37	36
	Test Statistic	101.00	123.50
	Standard Error	36.85	39.17
	Standardized Test Statistic	-1.66	-1.32
	Asymptotic Sig. (2-sided test)	.095	.184
Placebo	Total N	38	37
	Test Statistic	136.50	199.00
	Standard Error	55.52	50.63
	Standardized Test Statistic	-2.59	-.96
	Asymptotic Sig. (2-sided test)	.010	.333

Table 19: The Wilcoxon Signed Rank Test shows VAS scores did not significantly improve at the six-months follow-up.

VAS MCID:

The minimally clinical important change was set at 0.99 based on previously published evidence as detailed in the methods section previously. In our series the mean change in scores at three months was -1.23 in the PRP group and -1.62 in the placebo group. Twenty-two patients have achieved 0.99 or more MCID in the PRP group and 16 in the placebo group at three months. Comparing the two groups the difference is not statistically significant (P value using the Fisher's Exact test was 0.257). The mean change in scores at six months was -0.65 in the PRP group and -0.84in the placebo group. Twenty-two patients have achieved 0.99 or more MCID in the PRP group and Twenty-two in the placebo group at six months. Comparing the two groups the difference is not statistically significant (P value using the Fisher's Exact test was 1.000). Comparing the change of scores between the two groups at three and six months using the Mann-Whitney U Test revealed no statistically significant difference (P 0.597, P 0.794 respectively).

4.2.3 Modified Harris Hip Score (mHHS)

The test of normality confirmed that the mHHS scores are normally distributed in the two groups at baseline and the boxplot revealed no outliers (table 20 and figure 25).

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	intervention	Statistic	df	Sig.	Statistic	df	Sig.
mHHS Baseline	PRP	0.084	39	0.200	0.967	39	0.314
	Placebo	0.081	39	0.200	0.978	39	0.625

Table 20: Test of normality shows normalised data

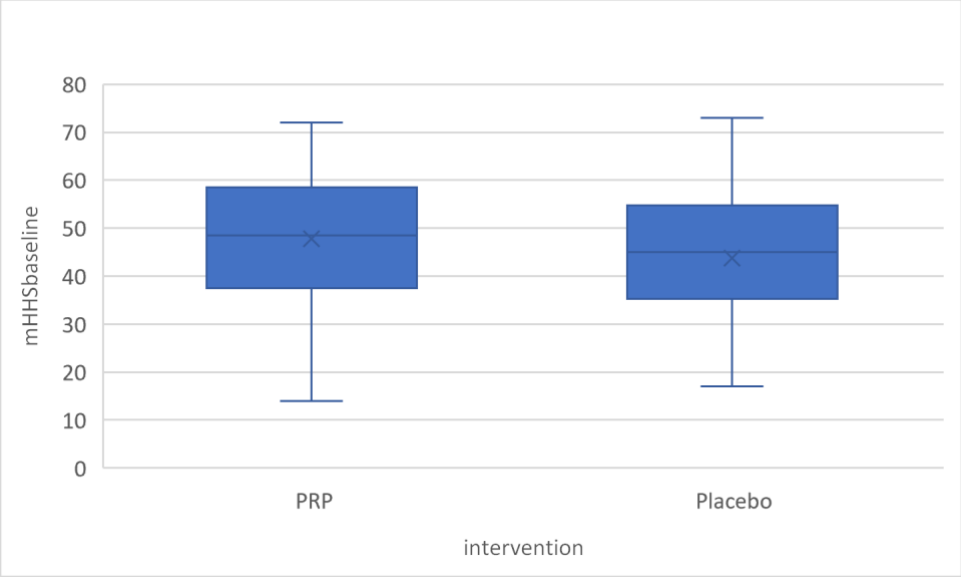

Figure 25: The mHHS Boxplot at baseline shows no outliers

The mean mHHS score of the PRP group at baseline was 48.87 (SD±14.12). The mean score increased to 57.89 (SD±18.44) at the three-month follow-up. The mean change of scores was 9.0. At the six-month follow-up, the mean score decreased to 53.83 (SD±18.82) and the mean change of scores was 5.9 (Table 21).

The mean mHHS score of the placebo group at baseline was 43.30 (SD±13.79). The mean score increased to 54.39 (SD±20.01) at the three-month follow-up. The mean change of scores was 10.94. At the six-month follow-up, the mean score increased to 56.40 (SD±20.57) and the mean change of scores was 13.08(Table 21).

Groups		Baseline mHHS (Patients Number)	3 months mHHS (Patients Number)	Change of score from Baseline	6 months mHHS (Patients Number)	Change of score from Baseline
PRP	Mean	48.87 (39)	57.89 (37)	9.0	53.83	5.9 (36)
	St Deviation	14.12	18.44		18.82	
Placebo	Mean	43.30 (39)	54.39 (38)	10.94	56.40 (37)	13.08
	St Deviation	13.79	20.01		20.57	

Table 21: compares the mHHS scores between the PRP and the placebo groups

To compare the mean baseline score with the three-months mean score and baseline with the six-months mean score, a paired T test was conducted. The mean scores significantly improved at three- and six-months follow-ups in the two groups (P value < 0.05) (Table 22 and figure 26). Independent T test was then conducted to check for any significant difference between the two groups at baseline, three- and six-months follow-ups. Add to that we compared the mean change of scores at three and six months. The independent T test showed no statistically significant difference at all time points (P value > 0.05) (Table 23).

intervention		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Upper	Lower			
PRP	mHHS Baseline - Three months	9.00	16.31	2.68	14.43	3.56	3.35	36	.002
	mHHS Baseline - Six months	5.94	13.53	2.25	10.52	1.36	2.63	35	.012
Placebo	mHHS Baseline - Three months	10.94	21.57	3.49	18.03	3.85	3.12	37	.003
	mHHS Baseline - Six months	13.08	21.55	3.54	20.26	5.89	3.69	36	<.001

Table 22: shows mHHS statistically significant improvement achieved by both groups based on the Paired T test.

mHHS Scores PRP vs Placebo		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Baseline score	Equal variances assumed	.07	.784	1.76	76	.082	5.56	3.16	-0.73	11.85
	Equal variances not assumed			1.76	75.957	.082	5.56	3.16	-0.73	11.85
Three months	Equal variances assumed	.39	.533	.78	73	.434	3.49	4.44	-5.36	12.36
	Equal variances not assumed			.78	72.785	.434	3.49	4.44	-5.35	12.35
Three months Change of scores	Equal variances assumed	1.11	.295	-.44	73	.661	-1.94	4.42	-10.76	6.87
	Equal variances not assumed			-.44	68.819	.660	-1.94	4.40	-10.74	6.84
Six months	Equal variances assumed	1.13	.291	-.55	71	.579	-1.94	4.40	-10.74	6.84
	Equal variances not assumed			-.55	70.737	.579	-2.57	4.61	-11.78	6.63
	Equal variances assumed	6.20	.015	-1.68	71	.096	-2.57	4.61	-11.77	6.62

Six months Change of scores	Equal variances not assumed		-1.69	60.82	.094	-7.13	4.22	-15.56	1.29

Table 23: mHHS Independent T test shows no significant difference between the two groups during the follow-up period.

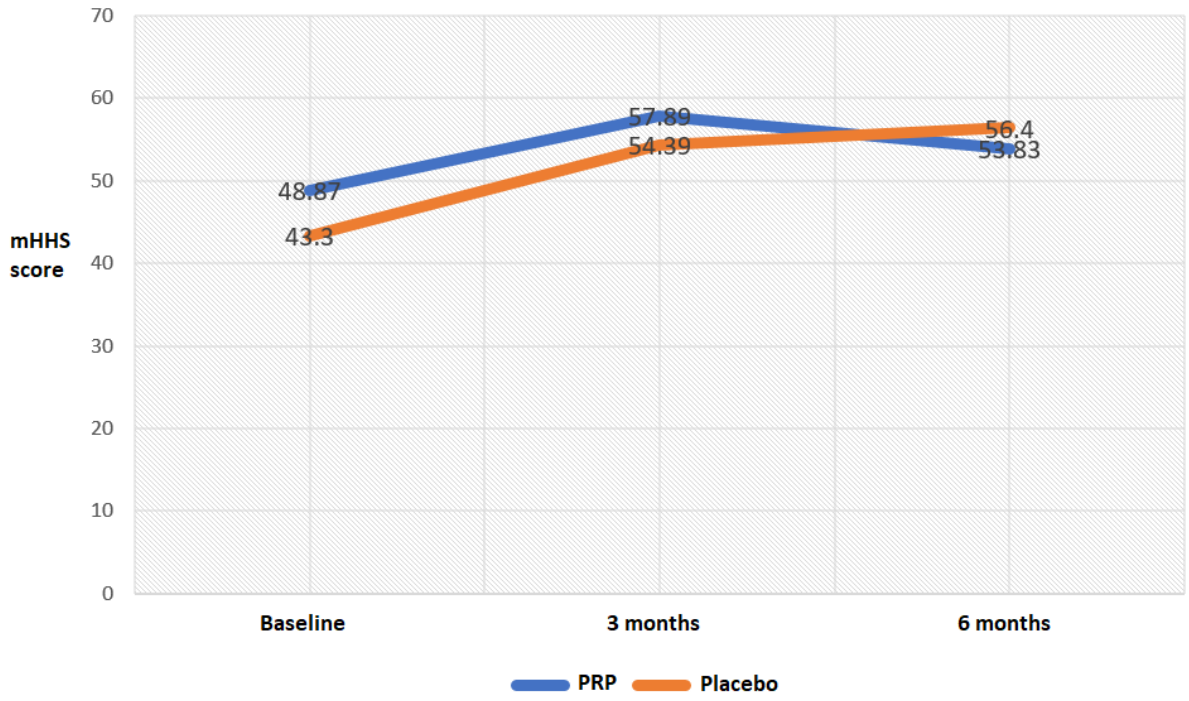

Figure 26: shows the improvement of the mHHS scores in the two groups.

MCID:

The minimally clinical important change was defined to be 8 by Kemp et al (156) as detailed in the methods section previously. In our series the mean change in scores at three months was 9.0 in the PRP group and 10.9 in the placebo group. Fifteen patients have achieved 8 or more MCID in the PRP group and 17 in the placebo group at three months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.786). The mean change in scores at six months was 5.9 in the PRP group and 13.08 in the placebo group. Thirteen patients have achieved 8 or more MCID in the PRP group and twenty in the placebo group at six months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.275).

4.2.4 EQ5D-3L (TTO and VAS components)

EQ5D-3L TTO:

The test of normality confirmed that the data is not normally distributed in both groups at the baseline (table 24). The Boxplot revealed no outliers in the two groups (figure 27).

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	intervention	Statistic	df	Sig.	Statistic	df	Sig.
EQ5D-3L TTO Baseline	PRP	.260	39	.000	.832	39	.000
	Placebo	.201	39	.000	.870	39	.000

Table 24: Test of normality shows EQ5D-3L TTO data is not normally distributed

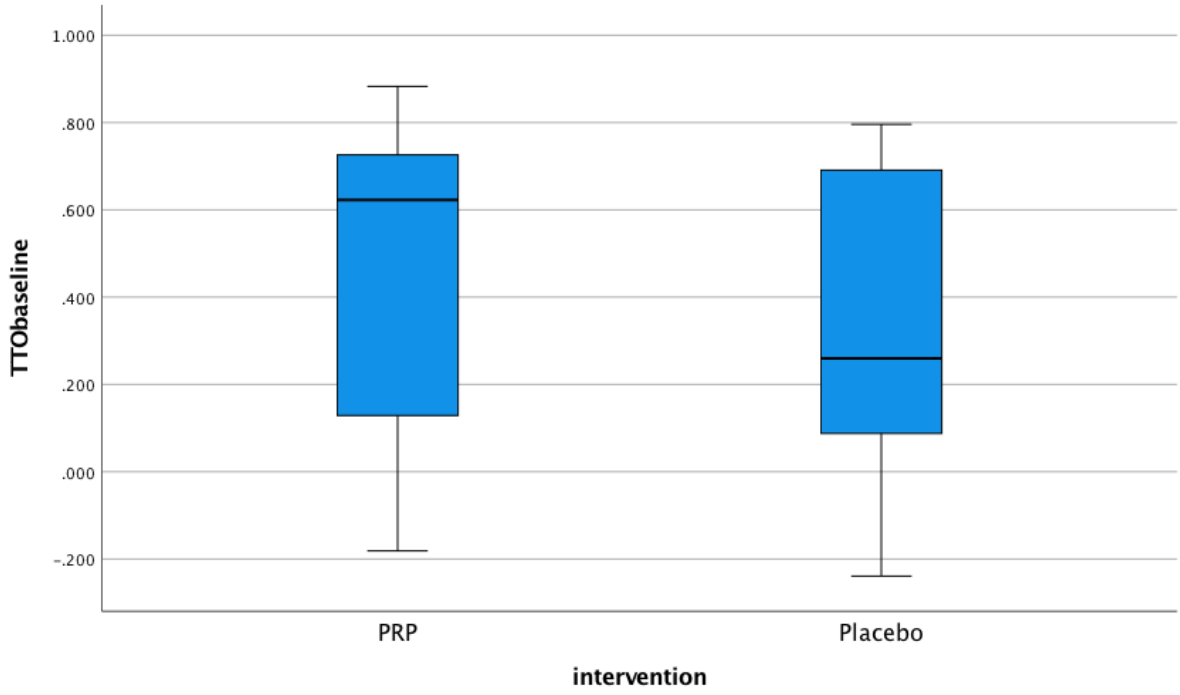

Figure 27: EQ5D-3L TTO Boxplot at baseline shows no outliers

The PRP group's mean baseline EQ5D-3L TTO score was 0.493 (SD±0.311). The mean score increased to 0.555 (SD±0.304) at the three-month follow-up. The mean change of scores was 0.073. At the six-month follow-up, the mean score declined to 0.503 (SD±0.342) and the mean change of scores was 0.029. The mean baseline iHOT12 score of the Placebo group was 0.349 (SD±0.333). The mean baseline score increased to 0.503 (SD±0.361) at the three-month follow-up and the mean change of scores was 0.158. At the six-month follow-up

subsequently, the mean score slightly improved to 0.505 (SD±0.379) and mean change of scores was 0.167 (table 25 and figure 28).

Groups		Baseline EQ5D TTO	3 Month EQ5D TTO	Change of score from Baseline	6 Month EQ5D TTO	Change of score from Baseline
PRP	Mean	0.493 (39)	0.555 (37)	0.073	0.503 (36)	0.029
	SD	0.311	0.304		0.342	
Placebo	Mean	0.349 (39)	0.503 (38)	0.158	0.505 (36)	0.167
	SD	0.333	0.361		0.379	

Table 25: compares the EQ5D-3L TTO scores between the PRP and the placebo groups.

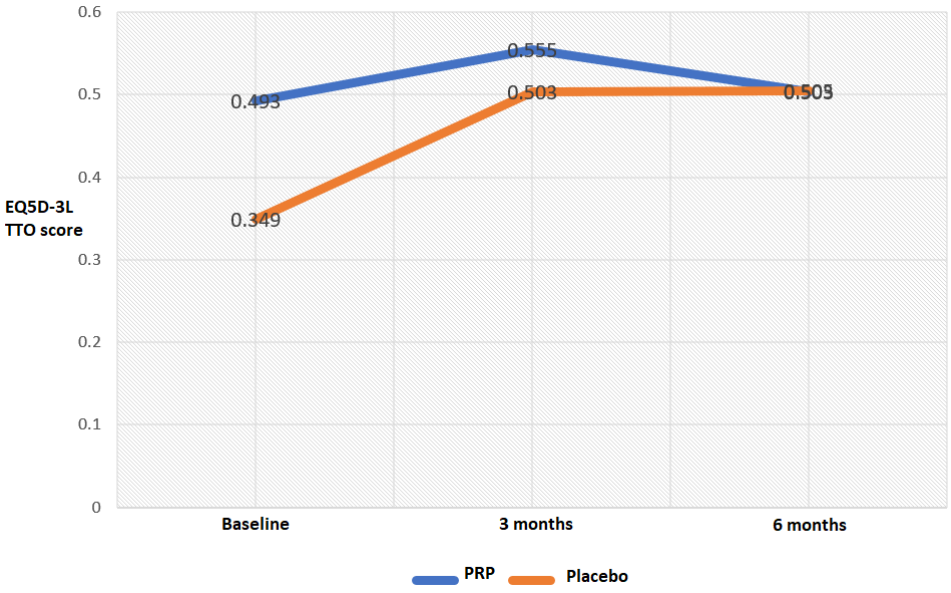

Figure 28: compares the EQ5D-3L TTO scores between the PRP and the placebo groups.

Non-parametric tests were used to analyse this data as detailed below. Age and BMI were revealed to have no effect on scores (P 0.889 and P 0.545 respectively) based on the Independent-Sample Mann-Whitney U Test. There was a significant difference between the mean scores at the baseline according to the Mann-Whitney U Test (P 0.045) (Figure 29) but

no significant differences at the three (P 0.651) and six-months follow-ups (P 0.923) (figures 30 and 31).

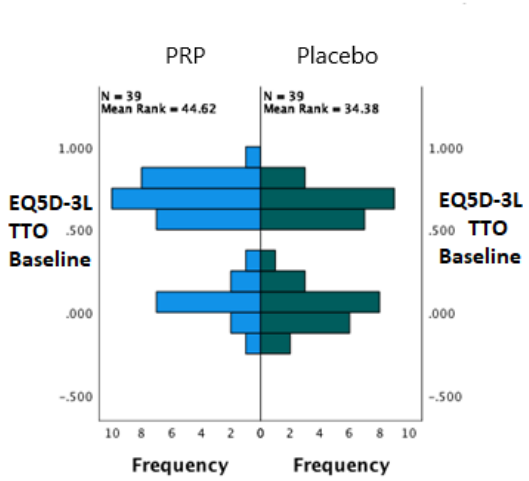

Figure 29: Mann-Whitney U test at baseline shows significant difference between the two groups.

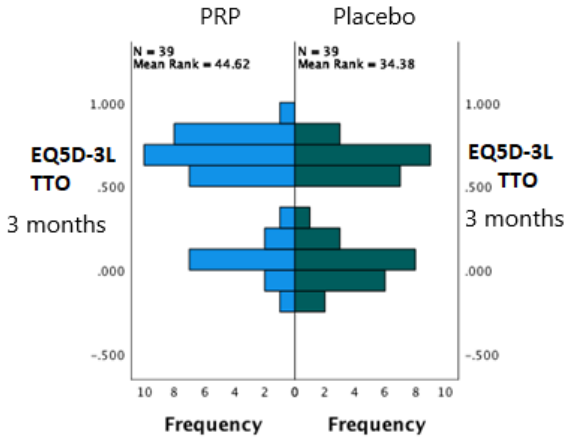

Figure 30: Mann-Whitney U test shows no significant difference at three months follow-up.

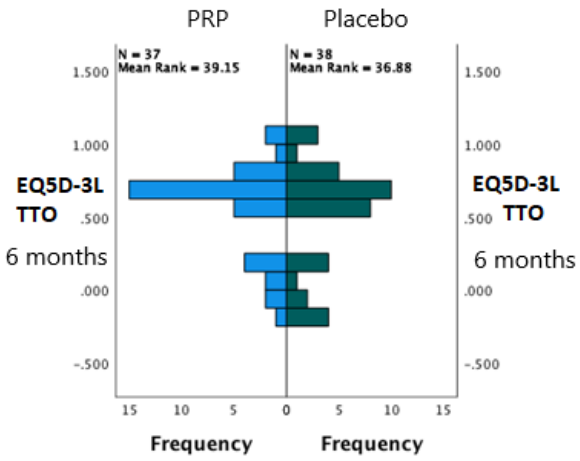

Figure 31: EQ5D-3L TTO Mann-Whitney U test shows no significant difference at six months.

The mean change of scores at three and six months was not significantly different between the two groups (P 0.288 for both). The Wilcoxon Signed Rank Test showed the Placebo group significantly improved at the three- and six-months follow-ups (P 0.038 and P 0.020 respectively) while the improvement achieved by the PRP group at three and six months was insignificant (P 0.271 and 0.245 respectively) (table 26).

	Intervention	EQ5D-3L TTO Baseline vs three months	EQ5D-3L TTO Baseline vs six months
PRP	Total N	37	36
	Test Statistic	286.00	254.00
	Standard Error	48.56	43.89
	Standardized Test Statistic	1.10	1.16
	Asymptotic Sig. (2-sided test)	.271	.245
Placebo	Total N	38	36
	Test Statistic	465.00	366.50
	Standard Error	63.57	51.00
	Standardized Test Statistic	2.07	2.32
	Asymptotic Sig. (2-sided test)	.038	.020

Table 26: Related-Samples Wilcoxon Signed Rank Test shows significant results at three and six months achieved by placebo group.

The EQ5D-TTO MCID:

The estimated MCID cut-point for EQ-5D TTO based on a general-health anchor was 0.310 (CI: 0.29–0.33). In our series the mean change in scores at three months was 0.073 in the PRP group and 0.158 in the placebo group. Eight patients have achieved 0.310 or more MCID in the PRP group and 13 in the placebo group at three months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.403). The mean change in scores at six months was 0.029 in the PRP group and 0.167 in the placebo group. Four patients have achieved 0.310 or more MCID in the PRP group and 11 in the placebo group at six months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.127). Comparing the change of scores between the two groups at three and six months using the Mann-Whitney U Test revealed no statistically significant difference (P 0.288 for both).

EQ5D-3L VAS:

The test of normality revealed that the PRP group baseline data were not normally distributed hence non-parametric tests were used for analysis. The boxplot revealed no outliers in the two groups.

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	intervention	Statistic	df	Sig.	Statistic	df	Sig.
EQ5D-3L VAS Baseline	PRP	.149	39	.030	.970	39	.365
	Placebo	.115	39	.200	.955	39	.121

Table 27: Test of Normality shows data is not normally distributed.

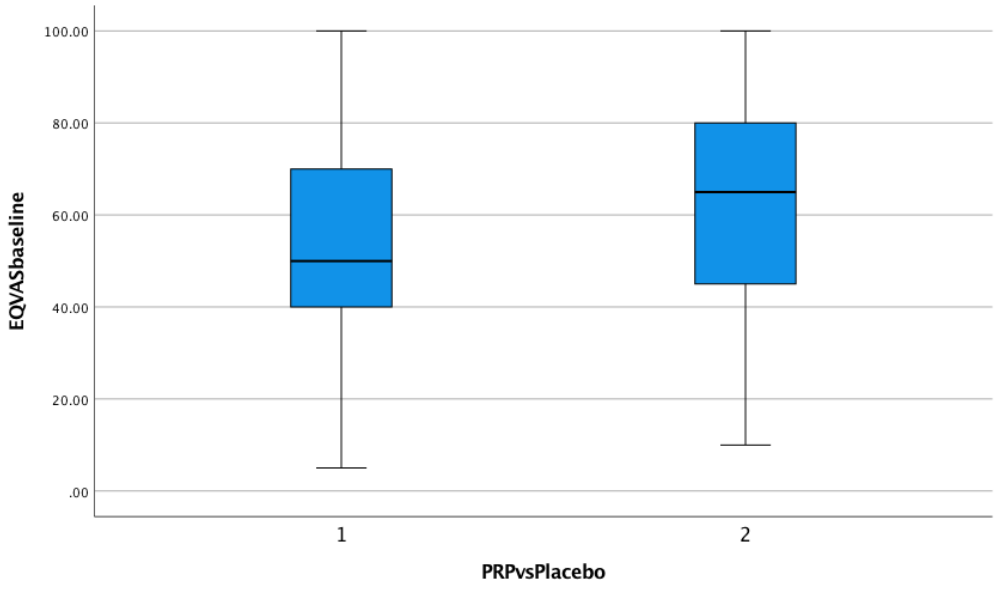

Figure 32: EQ5D-3L VAS Boxplot at baseline shows no outliers.

The PRP group's mean baseline EQ5D-3L VAS score was 56.15 (SD±21.99). The mean score increased to 58.32 (SD±24.32) at the three-month follow-up and the mean change of scores was 3.59. At the six-month follow-up, the mean score declined to 56.75 (SD±25.83) and the mean change of scores was 0.50. The mean baseline EQ5D-3L VAS score of the Placebo group was 62.05 (SD±24.43). The mean score increased to 62.74 (SD±21.55) at the three-month follow-up and the mean change of scores was 0.11. Subsequently, at the six-month follow-up, the mean score slightly declined to 61.41 (SD±20.88) and the mean change of scores was 0.06 (table 17 and figure 18).

Groups		Baseline EQ5D VAS	3 Month EQ5D VAS	Change of score from Baseline (%)	6 Month EQ5D VAS	Change of score from Baseline (%)
PRP	Mean	56.15 (39)	58.32 (37)	3.59	56.75 (36)	0.50
	SD	21.99	24.32		25.83	
Placebo	Mean	62.05 (39)	62.74 (38)	0.11	63.11 (36)	0.056
	SD	24.43	21.55		20.88	

Table 28: compares the EQ5D-3L VAS scores between the PRP and the placebo groups.

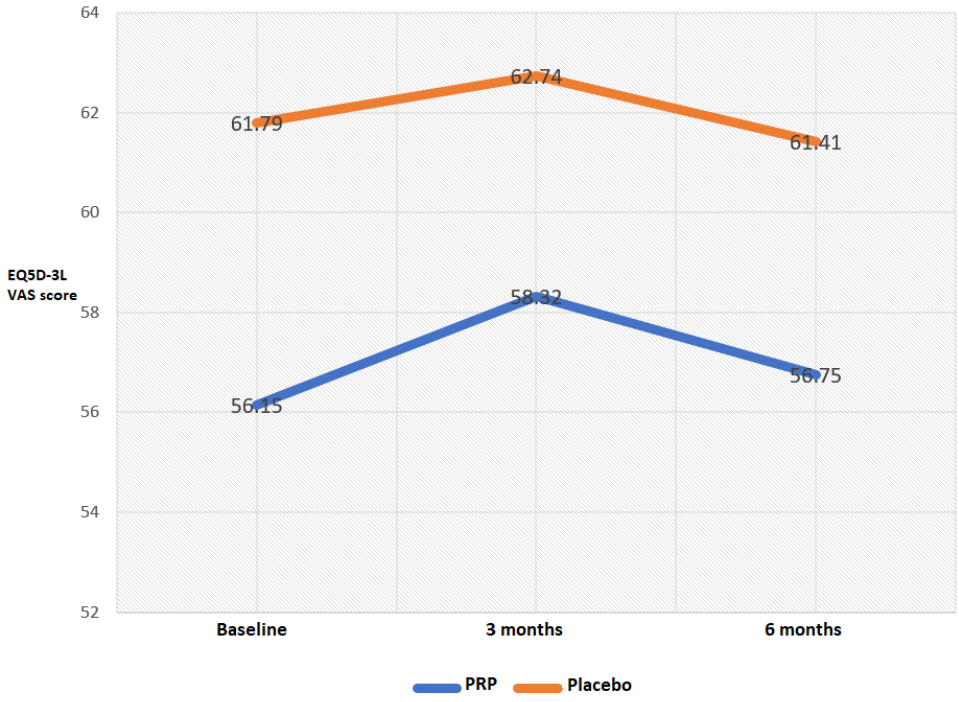

Figure 33: compares the EQ5D-3L VAS scores between the PRP and the placebo groups

Non-parametric tests were used to analyse this data as detailed below. Age and BMI were revealed to have no effect on scores (P 0.889 and P 0.545 respectively) based on the Independent-Sample Mann-Whitney U Test. There was no significant difference between the mean scores at the baseline (P 0.231) three (P 0.664) and six-months follow-ups (P 0.403) (figures). The Wilcoxon Signed Rank Test was used to compare the mean scores at baseline with means at the three- and six-months follow-ups. The test showed no significant improvement was achieved throughout the follow-up in both groups (table 29).

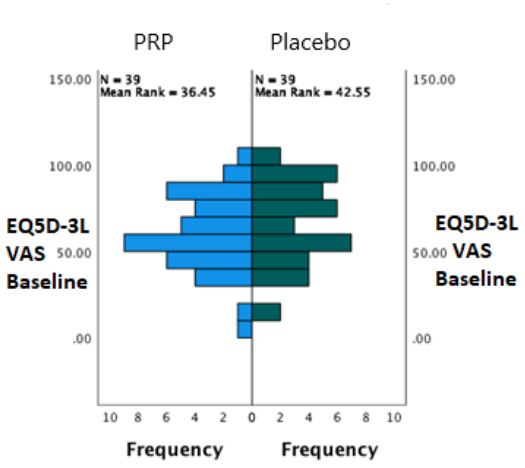

Figure 34: EQ5D-3L VAS Mann-Whitney U test at baseline

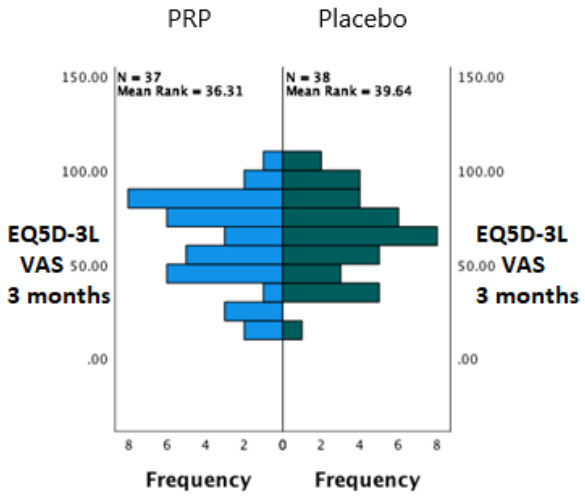

Figure 35: EQ5D-3L VAS Mann-Whitney U test at three months

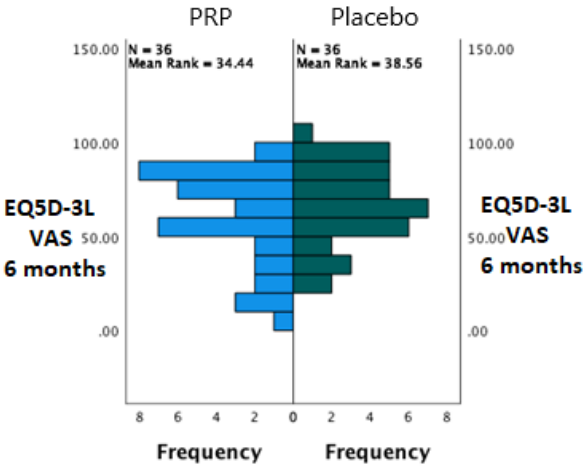

Figure 36: EQ5D-3L VAS Mann-Whitney U test at six months

	Intervention	EQ5D-3L VAS Baseline vs three months	EQ5D-3L VAS Baseline vs six months
PRP	Total N	37	36
	Test Statistic	256.00	247.00
	Standard Error	46.12	50.89
	Standardized Test Statistic	.83	-.020
	Asymptotic Sig. (2-sided test)	.404	.984
Placebo	Total N	38	36
	Test Statistic	295.50	222.00
	Standard Error	60.91	48.43
	Standardized Test Statistic	-.32	-.21
	Asymptotic Sig. (2-sided test)	.749	.828

Table 29: The Related-Samples Wilcoxon Signed Rank Test shows no EQ5D-3L VAS significant improvement was achieved throughout the follow-up.

The EQ-VAS MCID:

The estimated MCID cut-points for EQ-5D VAS based on a general-health anchor was 23 (CI: 21–25). In our series, eight patients have achieved 23 or more MCID in the PRP as well as the placebo group at three months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.839). Nine patients have achieved 23 or more MCID in the PRP group and six in the placebo group at six months. Comparing the two groups the difference is not statistically significant (P value using the Chi-Square test was 0.685). Comparing the change of scores between the two groups at three and six months using the Mann-Whitney U Test revealed no statistically significant difference (P 0.383, P 0.874 respectively).

4.3 Effect of BMI, age and gender on outcome scores:

A two-way ANOVA was performed to analyse the effect of the interventions (PRP vs Placebo) and the BMI on the outcome scores. A two-way ANOVA revealed no statistically significant interaction between the effects of the interventions and the BMI ($F = 0.904$, $p = 0.565$). Simple main effects analysis showed that the interventions did not significantly affect the

outcome scores (p = 0.385). Simple main effects analysis showed that BMI did not significantly affect the outcome scores (p = 0.173).

A second two-way ANOVA was performed to analyse the effect of the interventions (PRP vs Placebo) and the Age on the outcome scores. A two-way ANOVA revealed no statistically significant interaction between the effects of the interventions and the Age (F = 1.124, p = 0.329). Simple main effects analysis showed that Age and interventions did not significantly affect the outcome scores (p = 0.816 and p = 0.695, respectively).

A third two-way ANOVA was performed to analyse the effect of the interventions (PRP vs Placebo) and the gender on the outcome scores. A two-way ANOVA revealed no statistically significant interaction between the effects of the interventions and the gender (F = 0.584, p = 0.872). Simple main effects analysis showed that gender and interventions did not significantly affect the outcome scores (p = 0.641 and p = 0.725, respectively).

4.4 The cost of Ultrasound-guided PRP injections

According to the Department of Health, the hospital outpatient consultation with an ultrasound scan costs the NHS £145.74 (162). This cost includes the costs of a consultant radiologist and a nurse lasting 30 minutes of patient contact and an ultrasound scan. The centrifuge used to prepare the PRP is normally consigned; hence the hospital only pays for the PRP kits. The cost of the kit ranges between £193 and £265, depending on the size of the kit. The total cost of an outpatient ultrasound guided RPR injection is between £339 and £410. On the other hand, the price of a steroid injection (1ml methylprednisolone (40 mg) and 1ml 2% Lignocaine), according to the BNF, is only £3.74 (163).

4.5 Adverse events

We contacted patients one week following the injection to check for adverse events such as allergic reactions, pain, nerve-related symptoms and infection. None of our patients reported any early or late complications following this procedure.

Chapter 5: DISCUSSION

5.1 Why PRP:

PRP is an autologous blood product that promotes healing in damaged or inflamed tissues, including muscles, ligaments, bones, and tendons. Many systems and techniques are used to obtain PRP, but they share the basic principles of withdrawing blood from a patient with some anticoagulant (76). The blood is then spun in a centrifuge one or more times, separating it into its constituent layers. Platelet-rich plasma is extracted and sometimes activated using thrombin or Calcium Chloride (CaCl). This volume of PRP can then be applied to the tissues. The platelet concentration is thought to increase 3-8 folds (120). The concentration of leucocytes in different preparations also varies and can impact its efficacy (120, 139). Platelets are made up of various substances, including growth factors and cytokines that aid in tissue healing. The tissue injury, inflammation, and repair processes utilise these growth factors. Therefore, the theory is that the higher the concentration of platelets, the more growth factors there will be present to promote the healing process (120, 139).

PRP has been applied in other fields of medicine, including regenerative therapies in oral and maxillofacial surgery. Its use has been studied in various orthopaedic applications, including tendinopathy, osteoarthritis, bone healing, fasciopathies, operative adjuncts, and ligament/tendon repair (120, 139). PRP's efficacy in orthopaedics has been under much debate, not helped by the lack of good quality comparative studies and variations in PRP preparation (120, 139). With varying evidence supporting or refuting its use, it remains an evolving topic, with new studies published each year. Our interest in PRP came from the fact that surgery will be required when non-operative measures fail, such as steroid injections. Surgery carries risks of infection, bleeding, and damage of soft tissues, and it may not help the patient's symptoms.

Furthermore, steroids lose their effect after a few injections, which must be spaced. The damage steroid causes to soft tissues is also well known. On the other hand, PRP is the patient's own blood and this eliminates the risk of blood borne infections. Add to that, PRP has anti-microbial properties, which reduces the risk of infection, not like steroids which are known to lower patients' immunity (120, 139). Hence PRP can be given regularly if proven

beneficial. The PRP is not cost-effective compared to steroids, so we must provide robust evidence advocating its efficacy to support its routine use in the NHS.

5.2 The placebo effect:

According to Evans (168), the name placebo comes from Psalm 116:9 of the 14th-century Latin bible, which means 'I will please.' Ironically, this is due to a typographical error: the Hebrew ethhallech, which means 'I shall walk [with the Lord in the land of the living]', was mistranslated into Greek as euarestaso ('I shall please...') and thence into Latin as 'placebo' (168). In Catholic vespers for the dead, the psalm is sung. Some people used to think the priests' fees for singing these prayers were expensive, and their motives were suspect; as a result, the word placebo evolved to stand for dishonest but comforting remarks.
A placebo can be any sort of potential intervention, it is not always a drug. Researchers compare the results of an experimental treatment for an ailment with those acquired from a placebo to prove a novel treatment effective above and beyond the psychological impacts of a mere belief in the drug's power to cure. The placebo-controlled trial is commonly considered the gold standard for evaluating the efficacy of new treatments (169).

Beecher, who discovered that soldiers in the Second World War reported an analgesic effect with saline, was the first to document the placebo effect scientifically. His clinical evaluation of typically uncontrolled placebo analgesia studies indicated that the placebo effect could account for 30% of the clinical impact (170).
Placebo effects are defined by the Society for Interdisciplinary Placebo Studies as changes due primarily to placebo mechanisms, including neurobiology and psychology. So even though placebo reaction relates to all health changes resulting from using a non-active treatment, including regression to the mean and pure course of the illness (171).
Various factors contribute to placebo effects from a psychological standpoint, including expectations, learning, memory, motivation, physical concentration, reward, and anxiety reduction (172, 173).
The neurobiology of the placebo effect has mostly focused on placebo analgesia. As a result, the neurobiology of placebo effects is typically thought of as part of the opioid and non-opioid processes (174, 175). Several studies have shown that the opioid antagonist naloxone can entirely or partially reverse placebo effects, implying that endogenous opioids are involved in some placebo analgesic effects (176-179). Furthermore, the peptide cholecystokinin (CCK), which is potentiated when a CCK antagonist is given, is likely to limit

the analgesic effects of the placebo. When taken together, some studies found that some placebo mechanisms work by changing the activity of both CCK and endogenous opioids (177, 179, 180).

Hafliadóttir and colleagues (181) conducted a systematic review of 186 studies (16,655 patients). Placebo effects accounted for 54% (0.54, 95% CI 0.46 to 0.64) of the overall treatment effect. Trials with a blinded outcome assessor and disguised allocation had more placebo effects. They concluded that contextual effects and not the specific effect of treatments account for about half of the overall treatment effect in RCTs. The true proportion of placebo effects may differ from the study's results because the study did not cover all key contextual components such as patient-investigator interaction. The contextual factors should be considered when evaluating therapy results in clinical practice (181).

Howick et al. (182) reviewed the literature to see any differences in the treatment and placebo effects in similar trial populations. They used three-armed trials (no treatment, placebo, and treatment) to compare placebos to no treatment and assess treatment and placebo differences within the same trials. They compared mean differences between placebo and no treatment with mean differences between treatment and placebo for continuous outcomes. They evaluated the risk ratio for treatment benefit (vs placebo) with the risk ratio for placebo benefit for binary outcomes (versus no treatment). They carried out several pre-planned subgroup analyses, including objective vs subjective outcomes, conditions tested in three or more trials, and trials with varying bias. The conclusion was impact sizes of placebos and treatments are frequently comparable. Patients can benefit from placebos with relatively strong effects on their own or as part of a therapy regimen, but such trials must be carefully blinded.

Tuttle et al. (183) gathered information from published RCTs of drugs used to treat persistent neuropathic pain. They discovered that while treatment responses have stayed stable, placebo responses have increased dramatically, resulting in a loss of treatment benefit. When participant and studies characteristics were considered, it was discovered that RCTs have grown in size and length in the United States but not abroad. These variations are linked to a higher placebo reaction. Individual RCT time courses revealed variable kinetics for treatment versus placebo responses. The former grew faster than the latter and plateaued, indicating that the maximum treatment advantage was achieved within four weeks.

In clinical research, there are valid scientific and ethical reasons to include a control group. Placebo-controlled studies are justified when established on good methodological considerations and do not put research participants at undue risk of harm. Investigators should keep in mind that including the best-available therapeutic control group in a trial does not negate the trial's scientific merit as long as the placebo control group causes little harm to the participants and, more importantly, the trial offers potential benefit to the subjects. In our trial, we used the placebo to assess the effectiveness of the PRP as a treatment for GTPS. Although the use of a placebo is not equivalent to the absence of treatment, we added a physiotherapy programme as a standard care method in order to minimise exposure and harm such as pain, weakness and mood changes.

5.3 Our findings:

Seventy-eight patients were included in this analysis. The majority were middle-aged females who were obese or overweight, and men and young females represented a small percentage in PRP and placebo groups. The demographics of this cohort are similar to previously published papers.

The iHOT12, our primary outcome measure, improved significantly in both groups at three and six months ($P < 0.05$) based on the paired T-test. There were no significant statistical differences between the two groups using the independent T-test ($P > 0.05$). The scores change from baseline to three- and six-month follow-ups were also calculated to assess the MCID. Comparing the numbers of patients who achieved scores over the MCID between the two groups did not reveal any significant difference based on the Fisher's Exact test (P 0.482), although the mean change of scores was higher in the placebo group at both three- and six-months follow-up. The results of the primary outcome measure concluded PRP is not superior to placebo. Similarly, the analysis of the mHHS showed that the two groups significantly improved from their baseline at the three- and six-months follow-ups ($P < 0.05$) without any significant difference between the two groups ($P > 0.05$). Add to that, comparing the numbers of patients who achieved scores over the MCID, there was no significant differences at three and six months (P 0.786 and P 0.275 respectively). These results again confirm that the PRP is not superior to placebo.

According to the Independent-Samples Mann-Whitney U test, there were no statistically significant differences between the two groups' mean VAS scores at baseline (P 0.436) despite the placebo group having a worse baseline mean score. There was no significant

difference at three months (P 0.827); however, the improvement from baseline was significant in the placebo group according to the Wilcoxon Signed Rank Test (P 0.010). This can be because baseline values are negatively correlated with change. After all, patients with low scores at baseline generally improve more than those with high scores (184). There was no significant difference at the six-month follow-up (P 0.920), and the score changes from baseline were not statistically significant. These results conclude that there was no significant difference between the PRP and the placebo groups throughout the follow-up period; hence the PRP is not superior. The analysis of the TTO component of the EQ5D-3L showed a significantly lower baseline mean score in the placebo group (P 0.045), which reflected on the mean score change at the three- and six-month follow-ups. The placebo changes of scores from the baseline were significantly better than the PRP group, although the mean scores at three and six months were not significantly different. Furthermore, the number of patients who achieved scores over the MCID was comparable between the two groups at three- and six-months follow-ups (P 0.403 and 0.127, respectively). The analysis of the VAS component of the EQ5D-3L showed no statistically significant difference between the two groups when compared the mean scores at baseline, three- and six-month follow-ups, as well as change of scores and achieving the MCID. These results further prove that PRP is not superior to placebo when treating GTPS.

In addition, this study found no complications other than soreness at the injection site, demonstrating that this treatment is safe when performed correctly in the outpatient department and under aseptic conditions.

5.4 Comparison with published literature:

Our results are in agreement with Thompson, Ribiero and Jacobson et al (127, 130, and 131). Thompson et al. (127) had 24 patients in each arm (PRP and saline injection). The majority were middle-aged females with a mean BMI of 28.8±4.7, similar to our cohort. Average pain decreases considerably with duration and timepoint increases with BMI, according to fixed-effect parameters for the model without interaction; however, there is no proof of an effect for autologous PRP injection (P=0.44). The least and most severe pains yielded similar findings. In our study, the BMI did not affect the outcomes of the treatment.
Thompson et al believed that imaging frequently provides false-positive results for lateral hip pain and is more helpful in detecting other rarer pathology rather than making a positive contribution to the diagnosis of GTPS. The diagnosis of GTPS is a clinical one, and hence they

relied on clinical history taking and examination for diagnosis and precise focal tenderness for injection placement. On the contrary, our study highly valued imaging as it confirms the diagnosis and roles out other hip pathologies, which can produce similar symptoms. Additionally, image guided injections are more accurate, especially in overweight patients who represent the majority in these cohorts. Thompson et al. attempted to reduce the risk of missing the target area by injecting the bulk of the PRP at the site of maximal tenderness with smaller aliquots around this site. In addition, Thompson et al. analysed Platelet concentration in 23 samples and ranged from 1.12 to 7.67, with a mean of 4.9 (SD 1.8), and this is considered a broad concentration range in the post-centrifuge samples. Thompson et al.'s results showed a reduction in GTPS pain intensity in the first six months in both the PRP and control groups. There was no statistically significant difference between the two arms for any outcome at any time point, whether with or without adjustment for age, BMI, pain location or analgesia. Consequently, Thompson et al. suggested no effect of PRP injection of a clinically meaningful magnitude.

Ribiero et al. (130) randomised 20 hips with GTPS in two groups and treated them with PRP or triamcinolone infiltration guided by ultrasound. The mean age was 49.8, and 44% were males which is high percentage comparing with our cohort. They assessed pain and function at baseline and after 10, 30 and 60 days through the Facial Expressions Scale for Pain and the Western Ontario McMaster and Harris Hip Score questionnaires. The HHS of the PRP group improved from 65.2 at baseline to 70.6 at two months while the steroid group started with a lower baseline (57.2) and achieved a higher mean score at two months (79.4). Compared to the pre-intervention period, the steroid group showed pain reduction ($p=0.004$) and improved function ($p=0.036$) on the HHS questionnaire at 10, 30, and 60 days after treatment. There was no statistical improvement in any of the parameters in the PRP group. The authors concluded that PRP infiltration does not affect pain alleviation or function improvement in the treatment of trochanteric syndrome after two months.

Jacobson et al. (131) compared ultrasound-guided percutaneous tendon fenestration to PRP injection to treat GTPS. They studied 30 patients with tendinosis or partial-thickness tears of the gluteus minimus or medius tendon. In our series, we included all tendon tears and were not strict about the degree of the tear as some MRI reports were not very detailed. The majority of their patients were females with a mean age of 57 years, of whom 15 were treated with fenestration and 15 injected with PRP. The randomisation process in this study had an increased risk of bias. Patients were randomised based on the previous patient's

treatment so that fenestration and PRP treatments would alternate between each subsequent patient. Add to that; when there was an error in the PRP process, the involved patient would be moved to the fenestration treatment arm.
In Jacobson et al.'s study, tendinosis was present in all patients. The gluteus medius was treated in 73% and 67% in the fenestration and PRP groups, respectively. The fenestration group achieved better scores during the follow-up period (from 32.4 at baseline to 15.2 at last follow-up) compared with the PRP group (31.4 at baseline to 19.4 at last follow-up) but no difference between treatment groups (P = .1623). The authors concluded that both ultrasound-guided tendon fenestration and PRP injection are effective treatments for gluteal tendinosis and PRP is not superior to fenestration.

On the other hand, Begkas, Fitzpatrick and lee et al. achieved a statistically significant improvement using the PRP injection. Begkas et al. (126) studied the effectiveness of ultrasound guided PRP injections versus corticosteroid injections in the treatment of GTPS. They used the SW-PRP system provided by NTL Biologica to prepare the PRP which is the same system we used in our trial. They had 12 patients in each arm, which is small compared to 39. In their study, both groups improved from baseline based on VAS and HHS. In the PRP group, the mean VAS score at baseline was 7.21 and improved to 3.16 at three months and 1.52 at six months. This is a remarkable improvement compared to our results as we only achieved a 5.3 VAS score at six months. Based on their results, Begkas et al. concluded that patients with GTPS show improved and longer-lasting clinical outcomes when treated with ultrasound-guided PRP injections compared to those with corticosteroid injection.
Fitzpatrick et al. (128, 129) conducted an RCT investigating the role of PRP in treating GTPS. They included 80 patients randomized 1:1 to receive ultrasound-guided LR-PRP or corticosteroid injection. They excluded all full-thickness tears (grade 4) demonstrated radiologically. The majority were middle-aged females with a mean body mass index of 27 and a mean length of symptoms of 15 months. An open-labelled extension allowed patients to receive crossover treatment after three months.
The mean mHHS improved remarkably at three months in the PRP group to 74.05 compared to the corticosteroid injection group who achieved 67.13 (*P* 0.048). In our series, the PRP group improved to 57.89. At six months, the LR-PRP group in Fitzpatrick et al. study improved further to 77.60 (*P 0*.0003) while scores of the corticosteroid injection group and our PRP group declined (65.72 and 53.83, respectively). Twenty-seven patients failed the

corticosteroid injection treatment between four and six months, with a mean exit score of 59.22, and then received treatment with LR-PRP. The crossover group improved with the LR-PRP from 59.22 at baseline to 75.55 at three months, 77.69 at six months, and 77.53 at 104 weeks. The LR-PRP group retained 38 of 39 patients to 52 weeks and continued to improve. Their baseline scores of 53.77 (SD, 12.08) improved to 82.59 (SD, 9.71) at 104 weeks (*P* =0.0001).

Lee et al. (133) prospectively assessed the efficacy of intra-tendinous PRP injections as treatment for chronic recalcitrant gluteus medius tendinopathy in 21 patients. The majority were female, with a mean age of 48 years and a mean follow-up of 19.7 months. Patients presented with recalcitrant gluteus medius tendinosis with or without partial tears of the tendon associated with moderate to severe lateral hip pain for longer than three months. All participants were assessed pre- and post-injection with the mHHS, HOS-ADL, HOS-Sport, and iHOT-33. A needle tenotomy technique followed, consisting of 6 to 9 needle passes through the hypoechoic regions of the gluteus medius tendon. This is a unique technique that other authors have not practiced. The mean improvements from pre- to post-injection follow-up were 56.73 to 74.17 for mHHS. This is a remarkable improvement compared to our results highlighted previously. All mean outcome measure improvements were clinically and statistically significant (P < .001). These results concluded that ultrasound-guided intratendinous PRP injections are a safe and effective treatment option for chronic recalcitrant gluteus medius tendinopathy due to moderate to severe tendinosis with or without severe tendinosis without partial tendon tears.

5.5 The effect of PRP preparation on the outcome:

The use of PRP in the treatment of tendinopathy has been controversial, with many published papers reporting different results. The type of PRP used in these studies has also been variably reported. In our study, we used Leukocytes rich PRP (LR-PRP) as demonstrated to be effective in treating tendinopathies compared to leukocyte poor PRP. Fitzpatrick et al. (128, 129) demonstrated that LR-PRP, which was prepared using the GPS III kit, has promising results in the management of tendinopathy. In our trial, we used the NTL Biologica system which was also used by Begkas et al. (126) who reported good results as detailed in the literature review section.

Generally, the techniques used by each set of authors in preparing PRP varied between all of them, even despite some quoting the same system or technique. Variation existed

between the volume of blood drawn, number of and nature of centrifuge cycles, final PRP volume, whether platelet assays/platelet counts/PRP activation/growth factor assays were performed, number of injections, volume per injection, and mode of administration. It was unclear as to the time interval between PRP preparation and administration for all authors. Battaglia et al. (185) and Samy (186) used the technique described by Filardo et al. 2012 (187). They used two centrifuge cycles (15 minutes and 10 minutes) which varied between the authors regarding the spin speed at each cycle (1800rpm vs. 1480rpm, 3500rpm vs. 3400rpm). Battaglia et al performed platelet assays, platelet counts, activated the platelets with CaCl, and froze their samples, Samy et al did not do this. The final volume of PRP was the same for both authors. In our study we did not carry out quality control to ensure that we had PRP in each injection. Although the quality of the PRP was guaranteed by the NTL Biologica, this is considered one of the limitations in our study. Battaglia et al. used three injections (5ml each) at two-week intervals using a frozen sample at injections 2 and 3 thawed from the first preparation. Samy et al administered all 15mls in one go.
Klaassen et al. (188) and Rafols et al. (189) used the GPS Biomet system, with the GPS III system specified for the latter. They withdrew different amounts of blood, 55mls and 52mls, respectively, but used one centrifuge cycle (3200rpm for 15 minutes), resulting in a final PRP volume of 6mls. Klaassen et al. (188) activated their PRP with bovine thrombin in CaCl and administered their PRP via a spray onto the surgical field, whereas Rafols et al. (189) did not activate their PRP and administered using an injection. The GPS system also uses sodium bicarbonate as a buffer in the final injection volume, postulated to maximize pH's effect on platelet activity. Sanchez et al. (190) described their technique collecting 40mls of blood centrifuged at 580g for 8 minutes, giving a final volume of 8mls. They did not perform a platelet assay/count or freeze their sample. They activated it using CaCl. They performed three injections over 1-2 weeks intervals using a fresh sample each time. Griffin et al. (191) used the Genesis CS Component Concentrating System; however, we could not access the technique protocols they quoted, and it was not present in their published RCT protocol, so their method was somewhat unclear. They reported using one injection of 3mls of PRP, which was not activated. When we examined the Pure PRP II Genesis CS Component Concentrating System's video, it illustrates that it withdraws 50mls of blood with two spin cycles at 3800rpm for 1.5minutes; the platelet-rich suspension is then removed and spun at 3800rpm for 5 minutes. Redmond et al. (192) used the Arthrex system where 16mls of blood was drawn and spun once at 1500rpm for 5 minutes giving a final volume of 4-7mls with one

injection. They did not perform platelet assays or activation. Safdar et al. (193) and LaFrance (194) used the Accelerate Plate Concentration System by Exactech withdrawing 52mls of blood with one spin cycle (speed/time unspecified). They did not perform platelet assays or activation. Their method of delivery was unclear. Martin et al. (195) used their technique of combining PRP with bone marrow aspirate and injecting this, simultaneously following core decompression of an osteonecrotic femoral head. They withdrew 120mls of blood with one spin cycle (unspecified speed) for 15 minutes, giving a total of 12mls of PRP. They did not report whether they performed platelet assay/activation. Clanton et al. (196) used the Osteokin Arthrex Biosystem to create their osteoconductive gel utilising bone marrow aspirate and bone chips with the PRP. Their methods of PRP preparation were not described otherwise. This variation of preparing and administering PRP techniques is evident, which adds further heterogeneity when comparing the results of different studies. This has been well documented in other articles reviewing PRP in other conditions. Further studies should ideally use the same system with the same preparation with/without activation with theoretically the same properties, however, we do not live in an ideal world, and different clinicians and companies will think their way of preparing and administering PRP is the correct one. However, this will not help compare further studies unless there is some standardisation and reproducibility. PRP platelet counts are higher with double versus single spins, with variations in cytokine concentrations between different manufacturers of PRP preparation systems (Biomet, Arthrex, and Prodizen Prosys). Delong et al. (197) designed and applied the PAW (Platelet concentration, activation method, and white cells) classification to PRP preparations that concentrated on PRP properties, which are thought to have a significant effect on potentiating its efficacy. They divided the preparations according to whether they were plasma or buffy coat based, with the latter being higher in leucocyte concentrations relative to natural blood levels. It would seem wise to employ a classification system of PRP preparations in studies allowing standardised documentation and better comparisons. This system would compensate somewhat for the variations in PRP preparation by focusing more on the critical modifying factors in its preparation and the end product, which appears to be the platelet concentration, whether the preparation was activated or the concentration of leucocytes.

5.6 The Role of Physiotherapy:

The evidence that discusses the benefits of physiotherapy or the modalities used in the management of GTPS is minimal. Generally, the literature suggests that when physical therapy is utilised to improve flexibility, muscle strengthening, and joint mechanics, the symptoms of GTPS will improve (17). Other physical therapy interventions mentioned are ultrasound, moist heat, educating the patient on activity modification, and correcting possible training errors (198). There are also other treatments that a physiotherapist can use, such as electrotherapy, acupuncture, taping techniques, soft tissue massage, and the temporary use of a mobility aid to off-load the affected side (10). The second phase is to reinforce the patient's strength and to restore the normal range of motion. The physiotherapist will also improve the muscle length and resting tension, proprioception, balance, and gait through a supervised and thorough exercise rehabilitation programme (52). The next phase of rehabilitation is the restoration of all functions. Many patients develop Trochanteric Bursitis due to their everyday activities like running and walking. The physiotherapist's goal is to provide a specialized programme for the patient to improve the movement and reduce the pain so that the patient can perform his daily activities with less difficulty. The final phase is to prevent a relapse. It may be as simple as training core muscles or fabricating foot orthotics to address any biomechanical faults in the lower limbs. The therapist will examine hip stability and function by addressing any deficits in the core strength and balance (52). Furthermore, teaching the patient some self-management techniques. The ultimate goal is to see the patient safely return to his former sporting or leisure activities.

Rompe et al. (67) compared the results of different treatment protocols. They assigned 229 patients with chronic unilateral greater trochanteric pain syndrome to either: a single local corticosteroid injection, a repetitive low-energy shockwave treatment, or a home training program that included specific hip abductor/rotator stretches and exercises as follows, performed twice daily, seven days a week for 12 weeks: Piriformis stretch, Iliotibial band stretch, Straight-leg raise, Wall squat with a ball and Gluteal strengthening. Patients were re-evaluated at one, four, and 15 months to evaluate the degree of recovery and severity of pain. Study findings were interesting in that corticosteroid injection produced significant short-term improvements, while shockwave treatment and home stretches/exercises produced good long-term results. For example, at the one-

month mark, 75 percent of the subjects receiving corticosteroid injections reported significant reductions in pain, whereas only 13 percent of the shockwave group and 7 percent of the home exercise group showed significant pain reductions. However, at the four-month follow-up, 68 percent of the individuals receiving radial shockwave presented significant pain reductions, compared to 51 percent of the corticosteroid group and 41 percent of the home stretches/exercises group. By the 15-month follow-up, the home stretching/exercise group had the best outcomes, with 80 percent reporting significant pain reductions, compared to 74 percent of the shockwave group and 48 percent of the corticosteroid injection group.

A progressive lower limb exercise programme for the gluteal, quadriceps, and calf muscles was recently compared with sham exercise in postmenopausal females with GTPS. Both groups also received an education, and similar improvements were observed at 52 weeks (52). Isometric exercises, which have recently gained popularity in managing other lower limb tendinopathies, were compared with an isotonic programme in Australian volleyball and basketball players with patella tendinopathy. After four weeks, both programmes were equally effective in reducing pain and improving function, possibly indicating that the specific muscle contraction type may be less important than the loading intensity (198).

Furthermore, a systematic review examining tendon adaptation in response to exercise concluded that loading magnitude and muscle contraction intensity was more important than muscle contraction type (199). In addition, some authors suggested exercise as the first-line treatment for tendinopathy and recommended at least 12 weeks of progressive loading (200). Isometric and isotonic exercise programmes have not been directly compared for GTPS, and it is unclear whether the improvements observed in other lower limb tendinopathies could be replicated in GTPS. The LEAP study by Mellor et al. (52) compared the effectiveness of load management education plus exercise with corticosteroid injection and a "wait-and-see" approach. The participants received 14 physiotherapy sessions over eight weeks. They had to follow a daily exercise program that progressed the difficulty over 4-6 weeks to allow muscle strength and function improvement while limiting pain aggravation and was dependent on the response to loading. Education and exercise resulted in a 77.3% success rate on the global rating of change and hip pain intensity in both short and long terms.

The home exercises in the LEAP study (52) focused on hip strengthening (mainly abductors), functional retraining, and adduction control during functional tasks. Bridging variations, squatting, and lunges were used for functional Loading progressions and pelvic control training.

Isometric exercises exhibit an analgesic effect due to activation of segmental and extra-segmental descending pain inhibitory pathways; therefore, they are used for pain management. Low load, low-velocity isometric hip abduction may be performed in side-lying, supine and standing positions for multidirectional training. Clifford et al. (200) conducted a randomised controlled pilot trial that recruited 30 participants with GTPS to compare the effectiveness of isometric and isotonic exercise for individuals with GTPS. The isometric exercise programme consisted of the hip abduction hold and the weight-bearing gluteal contraction exercise. The isotonic exercise programme also consisted of two exercises: Side-lying hip abduction and the hip abduction slide. All participants attended eight individual physiotherapy appointments during the 12-week programme. During the first appointment, participants were allowed to practice their exercise programme under the supervision of the chief investigator to ensure correct technique. Following this, participants attended weekly for the next 2weeks and thereafter for a further five sessions over the next ten weeks to ensure correct exercise technique and exercise progression. Simple analgesia was permitted, but participants were asked to refrain from seeking other forms of treatment during the study. Participants were also encouraged to remain physically active within their limits of pain. The primary outcome measure was the Victorian Institute of Sport Assessment-Gluteal (VISA-G), and secondary outcome measures included the Numeric Pain Rating Scale (0–10) and an 11-point Global Rating of Change Scale. Outcome measures were assessed at baseline, 4 and 12 weeks. Twenty-three participants completed the trial. After 12 weeks, mean VISA-G scores improved in both groups; 55–65 in the isometric group and 62–72 in the isotonic group. 55% of the isometric group and 58% of the isotonic group reduced the pain of at least 2 points (MCID) on the Numeric Pain Rating Scale. 64% of the isometric group and 75% of the isotonic group had improved by at least 2 points (MCID) on the Global Rating of Change Scale. The trial concluded that Isometric and isotonic exercise programmes appear to be effective for individuals with GTPS and should be considered in the loading management of patients with this condition. French et al. (201) conducted a cross-sectional observational survey to assess the physiotherapy management of GTPS in

Australia using an online survey. They found that all physiotherapists used education and strengthening and neuromuscular control exercises primarily targeting the gluteal muscles. Other interventions included massage therapy (90%), stretching exercise (53%), range of motion exercise (40%), thermal modalities (50%), taping (38%), and electrotherapy (25%), while 40% commonly recommended up to 2 to 3 corticosteroid injections per patient/per annum. They also found that 79% of the physiotherapists used pain severity scales as their primary outcome measure. Single leg stance was the most common physical measure used (68%), and global rating scores or standardised physical measures were less commonly used.

When we initially contacted our physiotherapy department at North Tyneside General Hospital, we found no specific protocol for GTPS. We formulated a programme based on the available limited evidence. The two groups in our study followed the same physiotherapy programme. They started exercises three days after receiving the injections. Our physiotherapy programme included Specific strengthening for the muscles around the hip, such as Side-lying leg lift, Clam (bent knee), Hip extension (Gluteal kickback), and Balance exercise to improve proprioception. Our physiotherapy programme also included: Exercises to stretch the surrounding area, which include Iliotibial Band (ITB) stretches, Piriformis stretches, Prone lumbar extension, Supine lumbar rotation, and Cat stretch. Because the typical greater trochanteric pain syndrome is associated with tendinopathy of the gluteus medius and atrophy of the gluteus minimus, it is important to isolate these muscles with specific stretches and eccentric exercises. These exercises are beneficial when treating individuals with coxa valgus since a high femoral neck angle reduces the mechanical efficiency of the hip abductors, and a strong gluteus medius is necessary for injury prevention. Tensile loading program aiming to reduce pain and improve tendon loading capacity. Combined strengthening and functional exercises to optimise movement control patterns and obtain pelvic control. After one week from receiving the injections, patients were contacted, and they all confirmed starting the physiotherapy exercises. Their follow-up at three months and six months did not include the status of the physiotherapy, so we do not know if patients continued to do their exercise or stopped for any reason. Patients were advised to contact the research department if they have difficulty with specific exercises to refer them to see the physiotherapist.

5.7 Study strengths and limitations:

One of the study's strengths is that it is a well-designed double-blind, randomised clinical trial. The goals were clearly stated and based on a thorough examination of the available evidence in the literature. We had strong participation and collected practically all of the follow-up data. To prevent the potential for bias, we utilised very specific inclusion and exclusion criteria. According to the Cochrane risk of bias tool, our study has a low risk of bias. We correctly randomised individuals once the random sequence creation was explicitly presented. We blinded participants, personnel, and result assessors, and only 3.7% of individuals withdrew.

Furthermore, the follow-up duration is adequate to reflect the treatment's immediate effects. The physiotherapy regimen can be considered a helpful management intervention for GTPS patients. Furthermore, there was no potential for a conflict of interest.

One of the limitations of this study is that different radiologists reported MRI scans, and most of the reports were not clear about the degree of the tendinopathy or the extension of the bursitis. Add to that; we could not repeat the MRI scan to monitor the healing process. MRI has been utilised in the clinical setting not only to diagnose tendinopathies but also to monitor the efficacy of treatments and evaluate the risk of developing symptoms (202-204).

Limitations also include not assessing anxiety and depression. Some authors suggest that depression and anxiety might have a significant role in patients' response to treatment (205), which we could have measured alongside the hip outcome measures and checked if anxiety and depression are related to poor outcomes. According to a literature study by Wong et al. (206), 22.8 percent-26.2 percent of patients with rotator cuff tendinopathy had depression, 23% had anxiety, and 70.2 percent-89 percent of patients had sleep disturbance or insomnia. Nine psychological characteristics were linked to pain, function, and quality of life in individuals with rotator cuff tendinopathy. According to the research of low-to-moderate quality, various psychological aspects are linked to pain, function, and quality of life in individuals with rotator cuff tendinopathy.

The majority of patients were happy to do their exercise at home. When we contacted them one-week post-injection, the majority confirmed that they were exercising regularly; however, they had no objective assessment by a physiotherapist to confirm their progression. Several studies showed high adherence; however, compliance was mainly higher in supervised programmes. Factors associated with greater commitment included good socioeconomic

status, Marital status, good health, physical and cognitive ability, and fewer depressive symptoms (207, 208). Wilcox et al., in 2006, (209) researched patients with musculoskeletal pain's perceptions of exercise barriers. Pain, psychological barriers such as attitudes and beliefs, a lack of time, desire, and enjoyment of exercise are all factors that affect adherence to a home exercise programme, according to the researchers. It is also essential to investigate the long-term benefits of physiotherapy in the treatment of GTPS. Other studies should look into the impact of physiotherapy after a PRP.

The concentration of PRP in the prepared injection samples was not measured, depriving us of the opportunity to understand PRP's action better. A second sample should have been obtained to assess the quality and quantity of growth factors available in these samples. These can be compared against patients' reported outcomes and see if the presence or absence of a specific factor has a significant role in improving patients' symptoms. At the end of the day, the PRP is the patient's own blood, and if they are deficient in a specific factor, the PRP will still be deficient, and if this factor plays a significant role in healing, those patients are unlikely to improve.

Chapter 6: CONCLUSIONS AND FUTURE WORK

Although PRP is becoming more popular as a treatment for GTPS and other tendinopathies, few studies in the literature have enough clinical data on functional outcomes, large sample sizes, long follow-up periods, and a complete explanation of the molecular and cellular mechanisms of PRP action. There is also a need to develop formal protocols for the preparation and standardisation of PRP and the post-treatment management of patients. The above indicates the necessity for further clinical and basic scientific research to meet these needs.

In our study, both the intervention and control groups showed a reduction in GTPS pain intensity in the first six months of the trial. Between the two arms, the placebo group achieved similar results to the PRP group hence our Null Hypotheses have not been rejected. As a result, we conclude that PRP injection has no clinically significant benefit. Natural history, the home exercises programme provided to both groups, and the placebo effect of the medical intervention could all explain the improvements in pain intensity in both arms of the trial.

The future work should include:

1- We need to continue the data collection to assess outcomes at 12 months and compare results between the two groups concerning our clinical trial. Fitzpatrick et al. (128, 129) followed patients for up to two years, and their results confirmed that the PRP group continued to improve.

2- MRI scans can be re-looked at by an MSK radiologist for a detailed report to assess if the tissues involved or the degree of the inflammation impact on the treatment. Guillibert et al. (210) looked at the effectiveness of a single PRP injection in the treatment of knee OA. A Magnetic Resonance Imaging (MRI) analysis was done at the start of the study and six months later. On MRI parameters, there was no change. In Oloff et al.'s (211) study, which investigated the effect of PRP on Achilles tendinopathy, both groups improved statistically significantly in pre-MRI and post-MRI imaging studies. Furthermore, Khattab et al. (212) looked at the use of ultrasound guided PRP injections in the treatment of tennis elbow. All patients had an MRI at baseline and six months after the surgery to validate the sonographic findings. The existence of tendon thickening, aberrant signal intensity, or a fluid-filled gap in

T2WI and STIR sequences were among the pre-procedure MRI results. At six months, an MRI revealed a considerable reduction in the degree of tendinosis.

3- To perform an assay of the growth/inflammatory markers to see any correlation between specific growth factors and clinical results. Suppose we can obtain blood samples from all patients who received PRP injection in our clinical trial and analyse the growth factors quantitatively and qualitatively. Then we can correlate this to their response and see if the non-respondent were lacking certain growth factors or maybe the respondents have higher concentrations of some factors. Cho et al. (213) investigated whether individual differences in growth factor concentrations influence the physiologic effects of PRP on human mesenchymal stem cells. They came to the conclusion that different growth factor concentrations may have varied biologic effects and that individual variability in GF levels should be taken into account for accurate interpretation of biologic functions and standardised PRP use.

4- We noticed a lack of consensus on GTPS exercise and rehabilitation programmes. The creation of a unified protocol should help clarify the role of physiotherapy in treating GTPS. In future studies, there are several avenues to investigate.

5- To study the effect of multiple injections and if a combination of PRP and fenestration will produce better results.

6- Ideally appropriate funding would be obtained to run a multi-arm multi-stage RCT that would allow patients to be randomised to physio only, then injections with CSI versus PRP versus fenestration only versus saline. Arms can be added is a new treatment option becomes available and if an option is not working then it can be dropped.

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Appendices

Appendix One: Patient Information Sheet (PIS)

PATIENT INFORMATION SHEET

A Double-Blind Randomised Control Trial Investigating the Efficacy of Platelet Rich Plasma versus Placebo for the Treatment of Greater Trochanteric Pain Syndrome

HIPPO – Hip Injection PRP vs Placebo for Greater Trochanteric Pain Syndrome

Researchers: Mr E Oderuth, Specialty Registrar in Orthopaedics

Mr Mohammed Ali, Specialty Registrar Orthopaedics
Mr A Malviya, Consultant Orthopaedic Surgeon

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Greater trochanteric pain syndrome (GTPS), also known as trochanteric bursitis, is a painful condition of the hip characterised by pain on the outside of the hip joint on movement and when lying on that side. It is caused by inflammation of the trochanteric bursa or tendons attaching to this outer part of the hip. Normally it can be treated conservatively with painkillers and physiotherapy. However in some cases this does not work and steroid injections can be used to reduce the inflammation and symptoms. Surgery is a last resort when all other treatments have failed.

A new treatment has emerged called platelet rich plasma (PRP). We think PRP can be used as an injectable treatment instead of steroid injections or after conservative treatments or steroid injections have failed. PRP is a concentrated formulation of platelets which is obtained from a small sample of your own blood. Platelets main function in the body is to help the blood clot, for example when you have cut yourself. However, they also contain important proteins which play a vital role in healing. The theory of injecting this higher concentration of platelets, in the same way as steroids are injected, into the inflamed area in patients with GTPS is that they will enhance the healing process and treat this painful condition.

Steroid injections are an established injectable treatment for GTPS however their effectiveness can be variable and does not always provide lasting symptomatic relief. This has been demonstrated in studies. PRP has been shown in studies to be effective in treating conditions such as patellar tendonitis and golfer/tennis elbow.

We do not yet know if PRP is effective or how long its effects last in treating GTPS. One study has shown that PRP provides more effective and longer lasting treatment than steroids in GTPS. However this is just one study and more research is needed assess PRP's effectiveness as a treatment. If we find that PRP has beneficial effects then it could be used instead of steroid injections or when steroid injections have failed therefore providing symptomatic relief in this painful condition and prevent the need for the last resort, surgery.

We hope to answer this question in our study comparing PRP with a placebo (normal saline solution)

What is a placebo?

You will be allocated at random to receive either PRP or an injection of normal saline. Normal saline is essentially just salt water. In those receiving the placebo treatment, normal saline, we do not expect to see a benefit.

Why would we allocate participants to receive the placebo?

The reason for allocating half the participants in our study to receive the placebo is so that we can effectively assess the effects of PRP with a treatment that we know has a neutral effect. Conducting the study this way is the most effective way to assess whether a treatment works or not and is one of the most valuable methods of research. You will still be able to receive your regular treatments such as pain killers and physiotherapy.

Why have I been invited?

Your doctor has deemed that you are suitable for entry into this study as you continue to suffer from GTPS despite conservative treatments or previous steroid injection therapy.

Do I have to take part?

No, your participation is voluntary. If you would like to participate we will invite you to meet one of our research team who will go through the study with you again, answer any questions you may have and ask you to sign a consent form. You will be given a copy of the consent form, which you should keep with this information sheet. You are free to withdraw from the study before or after receiving your treatment without giving a reason. Not taking part in or withdrawing from the study will not affect the standard of care you receive.

What will happen to me if I take part?

At your first meeting with our research team, after you issue your consent to enter the study, you will be asked to fill out a few short questionnaires regarding your symptoms. You will then be asked to attend the hospital to receive either PRP or normal saline. Normal saline is

essentially salt water. You will be randomly assigned to either of these treatments but will not know which one until the whole study has been completed. The reason for this is because it has been proven that results of scientific studies are more accurate if the patient does not know which treatment they have received.

When attending the hospital for your treatment, the procedure will take place under sterile conditions providing the cleanest environment possible in either a clinic or operating theatre. We will advise you nearer the time which department in the hospital you will need to attend, and you will be looked after by our staff in that department. The clinician performing the procedure will take your written consent for the procedure. We advise that after procedure you will be able to walk, however you will need someone to accompany you home. We do not advise driving straight after the procedure. You will be able to go home the same day.

All participants will have 40mls of blood taken (One fifth of what is taken when donating blood) and then wait 20 minutes. For those receiving the PRP treatment this gives time for their blood to be processed and the platelets collected. In the meantime, some local anaesthetic will be administered to your hip to numb the skin.

One group will have PRP injected into their trochanteric bursa region and the other group will receive a normal saline injection. Your treatment will be delivered under ultrasound guidance by someone trained to perform the procedure. The procedure will be hidden from you by a screen, so you do not discover which treatment you are having. Both procedures feel the same and take the same amount of time. Afterwards you will be advised to rest the hip on the side of the procedure for 72 hours to allow the injected treatment to stay in the hip and take effect. Resting will involve not undertaking any strenuous activity or exercise and will require you to use crutches and put only partial weight on the side of the procedure when walking. You will receive outpatient physiotherapy.

You will be contacted by our research team one week after your procedure to ensure there have not been any problems with the injection. You will be seen again at 3, 6 and 12 months post procedure by one of our research team. They will not know what treatment you have received. They will evaluate your clinically and you will be required to fill out the same questionnaires that you completed at your first appointment. If at the 6-month stage we find that you have not had any benefit at all from your first injection then we will offer you another chance to have the same treatment. Sometimes more than one treatment is required. It is preferable for maintaining the integrity of the study for you to receive the same treatment, however if you wanted to definitely receive PRP then we would respect your wishes and allow you to have this. You would still be blinded from your initial treatment though.

After the study has ended, you can choose to be seen again by our clinical team for further evaluation and decision on further treatment.

How long will I need to be involved in the research?

From your point of view, the procedure and your management would be the same whether or not you decided to take part in the study or chose either one of PRP or steroid injections. The only difference being that you would be asked to fill out the questionnaires at each evaluation. These evaluations should take no more than 20 mins. You will be evaluated at the end of the study at 12 months and at intervals in between at 3 and 6 months.

Are there any risks?

The risks are very small for either injection of PRP or normal saline. These include pain, infection, bleeding, failure to resolve symptoms and recurrence of symptoms. These are not over or above that of a steroid injection that you may have received in the past. No serious side effects or risks from PRP have been reported.

Will I be paid to take part in the research?

No. You will not receive monetary incentives or reimbursements for expenses such as travel/parking as our provision of injectable treatments and their evaluation periods are not over and above what would be normally expected in the clinical setting. In the event of a claim, “no fault compensation”, would not be issued.

Where will my treatment take place?

Your treatment will take place at North Tyneside General Hospital.

What are the benefits of taking part?

You would not have any additional benefit from entering the study compared to receiving these treatments in normal care. The study will allow us to decide if PRP is effective in treating GTPS. No difference however may be demonstrated between the two treatments.

Will my taking part in the study be kept confidential?

Yes, all information taken about you will be kept strictly confidential according to our ethical and confidential practice. Any information that leaves the hospital will have all personal identifiable information removed from it so you cannot be recognised. Records will be kept securely at North Tyneside General Hospital and destroyed after 3 years.

What if relevant new information becomes available?

Our research team will meet to assess what effects this may have on the study and whether it should be continued. You will be informed immediately with regards to this.

What if there is a problem?

You will be informed immediately. We will discuss this with you and whether you should continue your participation in the study. Alternatively if you discover an issue or problem with the study, please raise it with us so we can act on it promptly.

Will my GP be informed?

Yes, with your consent.

What will happen if I am unable to continue with the study if I lose capacity?

If you lose capacity, which means you are unable to consent to further procedures or make decisions for yourself, after you have entered the study you will be withdrawn. However it would be valuable to keep and use any data we may have gathered by your participation up to that point. We would gain your consent in your initial meeting with our research team to use this information up to the point you are withdrawn.

What will happen with the results of the study?

We aim to present the results at national/international conferences and publish the results in scientific journals. It will not be possible to identify you from these. You will receive a summary of the results.

Who has reviewed the study?

All research in the NHS is reviewed by independent bodies called the Health Research Authority and Research Ethics Committee who have your safety, rights, wellbeing and dignity at the forefront of their concerns. This study has been reviewed by and given a favourable opinion by the local Research Ethics Committee.

Who do I speak to if I have further questions?

If you require any further information or have any questions, please contact our Research and Development Team or one of the other researchers listed above at North Tyneside

General Hospital (0191 2934087). If you would like to ask for independent advice you can contact Patient Advice Liaison Services (PALS) on 0800 0320202.

Taking part in this study is completely voluntary. If you decide not to take part, this will not affect the quality of care you receive.

You may withdraw from the study at any time by contacting your surgeon, or our research team, without affecting future care.

Appendix Two: Consent Form

CONSENT FORM

Patient Identification Number: ☐

Title of Project: Investigating the Efficacy of Platelet Rich Plasma versus Placebo for the Treatment of Greater Trochanteric Pain Syndrome (HIPPO – Hip Injection PRP vs Placebo for GTPS Trial)

Please initial each box

I confirm that I have read and understand the information sheet, Date:……. Version ……, for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that the relevant sections of my medical notes and data collected may be looked at by responsible individuals from the NHS trust or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to access to my records.	☐
I agree to my GP being informed of my participation in the study	☐
If I lose capacity after initially giving consent to participate, I agree that I will be withdrawn from the trial and data that has been collected from my participation up to the point of losing capacity can be utilised for analysis.	☐
I agree to take part in the study	☐

/ /

Name of Patient Date Signature

/ /

Name of person taking consent Date Signature

3 copies – 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix Three: Physiotherapy protocol

GREATER TROCHATERIC PAIN SYNDROME (GTPS)

Rehabilitation programme

The home exercise programme consists of the following:

[1]	[2]	[3]
Stretches of the surrounding area including the low back	Specific strengthening exercises for the muscles around the hip	Balance exercises to activate the muscles around the hip and low back

In addition to these rehabilitation exercises, it is important to progress back to regular physical activity to maximise health gains.

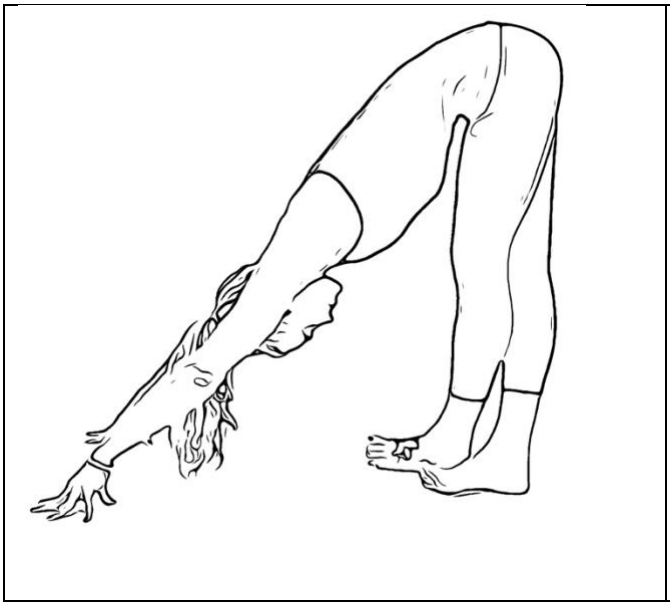
1. Stretches of the surrounding area

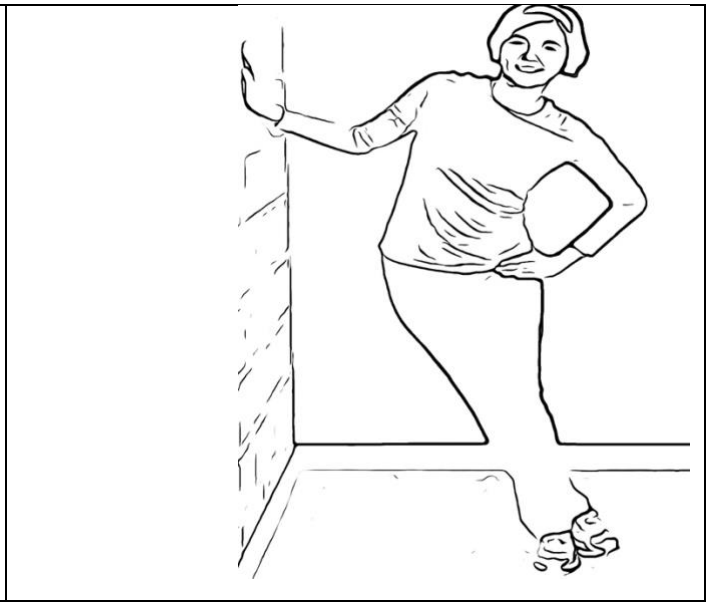
With all of the following stretches we normally recommend starting by holding the position for about 15 seconds, performing the stretch 3 times on each leg, and repeating these at least 3 times per day. Each week increase the stretch by 5 seconds, until you are holding the stretch for 30 seconds each time. The exception is the cat stretch below which is discussed in that section.

Iliotibial Band (ITB) stretches

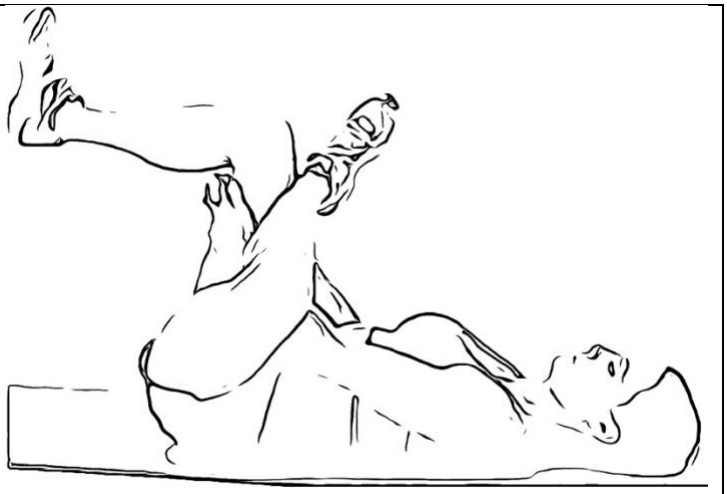
This stretch can be performed in either of two ways, so find the way that you prefer

Slowly cross one leg behind the other and lean forward as much as you can. Before returning to the upright posture, hold this position for a few seconds. A pull should be felt down the outside of your thigh. Rep the process on the other side.	**Cross one leg (the one closest to the wall) behind the other when standing near a wall. With the wall as a support, progressively push the hip closest to the wall towards the wall, feeling a stretch in the side of your thigh. Rep the process on the other side.**

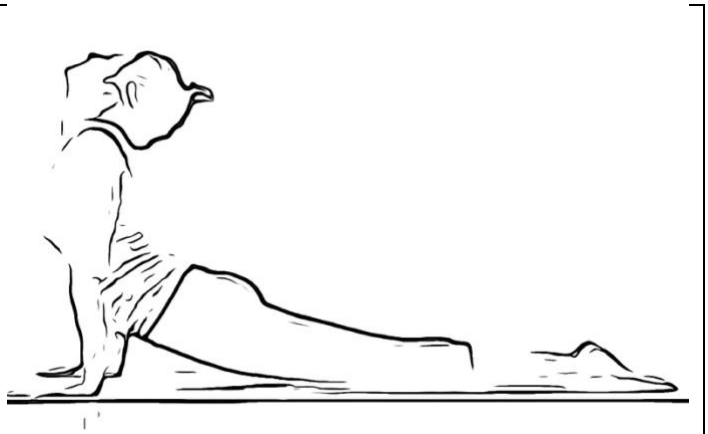




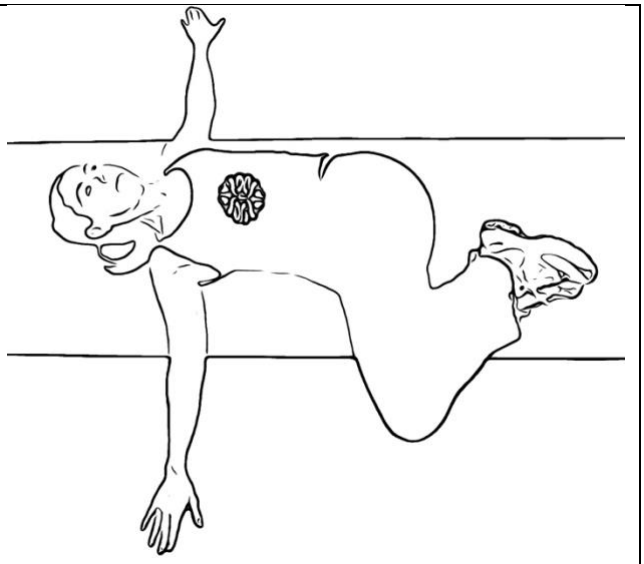
Piriformis stretches

Cross right leg over left leg at knee, reach through and clasp hands under left thigh, softly draw left leg towards chest & feel a tightness in right buttock, hold this position then release gently. Rep the process on the other side.	

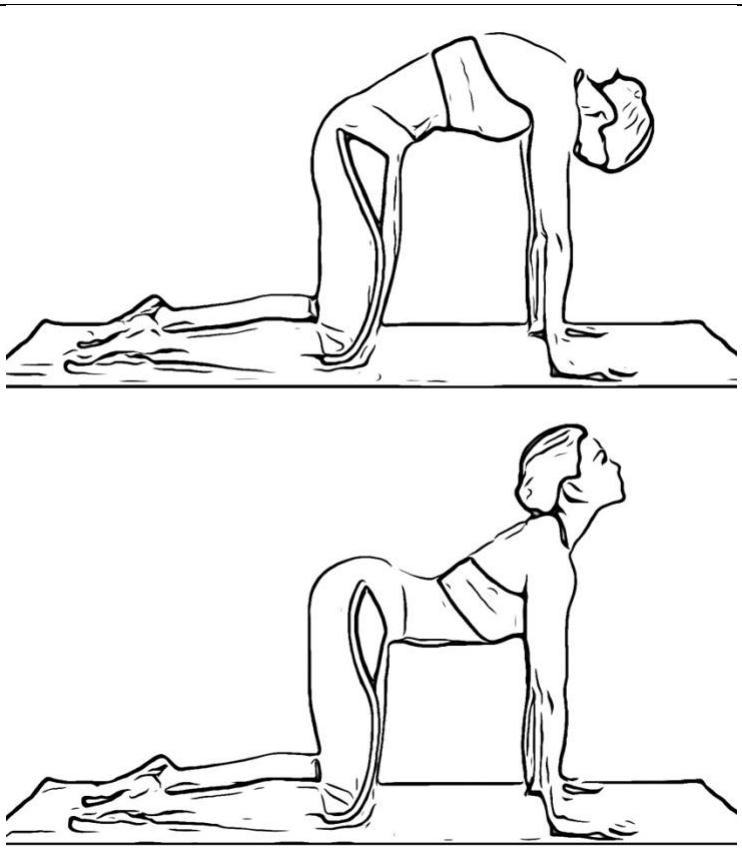
Prone lumbar extension

Bring your hands up beneath your shoulders in a press-up position while lying flat on your stomach. To get into an extended lower back position, gently lift your shoulders off the floor while keeping your hips on the floor. Hold this position for a few seconds before easing back to the beginning position.	

Supine lumbar rotation

Bend your knees to roughly half-way while lying flat on your back, keeping your knees together, your feet on the floor, and your arms outstretched to the side. Allow both knees to fall over to the right side as far as they will go by slowly twisting. Hold this stretch for a few seconds, then slowly return to neutral before shifting the knees to the left and repeating the stretch on the other side.	

Cat stretches

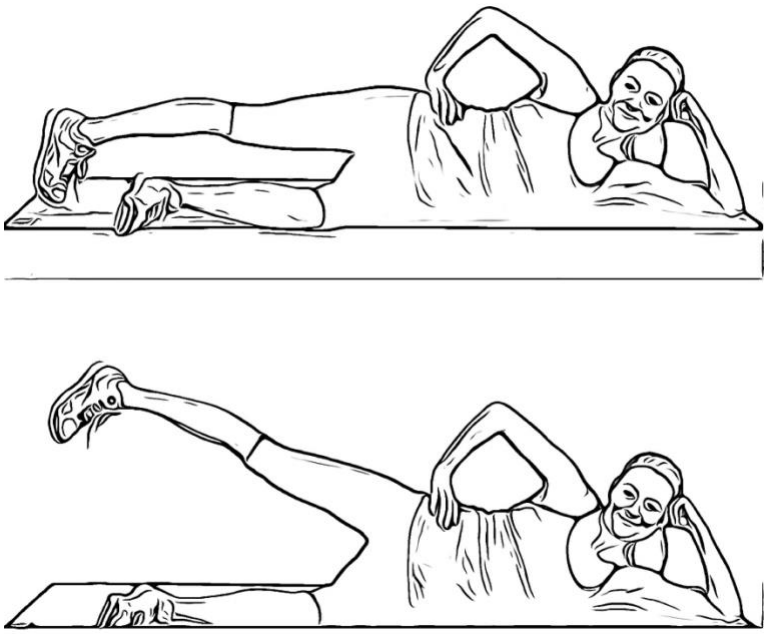
Kneeling on all fours, preferably on a soft surface Throughout this exercise, keep your arms straight and your knees about hip width apart. Raise your head and slowly lower your back to the floor, arching your back downwards. Hold this position for a few moments. Then slowly raise your tummy up and continue to arch your back up towards the ceiling in the neutral posture. Return to the neutral position after a few of seconds of holding this position. 5 or 6 times in each direction, repeat this stretch.	

2. Specific strengthening for the muscles around the hip

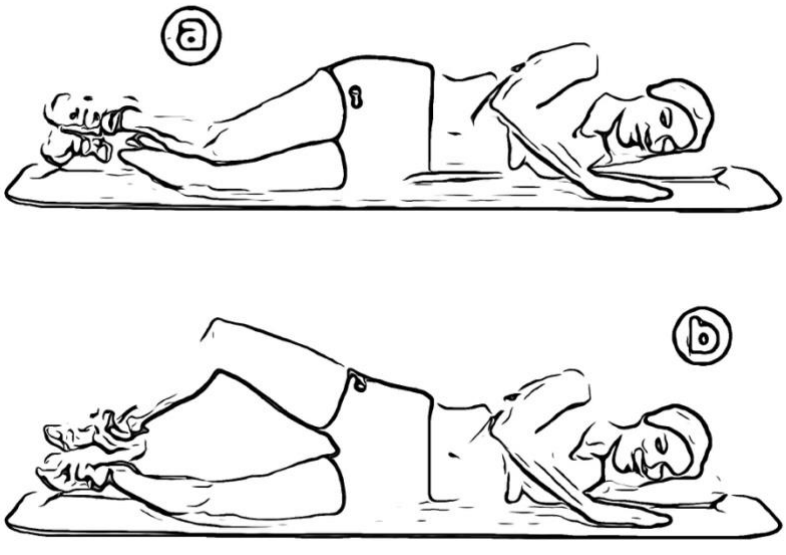
In order to relieve your pain, you should progress specialised strengthening exercises for the muscles around your hip in addition to flexibility exercises. Even if you only have symptoms on one side, there is some evidence that these exercises should be done on both sides. We usually recommend doing three sets of each of these exercises once a day, beginning with a number of repetitions where you can feel the strain. You should

gradually increase the number of reps you do each week. Each of these exercises should be performed slowly, since this will help you develop stronger movement control. During the recovery process, however, pay attention to your body and only go as far and as quickly as your symptoms allow.

Side-lying leg lift (straight knee)

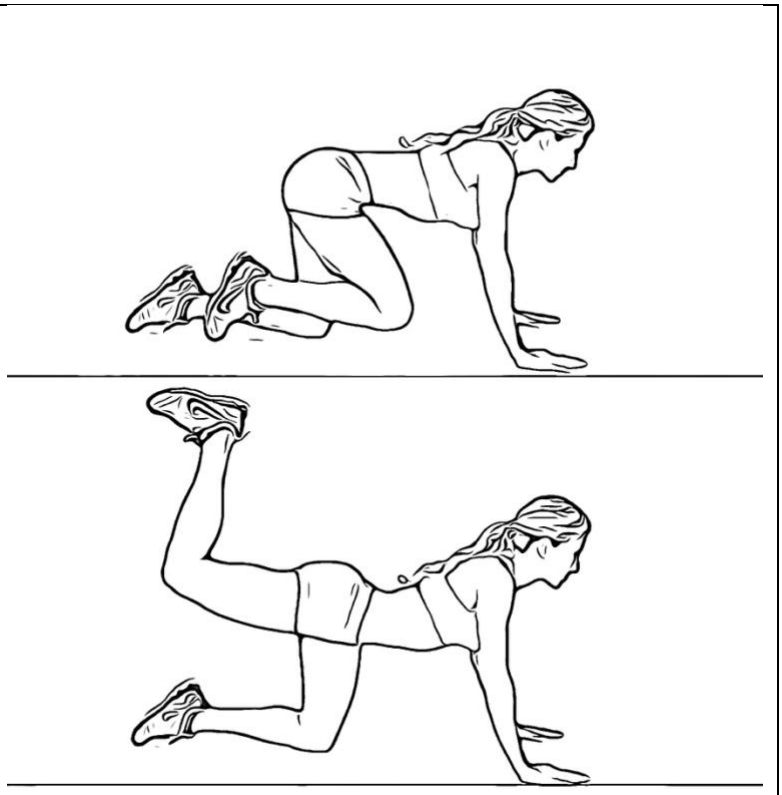
Lie down on your side on a firm surface like a bed or a rug. Slowly elevate your leg to the side while keeping it straight. Hold this position for a few seconds when you've gone as far as you can. Return the top leg to its original position slowly. Rep the procedure as directed. Repeat these exercises on both hips if you are able to lie on your bothersome side.	

Clam (bent knee)

Lie down on your side on a firm surface like a bed or a rug. Keep your feet and knees together as you bend both knees to about half-way. Raise the top knee slowly into the air, keeping your feet together. Hold this stance for a few seconds before lowering the leg slowly and steadily. The back should remain still throughout this exercise, with movement occurring at the hips rather than	

the back. Rep the procedure as directed. Repeat these exercises on both hips if you are able to lie on your bothersome side.	

Hip extension (Gluteal kickback)

Kneel on your hands and knees on a firm surface, such as a bed or a rug. Slowly raise one knee off the floor, bringing it closer to your chest. Extend your leg backwards until it is absolutely straight. Hold this position for a few seconds before slowly returning the knee to its original position. As directed, repeat on both sides. Normally, we would expect you to find one side of this exercise easier than the other, though doing the exercise on both sides is beneficial.	

3. Balance exercise (proprioception)

be careful not to fall & injure yourself with this exercise

This final set of exercises aims to improve balance and coordination while also increasing the activation of muscles in the hip and low back. Begin with standing on one leg on a firm, flat surface while keeping your eyes open. When you're just starting off, it's fine to grasp onto something solid like a worktop. Then proceed from holding something to softly touching a worktop, to intermittently touching, and finally not touching at all. Make sure your hips don't "drop" and that you maintain decent posture while doing this.

At least three times per day, stand for roughly 30 seconds on each leg. When you've mastered these exercises, lay a pillow under your standing foot (or use a wobble board) and progressively increase the amount of time you can balance for. When you've mastered standing on one leg on a firm surface, try doing it with your eyes closed - this will make the exercise more difficult because you won't be able to see if you're wobbling.

Thank you

Appendix Four: Case Reporting Formats (CRF)

EQ-5D-3L

Health Questionnaire

English version for the UK

(Validated for Ireland)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

SELF-CARE

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

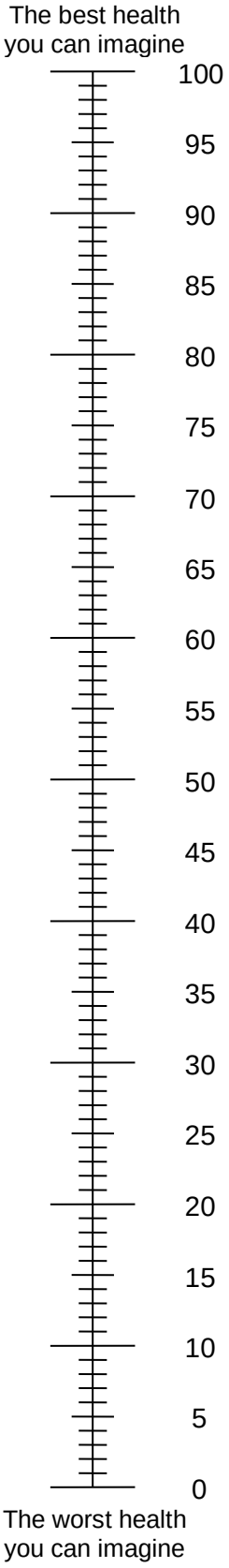
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

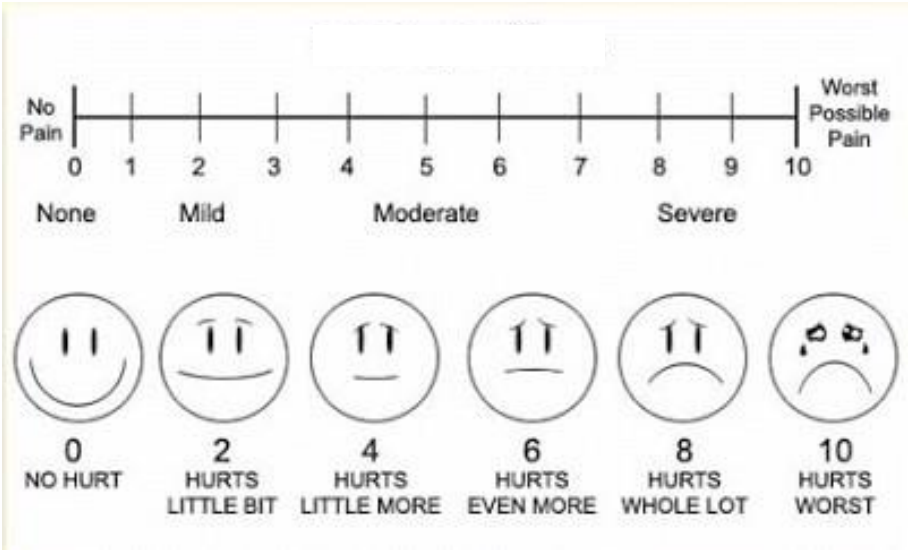


Visual Analogue Scale (VAS):

Participant Trial Number: [ ]

How would you rate your hip pain on a 0 to 10 scale at the present time, that is right now?

where 0 is "no pain" and 10 is "pain as bad as could be"?



International Hip Outcome Tool (IHOT12)

Participant trial number: ☐ **Side:** ☐ Left

Date of review: ☐☐☐☐☐☐☐☐ ☐ Right

(complete either the date of review or the follow up period below)

Simply place a vertical line at the position on the line below that corresponds accurately with your perception of your answer to the question. Please ensure that your line crosses the horizontal line, inside the shaded area.

1. Overall, how much pain do you have in your hip/groin?

Extreme pain ——— No pain at all

2. How difficult is it for you to get up and down off the floor/ground?

Extremely difficult ——— Not difficult at all

3. How difficult is it for you to walk long distances?

Extremely difficult ——— Not difficult at all

4. How much trouble do you have with grinding, catching or clicking in your hip?

Severe trouble ——— No trouble at all

5. How much trouble do you have pushing, pulling, lifting or carrying heavy objects?

Severe trouble ——— No trouble at all

6. How concerned are you about cutting/changing directions during your sport or recreational activities?

Extremely concerned ——— Not concerned at all

7. How much pain do you experience in your hip after activity?

Extreme pain ——— No pain at all

8. How concerned are you about picking up or carrying children because of your hip?

Extremely concerned ——— Not concerned at all

9. How much trouble do you have with sexual activity because of your hip?

☐ This is not relevant to me

Severe trouble ——— No trouble at all

10. How much of the time are you aware of the disability in your hip?

Constantly aware ——— Not aware at all

11. How concerned are you about your ability to maintain your desired fitness level?

Extremely concerned ——— Not concerned at all

12. How much of a distraction is your hip problem?

Extreme distraction ——— No distraction at all

Modified Harris Hip Score

Participant Trial Number [ ]

Please mark one choice for each topic:

Pain:

___None/ignores (44points)

___Slight, occasional, no compromise in activity (40 points)

___Mild, no effect on ordinary activity, pain after activity, uses aspirin (30 points)

___Moderate, tolerable, makes concessions, occasional codeine (20 points)

___Marked, serious limitations (10 points)

___Totally disabled (0points)

Function: Gait

Limp

___None (11 points)

___Slight (8points)

___Moderate (5 points)

___Severe (0 points)

___Unable to walk (0 points)

Support

___None (11 points)

___Cane, long walks (7 points)

___Cane, full time (5 points)

___Crutch (4 points)

___2 canes (2points)

___2 crutches (1points)

___Unable to walk (0 points)

Distance Walked

___Unlimited (11 points)

___6 blocks (8 points)

___2-3 blocks (5 points)

___Indoors only (2 points)

___Bed and chair (0 points)

Functional Activities:

Stairs

___Normally (4 points)

___Normally with banister (2 points)

___Any method (1 points)

___Not able (0 points)

Socks/Shoes

___With ease (4 points)

___With difficulty (2 points)

___Unable (0 points)

Sitting

___Any chair, 1 hour (5 points)

___Highchair, ½ hour (3 points)

___Unable to sit, ½ hour, any chair (0 points)

Public Transportation

___Able to enter public transportation (1 points)

___Unable to use public transportation (0 points