UNIVERSITY OF OXFORD

PATH2
Platelet Rich Plasma in Achilles Tendon Healing

ISRCTN54992179
Clinicaltrials.gov identifier: NCT02302664
NIHR CRN Portfolio Database ID: 17850

PATH-2 STUDY

PROTOCOL SUMMARY

A pragmatic, multi-centre, blinded, randomised placebo-controlled trial comparing Platelet Rich Plasma injection (PRP) to placebo (imitation) injection in adults with Achilles tendon rupture.

Study Design
Two systematic reviews concluded that there were encouraging signs that Platelet Rich Plasma (PRP) could be developed as an effective tendon therapy but called for an adequately-powered randomised controlled trial to establish efficacy with disease-specific outcome measures. We propose a multi-centre, UK-wide, blinded, randomised placebo-controlled trial of PRP in Achilles tendon rupture.

Hypothesis
That PRP application as an adjunct to standard care will achieve improved musculotendinous function and patient recovery after acute Achilles tendon rupture (ATR) in adults.

Aims
1. To evaluate the clinical efficacy of PRP in acute ATR in terms of:
    a. muscle-tendon function.
    b. patient-reported functional recovery, pain and quality of life.
2. To identify the key components of PRP that contribute to its mechanism of action.
3. To explore the immunohistochemical response of the healing tendon to PRP at the cellular and tissue level.

Population
All patients aged 18 or over with diagnosed acute ATR **within 12 days of injury** who are suitable for **non-surgical** treatment.

Setting
Trauma and Orthopaedic outpatient clinics in NHS hospitals.

Sample size
214 participants will be recruited over a 25 month period.

Collaborating sites
A minimum of 15 UK NHS hospitals.

Study participants and recruitment
Patients aged 18 or over who attend an outpatient clinic for treatment of an Achilles tendon rupture can be considered for the study. The treating surgeon (or an extended scope physiotherapist who is appropriately qualified) will confirm **non-surgical** treatment is appropriate and check the study inclusion/exclusion criteria:

Inclusion criteria
- Patient is willing and able to give informed consent for participation in the study
- Aged 18 or over
- Ambulatory prior to injury without the use of walking aids or assistance of another person
- Diagnosed with an acute, complete, Achilles tendon rupture
- Presenting and receiving study treatment within 12 days post-injury
- Patients in whom the decision has been made for non-operative treatment
- Able (in the Investigator's opinion) and willing to comply with all study requirements
- Able to attend a PATH-2 study hospital site for the 24-week follow-up

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Exclusion criteria

The participant may not enter the study if ANY of the following apply:

- Achilles tendon injuries at the insertion to the calcaneum or at the musculotendinous junction
- Previous major tendon or ankle injury or deformity to either lower leg
- History of diabetes mellitus
- Known platelet abnormality or haematological disorder
- Current use of systemic cortisone or a treatment dose of an anticoagulant (i.e. a prophylactic dose for preventing thrombosis would not be an exclusion)
- Evidence of lower limb gangrene/ulcers or peripheral vascular disease
- History of hepatic or renal impairment or dialysis
- Female patients who are pregnant or breast feeding
- Is currently receiving, or has received, radiation or chemotherapy within the last 3 months
- Has inadequate venous access for drawing blood
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the patient's ability to participate in the study

Treatment and Placebo groups

Following written consent and baseline data collection, the researcher will randomise the participant via the Oxford Clinical Trials Research Unit's randomisation service (telephone or web access). The participant will be allocated to one of two groups, either:

Group 1 (Treatment)	**PRP injection**: local anaesthetic injection to skin, followed by PRP injection into the tendon rupture gap
or	
Group 2 (Placebo)	**Imitation injection**: local anaesthetic injection to skin, followed by imitation injection into the tendon rupture gap (needle insertion, no PRP)

A blood sample is taken immediately **following** randomisation (up to 55 ml will be withdrawn), and immediately prior to intervention delivery. Blood samples must be prepared for treatment according to allocation-specific instructions (see full guidance provided in the PATH-2 intervention and blood processing training materials). The participant remains blind to allocation throughout the study. The clinical staff delivering the injection will be aware of the allocation to ensure the appropriate treatment is delivered. Those involved in follow-up activities will be blind to allocation. Standardised rehabilitation is required for this study to reduce the risk of efficacy signal interference from variations in rehabilitation.

Outcome measures

Primary

<u>24 weeks post-injection.</u>

Heel-Rise Endurance Test (HRET): a validated objective physical test to measure calf muscle capacity to work (measured in Joules).

Secondary

<u>0-2 weeks</u>

Participant completes pain diary daily at home

<u>Weeks 4, 7, 13, 24 and month 24</u>

- Achilles Tendon Rupture Score (ATRS): a validated patient-reported outcome measure of muscle strength, fatigue, pain and function
- Patient Specific Functional Scale (PSFS): a patient-reported tool that focuses on the patients' own functional recovery goals
- SF-12 (acute): a patient-reported tool, health related quality of life scale

Blood samples: the sample remaining after treatment will be prepared according to trial-specific instructions and sent to a central laboratory at the University of Birmingham for analysis (PRP analysis/cell count/activation/growth factor/ELISA analysis)

Selected sites only: Needle biopsy in 16 participants at 6 weeks post-treatment. Samples go to a central laboratory for analysis (pain receptors/angiogenesis/collagen markers).