Achilles Tendinopathy Management

PROTOCOL

Achilles Tendinopathy Management (ATM): A multi-centre placebo controlled randomised controlled trial comparing Platelet Rich Plasma (PRP) to placebo (imitation) injection in adults with Achilles tendon pain.

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WARWICK
CLINICAL TRIALS UNIT

Arthritis Research UK

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LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MCID	Minimal Clinically Important Difference
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
PI	Principal Investigator
PPI	Patient & Public Involvement
PRP	Platelet rich plasma
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TC	Trial Coordinator
TMG	Trial Management Group
TSC	Trial Steering Committee
US	Ultrasound
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Tendinopathy in the mid-substance of the Achilles tendon occurs because of the failure of the tendon to mediate its repair and degeneration processes[1]. The general population has an incidence of 2.35 per 1000 people, equivalent to approximately 150,000 people in the UK every year[2].

Achilles tendinopathy is characterised by pain and stiffness over the lower portion of the calf, impacting on all weight bearing activities. This functional impact has been reflected in the research teams published feasibility randomised controlled trial[3].

Patients face a range of non-operative treatments such as exercise, electrotherapy and injections, while operative management is usually the last line of treatment. The non-operative treatments available vary widely between musculoskeletal centres. With large variations in current practice, there is a pressing need to establish which non-operative treatments are effective and should be available to all patients, and which are not[4-6].

1.2 Existing knowledge

To develop this current protocol our research group have completed three phases of preliminary work to establish what the research priorities are in this area and if they are feasible.

- Cochrane Review

The Chief Investigator (CI) and co-investigators (Costa and Parsons) are lead authors on a Cochrane review of injection management for Achilles tendinopathy[7]. This work is currently on-going; however, search strategies have been developed following the Cochrane procedures and peer reviewed. They include the databases of MEDLINE, CINAHL, EMBASE, AMED and SPORTDiscuss. The results of these searches have revealed no previous studies addressing the proposed research question for this protocol.

One randomised controlled trial has been identified investigating the incremental benefit of adding PRP injections to usual care, in this case eccentric loading exercises[8]. Although the trial was small, it did exclude the pre-determined important difference in the primary outcome measure.

This trial was discussed in more detail during a subsequent Arthritis Research UK Achilles Tendon Think Tank. The group did not dispute the internal validity of this trial; it is the external validity which remains a question – would the results of the trial be replicable in an unselected group of patients in the context of a multi-centre trial in a UK NHS setting?

The group discussed that independent verification of this result in a different population and in the context of a large multi-centre trial would have real potential to change clinical practice and inform policy, as indicated by the 2013 NICE guidance[9]. Currently, despite the results of the single RCT, clinicians are still using Platelet Rich Plasma injections widely.

- Feasibility Study and Patient Consultation

Funded by the Chartered Society of Physiotherapy, our research group led and delivered a feasibility study[3]. This study used a process evaluation model to determine the feasibility and acceptability of trial procedures. This work was completed in consultation with a patient user panel and was later

presented at the Arthritis Research UK Achilles tendon Think Tank and published in a peer review journal.

- Arthritis Research UK Achilles tendon Think Tank

In April 2013, an Arthritis Research UK Achilles tendon Think Tank was held. It consisted of representatives from rheumatology, podiatry, orthopaedics, physiotherapy, general practice and research. The group were presented with an overview of the current literature, national guidance and current practice for each intervention. They were then asked to vote on the intervention that offered the most promising advances in management and required further research as a priority area. Platelet rich plasma injections were voted as the top priority.

1.3 Hypothesis

Research Question:
In adults with painful mid-substance Achilles tendinopathy lasting longer than three months, does a single injection of platelet rich plasma improve VISA-A (Victorian institute of Sport Assessment-Achilles) scores by a minimum of 12 points when compared to a placebo injection at six months post injection?

Null Hypothesis:
There is no difference in the VISA-A score at six months between adults with painful mid-substance Achilles tendinopathy treated with platelet rich plasma injection versus a placebo injection.

1.4 Need for a trial

Platelet rich plasma injections have gained national and international interest following national guidance published by the National Institute for Health and Care Excellence (NICE) in 2009 (updated 2013)[9] and international guidance published by the International Olympic Committee (IOC) 2010. Both have discussed platelet rich plasma injections as a priority area for research, which could reduce morbidity and the need for surgery in this patient group.

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 1998.

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, 357: 1191-1194).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

This will be a single blinded, multi-centre, randomised placebo controlled trial. The considered opinion of the Arthritis Research UK CSG Think Tank – which included representatives from rheumatology, podiatry, orthopaedics, physiotherapy, general practice and research – was that in the non-athletic population there is very limited evidence of the effectiveness of eccentric loading exercises, or indeed any other intervention, for this condition. It was the considered opinion of the Think Tank that there was no 'standard treatment' for the general population. Therefore, the

pivotal and crucial trial design which is likely to influence clinical practice should involve a placebo-arm.

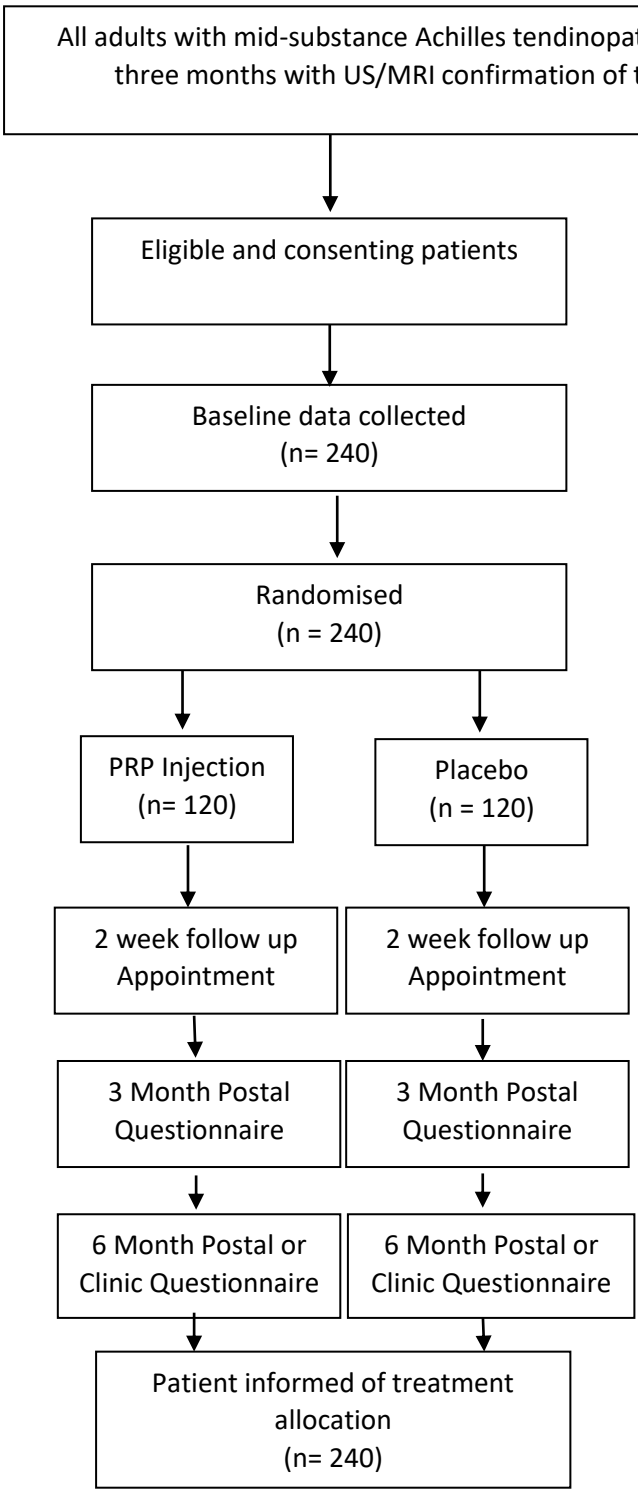
All patients who are willing to proceed will be approached by a suitably qualified member of the research team who are responsible for completing consent procedures and baseline demographic data and functional outcomes using VISA-A and EQ-5D-5L **before randomisation**. The patient will be randomised using a centralised telephone randomisation service to either the intervention or the placebo injection, on a 1:1 basis, stratified by centre and presence of bilateral symptoms. **After randomisation**, the suitably qualified member of the research team will then prepare the allocated injection for the principal investigator who will administer the injection. The participant will not know the treatment allocation.

Two hundred and forty patients will be randomised in total, across six participating centres. The intervention delivery will be standardised through initial training and on-going quality assurance checks by an independent researcher. The participants will then attend routine clinical appointments, (typically two weeks post injection to assess for any adverse events and six months post injection to review treatment efficacy). The participants will also receive two postal follow up questionnaires, as part of research procedures, at three and six months following randomisation.

The local principal investigator and research team at each site cannot be blind to treatment as they will be delivering the interventions. None of these team members will have a role in the collection of participant data after randomisation or analysis, beyond reporting adverse events.

All research outcomes used will be validated patient reported outcome measures (VISA-A and EQ5D-5L), the primary outcome point will be six months after randomisation. A trial management group, trial steering committee and data monitoring and ethics committee will oversee the trial.

Figure 1 Trial flow diagram



Exclusion criteria:

- Presence of systemic conditions (including: diabetes, rheumatoid arthritis, peripheral vascular disease)
- Pregnant or actively trying to become pregnant, or breastfeeding at the time of randomisation
- Have had prior Achilles tendon surgery or rupture on the index side.
- Previous major tendon or ankle injury or deformity to either lower leg.
- Have had a fracture of a long bone in either lower limb in the previous six months
- Have any contraindication to receiving a platelet rich plasma injection (haemodynamic instability, platelet dysfunction syndrome, cancer, septicaemia, systemic use of anticoagulant, local infection at site of the procedure)
- Are unable to adhere to trial procedures or complete questionnaires.
- Previous randomisation in the present trial.

2.2 Aims and objectives

2.2.1 Primary objective

Primary Objective:
To quantify and draw inferences on observed differences in the VISA-A between the trial treatment groups at six months after treatment.

2.2.2 Secondary objective

Secondary Objectives:
1) To quantify and draw inferences on observed differences in VISA-A status at three months after treatment.

2) To identify any differences in health related quality of life measurement between trial treatment groups at three and six months after treatment.

3) To determine the complication rate of platelet rich plasma injections at three and six months after treatment.

2.3 Outcome measures

Outcome measures from the patients' perspective are the focus of this trial. The Achilles Tendon Think Tank discussed the use of objective functional outcomes to supplement the patient-reported outcomes. However, the group considered that there was no specific objective measure for this condition. Calf muscle strength was considered as a surrogate for function but such measures are comparatively labour intensive to collect and ultimately have little clinical relevance in the general population (c.f. the sporting population). Since, clinical decisions in this population are based on what the patient reports (pain and function), the group considered that the patient-reported outcomes would provide all of the outcome data necessary to inform clinical practice in this area.

Robinson et al (2001)[10] suggested that despite Achilles tendinopathy being a common presentation, no reliable and valid outcome measure was available. They subsequently developed the VISA-A questionnaire. Currently this is the only patient reported outcome measure developed with supporting validation and reliability research, for this common musculoskeletal presentation.

The VISA-A is a condition specific numerical scale, designed to have greater sensitivity and specificity than general purpose scales. It tests three significant domains of dysfunction; pain, function and activity. This outcome measure is not designed to distinguish between body pains, but is a valid measure of severity of Achilles tendinopathy.

The VISA-A contains eight questions that cover three domains of pain, function and activity. An asymptomatic person would score 100, the lower the score the greater the disability. In the above paper it was shown to have good test-re-test reliability (r=0.93), inter-rater and intra-rater reliability (r=0.90) and construct validity when the mean scores were compered across patient populations with differing ranges of severity. A recent systematic review of the VISA-A score has confirmed these findings[11].

A recent Cochrane review on the topic of Injection therapies for Achilles tendinopathy completed by the applicants found the VISA-A to be the most commonly reported patient reported outcome measure. More specifically, to randomised controlled trials evaluating platelet rich plasma and autologous blood injections, the minimally clinically important difference (MCID) for the VISA-A

score was set between 10 and 12 points; this is in keeping with other comparable studies in musculoskeletal medicine that report MCID to lie between 10% - 15% of the scale [12].

The VISA-A is the only patient reported outcome measure with supporting research of reliability and validity. Consequently no other disease specific questionnaires are appropriate as secondary outcomes. However, the EQ-5D-5L generic quality of life questionnaire will be an important secondary outcome measure for this trial.

The EQ-5D[13] consists of five domains related to daily activities, with a five-level answer possibility. The EQ-5D has been subject to extensive validity and reliability testing, as outlined on its website (http://www.euroqol.org/home.html). In addition to this quality of life data, complications of the trial groups will also be reported for safety reporting reasons, outlined in the Data Monitoring Committee (DMC) charter.

2.3.1 Efficacy

- Primary: VISA-A
- Secondary: EQ-5D-5L

All outcome measures will be paper based and collected at baseline (pre randomisation) by a suitably qualified member of the research team, face to face at the recruiting site and then at three months post randomisation by postal questionnaire sent from Warwick CTU (WCTU) and six month face to face at final follow up or postal.

2.3.2 Safety

- Adverse event data

At each postal questionnaire follow up participants will be asked if they have had any adverse events and how they were managed. Additionally, at each participating site, the Principal Investigator (PI) will be asked to comply with procedures for reporting SAEs to the Trial Coordinator within 24 hours of becoming aware of an event – in line with Warwick SOPs outlined in sections 4.1.1.

2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.4.1 Inclusion criteria

- Aged 16 years or over
- Pain at the mid-substance of the Achilles tendon for longer than three months
- Ultrasound and/or MRI confirmation of tendinopathy.

2.4.2 Exclusion criteria

- Presence of systemic conditions (including: diabetes, rheumatoid arthritis, peripheral vascular disease)
- Pregnant or actively trying to become pregnant, or breastfeeding at the time of randomisation
- Have had prior Achilles tendon surgery or rupture on the index side.

- Previous major tendon or ankle injury or deformity to either lower leg.
- Have had a fracture of a long bone in either lower limb in the previous six months
- Have any contraindication to receiving a platelet rich plasma injection (haemodynamic instability, platelet dysfunction syndrome, cancer, septicaemia, systemic use of anticoagulant, local infection at site of the procedure)
- Are unable to adhere to trial procedures or complete questionnaires.
- Previous randomisation in the present trial.

The inclusion criteria are designed to be inclusive of the general population that sustain this debilitating condition. However, the Arthritis Research UK Think Tank group discussed that within this group of patients there are two distinct sub groups. The first group have an isolated Achilles tendinopathy; the second have tendinopathy secondary to a systemic condition. It was the view of the group that there was sufficient evidence of differences between these two sub groups, in terms of pathology and potential response to treatment, to not include them as one population.

Patients presenting with bilateral Achilles tendinopathy will be randomised and treated as one unit i.e. the patient will be randomised rather than the tendon. However an index tendon will be identified (this will be the one the patient perceives to be more severe at the point of randomisation). These broad eligibility criteria will ensure that the results of this study can be readily generalised to the wider population.

Screening logs will be collected throughout the trial to assess the main reasons for patient exclusion as well as number of patients willing to take part.

2.5 Informed consent

Eligible patients will be identified from foot and ankle clinics by the local PI and invited to speak to a suitably qualified member of the research team.

Patients will be provided with verbal and written information about the study. A list of information the research team should cover before consent is obtained will be provided to ensure that all essential information is discussed with the potential participant. Written informed consent will be obtained by a suitably qualified member of the research team at each site, after allowing sufficient time for the patient to consider their decision and ask questions about the trial. Timing and appropriateness of obtaining consent in this setting will be closely monitored by the Trial Management Group (TMG) and reviewed by the independent Trial Steering Committee (TSC).

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the TSC; if necessary this will be communicated to all participants. A revised consent form will be completed if necessary.

For reference, the participants GP will be informed by letter that the patient is taking part in this clinical trial. Participants may deny the research team to inform the GP of their trial involvement by not initialling the appropriate box on the consent form.

2.6 Recruitment and randomisation

2.6.1 Recruitment

Our feasibility study has demonstrated a recruitment rate of 2.3 patients per month. Furthermore, our study procedures indicated that the wide generalizable inclusion and exclusion criteria only excluded an average of one patient per month from the pool of presenting patients. However, working with the WCTU senior project management team we have identified that over their large portfolio of national multi-centre trials, recruitment rates outside of the lead centre consistently occur at a lower rate. Using this information, a recruitment rate of 1.4 patients per month per centre was considered a conservative estimate of recruitment rate for this trial.

Mechanisms consistent with successful recruitment rates in previous national multi-centre trials led by WCTU will be implemented. These include using a national network of PIs who have successfully collaborated on previous randomised controlled trials funded by Arthritis Research UK, Health Technology Assessment Programme (HTA), Research for Patient Benefit (RfPB), Action Medical Research, AO Foundation and Orthopaedic Research UK.

In addition to the dedicated network of PIs, WCTU collaborates closely with the Local Clinical Research Network. This will allow each PI to work with an experienced team within their foot and ankle clinic. Each PI will identify all eligible patients in their clinic and refer the patient to associate suitably qualified member of the research team who will inform patients both verbally and in writing about the trial, complete consent and randomisation procedures and collect baseline data.

Initial collaborating centres in this trial include University Hospitals Coventry and Warwickshire, Sheffield Teaching Hospitals, Addenbrooke's Hospital, The Princess Royal (The Shrewsbury and Telford Hospital NHS trust), Leicester Royal Infirmary and Norfolk and Norwich University Hospital. Each with proven ability to lead large research teams and achieve recruitment targets (UK Distal Radius Acute Fracture Fixation Trial: HTA; Warwick Arthroplasty Trial: RfPB; UK Fixation of Distal Tibia fracture Trial: HTA and Wound Management of Open Lower Limb Fractures Trial: HTA). A staged, centre set up will be implemented, additional centres may be added as appropriate to achieve recruitment target. .

Standard agreements will be issued to each recruiting centre, which will include the option to close down centres that are not recruiting to time and target. Recruitment by centre will be monitored and reported to the TMG and TSC.

If deemed necessary by the TMG and TSC additional centres will be included. Any future collaborating centres will have a strong record of accomplishment of working with the WCTU on previous multi-centre studies of national importance.

2.6.2 Randomisation

Pre-randomisation eligibility checks will be carried out to ensure that patients meet the eligibility criteria and are not randomised in error. Written informed consent for entry into the trial must be obtained prior to randomisation. Subjects will be randomised strictly sequentially, as they become eligible for randomisation.

The treatment group will be allocated using a secure, centralised, telephone-based randomisation service. The randomisation service will be available Monday-Friday, 9am-5pm each day to facilitate the inclusion of all eligible patients. The allocated treatment will be reported to a member of the research team who will prepare the treatment allocation and inform the PI. The PI will then administer the treatment allocation, however the allocation will remain concealed from the

participant. A sticker will be placed on participants clinical notes for flagging their inclusion in the trial.

Stratification by centre will help ensure that any clustering effect related to the centre itself will be equally distributed in the trial arms. The catchment area (the local population served by the hospital) will be similar for all of the hospitals; each hospital delivering a specialist foot and ankle clinic. Stratification based on bilateral presentation will also be implemented to account for the poorer outcome associated with this sub population.

Details of the WCTU randomisation service are below:

2.6.2.1 Post-randomisation withdrawals and exclusions

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. For participants explicitly withdrawing consent for follow up procedures, trial data obtained up until the point of withdrawal will be included in the final analysis of the study. Participants will have the option to withdraw from the trial-related questionnaires, but continue to provide routine NHS data for the purposes of the trial e.g. hospital records of subsequent treatment for the Achilles condition.

Participants who withdraw will not be replaced in the trial and a corresponding CRF will be completed by the Trial Coordinator (TC).

All of the outcome questionnaires can be completed over the phone, or in the follow-up clinic, if postal copies are not returned. Text messages may be sent to participants to inform them that a questionnaire is due or on its way. Text messages will only be sent to those participants who have given their prior consent to this by initialling the corresponding box on the consent form. Text messages will be sent via the WCTU mobile phone from a secure office.

Participants may be withdrawn from the trial at the discretion of the investigator and/or Trial Steering Committee due to safety concerns Trial treatments

2.6.3 Trial treatments

Pre-Injection
During their initial consultation, all participants will receive active treatment in the form of an advice sheet informing them of their condition, coping strategies and the use of rescue analgesia. All concomitant medication will be recorded at baseline.

At each centre the PI and RA will undertake a training programme delivered and documented by the lead applicant, Dr Rebecca Kearney. This will ensure standardised delivery of both trial arms. This will be alongside scheduled quarterly observations of interventional delivery, by an independent quality assurance member of the team. All injections will be prepared by a suitably qualified member of the research team and administered by the PI.

All participants, regardless of treatment allocation, will have approximately 10ml of whole blood withdrawn from the antecubital fossa (vein at the elbow). 5ml of 2% lignocaine (local anaesthetic)

will be injected into the skin overlying the painful tendon area for pain relief; this will be done with the participant in the prone (lying down and facing away) position on a treatment couch. The tendon itself will then be treated.

PRP Injection Procedure:
The whole blood will be centrifuged using the Glo PRP system (Glofinn, Salo, Finland). Each centre will be supplied with the same centrifuge system to allow standardisation of the intervention. **This will be done in a separate room away from the participant.**

Although the prone position means that the participant will be facing away from the surgeon, the treatment syringe will be masked to make sure that the participant cannot see the contents of the syringe. Participants will then have one injection of the prepared platelet layer (approximately 3ml). The platelet rich plasma injection will be injected into the Achilles tendon using a standard 'peppering' technique at the site of the tendon pain. This technique involves a single skin portal and then five penetrations of the tendon.

Placebo Injection Procedure:
For the placebo injection, the masked needle will be inserted under the skin, but not into the tendon. The participant will feel the needle but nothing will be injected.

There is an active debate pertaining to the treatment effect of needling trauma, or the trauma of injecting fluid directly into the tendon. Therefore, a true placebo arm would need to avoid these possible treatment effects. The group consensus was therefore not to administer the placebo injection intratendinously.

Post Injection:
The participant will not be aware which treatment they have received, but the PI administering the treatment will.

After both treatments all participants will receive the same post injection advice sheet. The post injection advice sheet will inform participants that they may have increased pain for 24-48 hours, after which period they can resume their normal activities as pain allows. It will also include advice on potential adverse events (e.g. infection and reddening of the skin) and what to do if they occur.

In the case of participants with bilateral presentations, the index tendon will be randomised and managed accordingly. Regarding the non-index tendon the participant will have two options, to have no treatment or to receive a second injection into the non-index tendon.

All participants will then be followed up at standard clinical follow up appointments. These usually occur on two further occasions at two weeks after the injection and six months. The appointment at two weeks will allow the PI to check for the occurrence of any early complications (e.g. infection). The appointment at six months will allow the PI to assess the outcome from a clinical perspective and discuss with the participant at this point if any further clinical management is required.

Research follow up will be by postal questionnaire and will take place at three and six months after randomisation.

2.6.4 Compliance

Quarterly quality assurance checks will be carried out by a member of the trial team to assess compliance with the above intervention delivery. The appointed researcher will be supplied with a checklist of the intervention and placebo procedures and each PI will be checked against this.

Any deviations noted from the outlined trial interventions will be monitored by the TMG and TSC. If required further training will be implemented to resolve any inconsistencies.

2.7 Blinding

2.7.1 Methods for ensuring blinding

Local Trial Management
At each participating centre, a suitably qualified member of the research team will collect the baseline data before randomisation, so this data will be blind. Once all baseline data has been collected the member of the research team will randomise the patient and be told the allocation to enable them to prepare the appropriate intervention. They will inform the PI who will deliver the appropriate intervention. The PI will take no part in the post-treatment data collection or analysis of the participant beyond reporting of SAEs as appropriate.

All participants will be blinded and not know their treatment allocation through masking of the treatment syringe to prevent them from seeing the contents.

All trial procedures will take place alongside a rigorous programme of quality control. The CI in conjunction with the TC will be responsible for ensuring adherence to the trial protocols at the trial sites.

The ATM treatment CRF will collect confirmation that allocated treatment was delivered but will not specify the treatment delivered. Where a treatment other than that allocated was received this should be noted on the CRF and the study coordinating team will contact the site for further details once the CRF has been received and processed in the study office.

When any hospital notes are updated relating to treatment or GP letters dictated, it should be recorded that an injection was delivered as per the random allocation assigned by the ATM study. The type of injection should not be recorded.

2.7.2 Methods for unblinding the trial

Code-break: is the term used for revealing treatment allocation. For ATM there will be a list of treatment allocations for all participants embedded in the database held at Warwick. The randomisation service is also provided by Warwick and the allocation data will be transferred internally from the randomisation service to the database, therefore allocation information will remain secure within Warwick.

Unblinding: The team delivering the injection treatment will be aware of the allocation. Unblinding of participants during the conduct of the trial is not allowed unless there are compelling medical or safety reasons to do so.

Emergency unblinding: The treatments in this study are considered low risk for the need for unblinding. However, if it is considered necessary to request unblinding after the treatment period the request should be directed to the CI via the 'ATM' central office, with full reasons for the request.

Unblinding after completion of the trial: The participants recruited to this trial may be invited to participate in longer term follow up and therefore may not be informed of their allocation at the end of the study. If follow up funding is not forthcoming within 12 months of the last participants 6 month follow up, participants will be informed by post, text or email of their treatment allocation if a request is made.

2.8 Concomitant illness and medication

2.8.1 Concomitant illness

Details of any concomitant illness will be recorded at trial entry and new illnesses recorded at follow up time points. If the change influences the participant's eligibility to continue in the trial, the CI will be informed.

2.8.2 Concomitant medication

Details of any concomitant medication will be recorded at trial entry. Any changes in concomitant medication will be recorded at each follow up questionnaire time point. If the change influences the participant's eligibility to continue in the trial, the CI will be informed.

2.9 End of trial

The trial will end when all participants have completed their six month follow-up.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing if the trial has been concluded or terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Visit Window (No. Weeks ± No. Days)	**Baseline**	**2 wk post randomisation**	**3 m (± 1 m) after randomisation**	**6 m (± 1m) after randomisation**
Written informed consent	✓			
Baseline data	✓			
Randomisation	✓			
Intervention	✓			
CRF completion	✓	✓		✓
Questionnaires	✓		✓	✓
Adverse events	✓	✓	✓	✓

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Event Management

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this treatment/intervention. All AEs will be listed on the appropriate Case Report Form for routine return to the 'ATM' central office.

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

All serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and faxed to a dedicated fax machine at WCTU within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the CI. SAEs that are deemed to be both unexpected and probably or definitely related to the trial will be notified to the Research Ethics Committee (REC) and sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

SAEs that may be expected as part of the injection interventions, and that do not need to be reported to the trial coordinating centre are: bruising and discomfort at the venesection site, syncopal (fainting) episode associated with venesection or tendon injection, infection, mild discomfort and bleeding at the injection site, swelling, skin discolouration and possible allergic reaction. Expected adverse events as detailed above will be recorded on the participants' CRF but do not have to be reported to the trial coordinating centre within 24 hours. All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act.

The Case Report Forms will be designed by the TC in conjunction with the TMG. All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of Warwick Medical School. Participants will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained for at least ten years after completion of the trial.

5.1 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

5.2 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

5.3 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

There is no consensus on a minimum clinically important difference (MCID) regarding the VISA-A score. However, previous studies propose that the MCID lies between 10 and 12 points and that this is in keeping with comparable patient reported outcomes in musculoskeletal medicine. We have therefore chosen an MCID of 12 points.

From our pilot data, the VISA-A data were observed to be approximately normally distributed with a standard deviation of 26. If the true difference between the experimental and control treatment group means is 12, a sample of 100 patients in each group will be required to reject the null hypothesis (population means of the experimental and control groups are equal) with probability 0.9 (90% power). This equates to an effect size of 0.46 (12/26), which we would consider to be moderate. The Type I error rate (significance level) associated with this test is 5%. Allowing approximately 20% loss to follow-up, this amounts to 240 patients in total

6.2 Statistical Analysis Plan

It seems likely that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the missingness will be carefully considered, including in particular whether data can be treated as missing completely at random or missing at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities (mice package) available in R (http://www.r-project.org/). The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarized. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the assumed distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarised to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

The main analysis will investigate differences in the primary outcome measure, the VISA A at six months after treatment, between the two treatment groups on an intention-to-treat basis. In addition, early functional status will also be assessed and reported at three months. The differences between treatment groups will be assessed using a Student t-test, based on a normal approximation for the VISA A score at 6 months, and at other occasions. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals.

The stratified randomisation procedure will ensure a balance in recruiting centres between test treatments. In addition to the unadjusted analysis (t-tests) we will also undertake regression analyses to adjust for any imbalance between test treatment groups in patient age or gender. The fixed effects analysis (linear regression model) will also be generalized by adding a random effect for recruiting centre to allow for possible heterogeneity in patient outcomes due more generally to the recruiting centre. VISA-A data will be assumed to be normally distributed during modelling, but subsidiary analyses may also be undertaken after appropriate variance-stabilizing transformation. The primary focus will be the comparison of the two treatment groups of patients, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions. Treatment effects will be presented, with appropriate 95% confidence intervals, for both the unadjusted and adjusted analyses.

Temporal patterns of any complications will be presented graphically and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of important complications (e.g. infection). The decision about whether to undertake a time-to-event analysis will be data dependent; that is it will be dependent on the number of complications reported by study participants. The independent Data Monitoring and Ethics Committee will advise on this and suggest appropriate modifications to the statistical analysis plan as data is accumulated.

From the pilot data two patients from a sample of twenty presented with bilateral Achilles tendinopathy. For the full trial this small group will be randomised and treated as one unit i.e. the patient will be randomised rather than the tendon. Therefore, study participants presenting with bilateral tendinopathy will receive the same treatment on both sides. One side will be randomly selected, and designated as the index Achilles tendon. For those outcome measures (complications) that are side specific, we will use data from the index side only in the analysis. Randomisation will ensure approximate balance in bilaterals between groups; however, bilaterality will also be adjusted for in the definitive analysis. This will be incorporated into the Statistical Analysis Plan.

The detailed statistical analysis plan will be agreed with the Data Monitoring and Ethics Committee at the start of the study. Any subsequent amendments to this initial statistical analysis plan will be clearly stated and justified. Interim analyses will be performed only where directed by the Data Monitoring and Ethics Committee. The routine statistical analysis will mainly be carried out using R (http://www.r- project. org/). Results from this trial will also be compared with results from other trials.

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

University of Warwick will act as sponsor for the trial, using WCTU's SOPs.

7.2 Regulatory authorities/ethical approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site will ensure that the local conduct of the trial has the approval of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by WCTU.

7.3 Trial Registration

The study will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

7.4 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.5 Trial timetable and milestones

Months	Years		Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6	**Total**	Notes
0	1	01/09/2015	ethics approval, ISRCTN registration Contracting & R&D centres 1-6							
1		01/10/2015	Finalise protocol, CRF's & training materials							
2		01/11/2015								
3		01/12/2015	Finalise DMC, TMG and TSC membership and WMS appointments							
4		01/01/2016	Purchase equipment							
5		01/02/2016								
6		01/03/2016	Training centres 1&2							
7		01/04/2016	Training centres 3&4							
8		01/05/2016	Training centres 5&6							
9		01/06/2016	1.4	1.4					2.8	Recruitment 1&2
10		01/07/2016	1.4	1.4					5.6	
11		01/08/2016	1.4	1.4					8.4	
12	2	01/09/2016	1.4	1.4	1.4	1.4			14	Recruitment 3&4
13		01/10/2016	1.4	1.4	1.4	1.4			19.6	
14		01/11/2016	1.4	1.4	1.4	1.4			25.2	
15		01/12/2016	1.4	1.4	1.4	1.4	1.4	1.4	33.6	Recruitment 5&6
16		01/01/2017	1.4	1.4	1.4	1.4	1.4	1.4	42	
17		01/02/2017	1.4	1.4	1.4	1.4	1.4	1.4	50.4	
18		01/03/2017	1.4	1.4	1.4	1.4	1.4	1.4	58.8	
19		01/04/2017	1.4	1.4	1.4	1.4	1.4	1.4	67.2	
20		01/05/2017	1.4	1.4	1.4	1.4	1.4	1.4	75.6	
21		01/06/2017	1.4	1.4	1.4	1.4	1.4	1.4	84	
22		01/07/2017	1.4	1.4	1.4	1.4	1.4	1.4	92.4	
23		01/08/2017	1.4	1.4	1.4	1.4	1.4	1.4	100.8	
24	3	01/09/2017	1.4	1.4	1.4	1.4	1.4	1.4	109.2	
25		01/10/2017	1.4	1.4	1.4	1.4	1.4	1.4	117.6	
26		01/11/2017	1.4	1.4	1.4	1.4	1.4	1.4	126	50% recruitment
27		01/12/2017	1.4	1.4	1.4	1.4	1.4	1.4	134.4	
28		01/01/2018	1.4	1.4	1.4	1.4	1.4	1.4	142.8	
29		01/02/2018	1.4	1.4	1.4	1.4	1.4	1.4	151.2	
30		01/03/2018	1.4	1.4	1.4	1.4	1.4	1.4	159.6	
31		01/04/2018	1.4	1.4	1.4	1.4	1.4	1.4	168	
32		01/05/2018	1.4	1.4	1.4	1.4	1.4	1.4	176.4	
33		01/06/2018	1.4	1.4	1.4	1.4	1.4	1.4	184.8	
34		01/07/2018	1.4	1.4	1.4	1.4	1.4	1.4	193.2	
35		01/08/2018	1.4	1.4	1.4	1.4	1.4	1.4	201.6	
36	4	01/09/2018	1.4	1.4	1.4	1.4	1.4	1.4	210	
37		01/10/2018	1.4	1.4	1.4	1.4	1.4	1.4	218.4	
38		01/11/2018	1.4	1.4	1.4	1.4	1.4	1.4	226.8	
39		01/12/2018	1.4	1.4	1.4	1.4	1.4	1.4	235.2	
40		01/01/2019	1.4	1.4	1.4	1.4	1.4	1.4	243.6	Total recruitment
41		01/02/2019	Final follow up							
42		01/03/2019								
43		01/04/2019								
44		01/05/2019								
45		01/06/2019								
46		01/07/2019								
47		01/08/2019	Data review and statistical analysis							
48	5	01/09/2019	Close sites							
49		01/10/2019								
50		01/11/2019	Final report and dissemination							
51		01/12/2019								
52		01/01/2020								

7.6 Administration

The trial co-ordination will be based at WCTU, University of Warwick.

7.7 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

7.8 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

7.9 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet after the first 50% of patients have been recruited and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The Data Monitoring Committee (DMC) will be established in line with the charter set by WCTU. The Data Monitoring Committee (DMC) will be independently chaired and established in accordance with the principles of Good Clinical Practice, WCTU Standard Operating Procedures (SOPs) and Arthritis Research UK Oversight Committee guidance.

(1) There will be no a priori stopping rules set for efficacy. Experience suggests that the nature of trial design is such that there is unlikely to be sufficient data available to make decisions regarding efficacy prior to the end of the recruitment phase of the study. This will in part be determined by the study recruitment patterns, which will be routinely monitored by DMC, therefore they may decide that a narrow window of opportunity does exist to assess treatment efficacy. If so, they are at liberty under the DMC charter to make recommendations and suggestions to the Trial Management and Steering Committees at end stage of the study.

(2) The study statistical analysis plan, which will be agreed with all parties at the commencement of the trial. The DMC will feedback their recommendation, on whether in their view the trial should proceed, to the TSC who will meet immediately after this time-point. The DMC

will make a recommendation only to the TSC, but ultimately it will be the responsibility of the independently chaired TSC to decide on whether the trial will proceed to the planned sample size, or be curtailed early.

(3) Regarding stopping rules for safety, these will be discussed and agreed by the independent committee prior to the commencement of recruitment and reviewed annually thereafter, or more frequently if deemed necessary.

7.10 Essential Documentation

A Trial Master File will be set up according to WCTU SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

We will institute a rigorous programme of quality control. The CI in conjunction with the Trial Coordinator will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by WCTU to ensure integrity of randomisation, study entry procedures and data collection. The WCTU has a quality assurance manager who will monitor this trial by conducting regular (yearly or more if deemed necessary) inspections of the Trial Master File. Furthermore the processes of consent taking, randomisation, provision of information and provision of treatment will be monitored.

To ensure that the intervention is delivered in a standard way by all PIs during the course of the trial the following two components will take place:

• Training of personnel in the delivery of the intervention. This will be undertaken at the start of the trial; further sessions may be necessary at a later stage to take account of staff changes. The CI and TC will take responsibility for organising training sessions.

• Quality assurance checks: In addition to standard quality assurance checks, in keeping with Warwick SOPs, a separate member of the team will be employed to assess adherence to the trial intervention delivery.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Following patient and public consultation nationally by the National Institute for Health and Care Excellence (NICE), guidance on autologous blood injections for tendinopathy was published. The key finding was that they may reduce pain and increase function, however further research is required in the context of randomised controlled trials. Subsequently, in line with INVOLVE guidelines, Dr Rebecca Kearney and Professor Matthew Costa (lead applicant and co-applicant) consulted with patients during their clinical appointments to ascertain if the research gaps highlighted nationally were of importance locally. Based on these responses a feasibility study evaluating platelet rich plasma injections was designed and funded by the Chartered Society of Physiotherapy and completed as part of an individual Scholarship with NICE, awarded to Dr Rebecca Kearney (lead applicant).

Following the pilot phase, views of patients were sought regarding trial processes. These initial consultations allowed the team to carefully consider information provided to patients and any ethical issues raised, to inform this current trial design. This, in combination with research and development mechanisms to keep patients and public members informed of trial progress, allowed identification of individuals to collaborate with for this current study.

Identified patients were asked if they would be interested in a consultation role for the development of the full trial and preparation of this application. Interested patients were directed to UNTRAP (Universities/User Teaching and Research Action Partnership) to enable collaborative working with the research team. The PPI representative is subsequently a lay representative for this application.

UNTRAP will support the training and development needs of our PPI representative, through on going provision of appropriate training events and development of good practice partnership working, through implementing agreed codes of conduct.

On completion of the research our PPI representative will also play key roles in contributing to the reporting of the study and dissemination of its findings. It is clear that the research will benefit hugely from further patient and public involvement through consultation and active collaboration.

10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The results of this trial will substantially inform clinical practice on the clinical effectiveness of the treatment of this injury. The results of this project will be disseminated through peer-reviewed journals, conference presentations, the National Library for Health and through local mechanisms at all participating centres.

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