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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University of Warwick
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2.0	21-DEC-2015	15-FEB-2016	Clarification to follow up procedures
3.0	03-MAR-2016	08-APR-2016	Clarification added for choice of comparator and MCID
4.0	30-SEPT-2016	30-NOV-2016	Updated recruitment timeline
5.0	15-FEB-2017	03-MAR-2017	Clarification of exclusion criteria 'cancer' to 'active cancer'
6.0	21-APR-2017	25-MAY-2017	Interim maternity cover Chief Investigator details added
7.0	01-AUG-2017	18-SEP-2017	Clarification that low dose Aspin use not a contraindication to PRP
8.0	15-JAN-2018	26-FEB-2018	Interim maternity cover Chief Investigator changed back to original Chief Investigator
9.0	16-FEB-2018	21-MAR-2018	All references to Trial Coordinator changed to Trial Manager
10.0	30-NOV-2018	19-DEC-2019	Updated recruitment timeline
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CONTACT NAMES AND NUMBERS

Sponsor:	Jane Prewett, Deputy Director/Head of Research Governance for Research & Impact Services, University House Ground Floor Annexe, University of Warwick, Kirby Corner Road, Coventry CV4 8UW Tel: 02476 522746 Email: sponsorship@warwick.ac.uk
Chief Investigator:	Rebecca Kearney, Associate Professor Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Coventry, CV4 7AL Tel: 02476 573156 Email: r.s.kearney@warwick.ac.uk
Chief Investigator Maternity cover (May 2017 to January 2018)	Prof Martin Underwood, Professor of Primary Care Research Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Coventry, CV4 7AL Telephone 02476 574 664 Email m.underwood@warwick.ac.uk
Co-investigators:	Matthew Costa, Professor of Orthopaedic Trauma, University of Oxford, The Kadoorie Centre, John Radcliffe Hospital, Oxford, OX3 9DU Email: Matthew.costa@ndorms.ox.ac.uk Jonathan Young, Consultant Orthopaedic Surgeon University Hospitals Coventry & Warwickshire NHS Trust, Trauma and Orthopaedics, Clifford Bridge Road, Coventry, CV2 2DX Email: jsyoung59@doctors.org.uk Nick Parsons, Principal Research Fellow Warwick Medical School, University of Warwick Coventry, CV4 7AL Tel: 02476 150540 Email: nick.parsons@warwick.ac.uk
Senior Trial Statistician:	Jane Warwick, Associate Professor Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Coventry, CV4 7AL Tel: 02476 522498 Email: J.Warwick@warwick.ac.uk

Trial Statistician:	Chen Ji, Senior Research Fellow Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Coventry, CV4 7AL Tel: 02476 151653 Email: c.ji.3@warwick.ac.uk
Randomisation:	Tel: 02476 150402 (Mon-Fri, 9am to 5pm) Fax: 02476 151586

For general queries and supply of trial materials please contact the 'ATM' central office:
Email: ATM@warwick.ac.uk
Tel: 02476 968626

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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
TM	Trial Manager
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]. 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 for a range of presentations.

- 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.

- **Intervention arm:** Platelet rich plasma injections were voted as the top priority, based on the evidence provided by the Cochrane review, the feasibility trial results and discussions amongst health care professionals and researchers at the Think Tank.

  In line with the previous published literature, currently ongoing NIHR funded research (ISRCTN54992179) and consultation with the algorithm published by MHRA to determine if a clinical trial is of an investigational medicinal product (CTIMP) it is widely established that platelet rich plasma injections do not fulfil the requirements of a CTIMP.

- **Comparator arm:** The considered opinion of the Arthritis Research UK Think Tank was that there is very limited evidence of the effectiveness of any one treatment for this condition. Therefore, the pivotal and crucial trial design which is likely to influence clinical practice should involve a placebo-arm.

  The possible placebos for this trial include all of the following:

  1. Injection into the tendon, injection of saline, and use of a 'peppering' injection technique of five penetrations of the tendon.
  2. Injection into the tendon, injection of saline, without use of a peppering injection technique.
  3. Injection into the tendon, a dry needle injection and use of a peppering technique.
  4. Injection into the tendon, a dry needle injection without a peppering technique.
  5. A subcutaneous injection (so not into the tendon, injection just under the skin), with injection of saline and a peppering technique
  6. A subcutaneous injection, with injection of saline but no peppering technique
  7. A subcutaneous injection, dry needle injection and use of peppering technique
  8. A subcutaneous injection, dry needle injection and no peppering technique

The choice of placebo injection in this patient population is contentious because commonly used saline injections and even dry needling alone (in which the needle is placed in the tendon but nothing is injected) are not true placebo treatments because they have been associated with therapeutic effects in themselves. This is secondary to the local trauma caused within the tendon by the needle, which may facilitate a healing response, which is absent in this pathology. Secondly, there are also possible treatment effects associated with pressure-volume changes within the tendon.

Therefore it was decided that in the control arm all patients will have a needle inserted under the skin, but not into the tendon. The needle will not contain anything, in keeping with previous placebo controlled trials involving the Achilles tendon. The patient will not be aware which treatment they have received, but the principal investigator administering the treatment will.

Consequently the results of this trial will demonstrate the superiority of PRP injection (which includes injection into the tendon, injection of PRP, and use of a 'peppering' injection technique of five penetrations of the tendon) to a subcutaneous injection, dry needle injection and no peppering technique. Given that this placebo has no therapeutic basis, any health gains will be attributed to the three mechanisms by which PRP theoretically provides benefit (volume change, dry needle peppering into the tendon and the PRP itself). This trial will not demonstrate the additional benefit of PRP injection over and above proposed therapeutic effects of dry needling or volume change.

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 (intra-tendinous injection of PRP with a peppering technique) improve VISA-A (Victorian institute of Sport Assessment-Achilles) scores by a minimum of 12 points when compared to a placebo (subcutaneous injection of a dry needle and no peppering technique) 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 general 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.

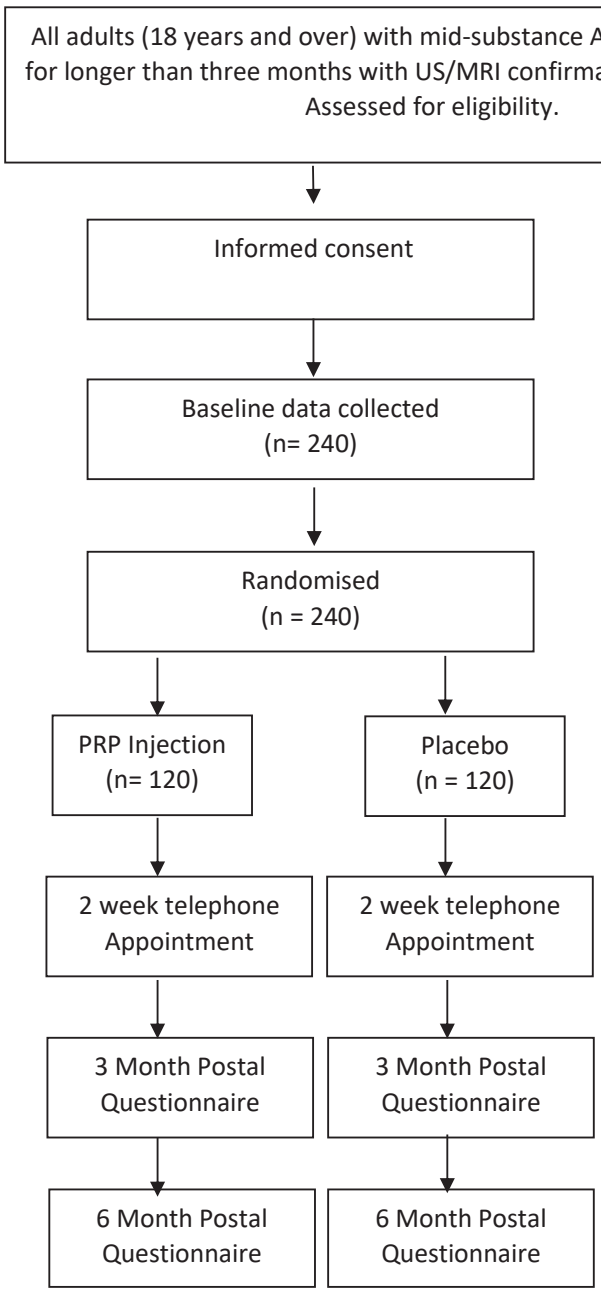
All patients who are willing to proceed will be approached by a suitably qualified member of the research team who are responsible for completing consent procedures and baseline demographic data and functional outcomes using VISA-A and EQ-5D-5L **before randomisation**. The patient will then be randomised 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 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 receive a telephone appointment two weeks post injection to assess for any adverse events and postal follow up at three and six months to review treatment efficacy. Patients will receive a £5 voucher incentive within the 6 month follow up questionnaire to aid retention and return.

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 (TMG), trial steering committee (TSC) and data monitoring and ethics committee (DMC) 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, active cancer, septicaemia, systemic use of anticoagulant therapy (warfarin, dabigatran, heparin), local infection at site of the procedure)

  NOTE - Low dose Aspirin use (or equivalent) is not a contraindication to receiving a platelet rich plasma injection

- Are unable to adhere to trial procedures or complete questionnaires.
- Previous randomisation in the present trial.
- Previous PRP treatment into a tendon.

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 identify any differences in pain measurements between trial treatment groups at two weeks, three and six months after treatment.

4) To determine the complication rate of platelet rich plasma injections at 2 weeks, 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]. The same review has highlighted the '*VISA-A has been shown to be sensitive to clinical changes and easily comprehensible to patients*'. The authors reviewed the responsiveness of the VISA-A across 18 RCTs with a total of 648 patients. They found that the VIA A scores of patients prior to intervention in clinical trials ranged from 24-63. A further 5 non interventional studies evaluating healthy individuals showed a range of VISA-A scores from 96-100. Therefore the interval for

improvement is large (24 – 96). Of the included trials the improvement in VISA-A scores ranged from 11- 72 points, indicating that the VISA-A is able to show meaningful changes with no evidence of floor or ceiling effects.

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. An additional pain score will also be collected. This consists of a visual analogue score of 0 – 100. No pain is equivalent to 0, and 100 is equivalent to worst imaginable pain

2.3.1 Efficacy

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

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 and six months post randomisation by postal questionnaire sent from Warwick CTU (WCTU).

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 18 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, active cancer, septicaemia, systemic use of anticoagulant therapy (warfarin, dabigatran, heparin), local infection at site of the procedure)

  NOTE - Low dose Aspirin use (or equivalent) is not a contraindication to receiving a platelet rich plasma injection
- Are unable to adhere to trial procedures or complete questionnaires.
- Previous randomisation in the present trial.
- Previous PRP treatment into a tendon.

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

Setting and patient identification:

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.

Consent materials:

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.

Timing of consent:

Written informed consent will be obtained by a suitably qualified member of the research team at each site as per the delegation log, after allowing sufficient time for the patient to consider their decision and ask questions about the trial. Sufficient time for some patients may result in a decision to take part in the trial immediately after receiving all relevant information, this is reflective of

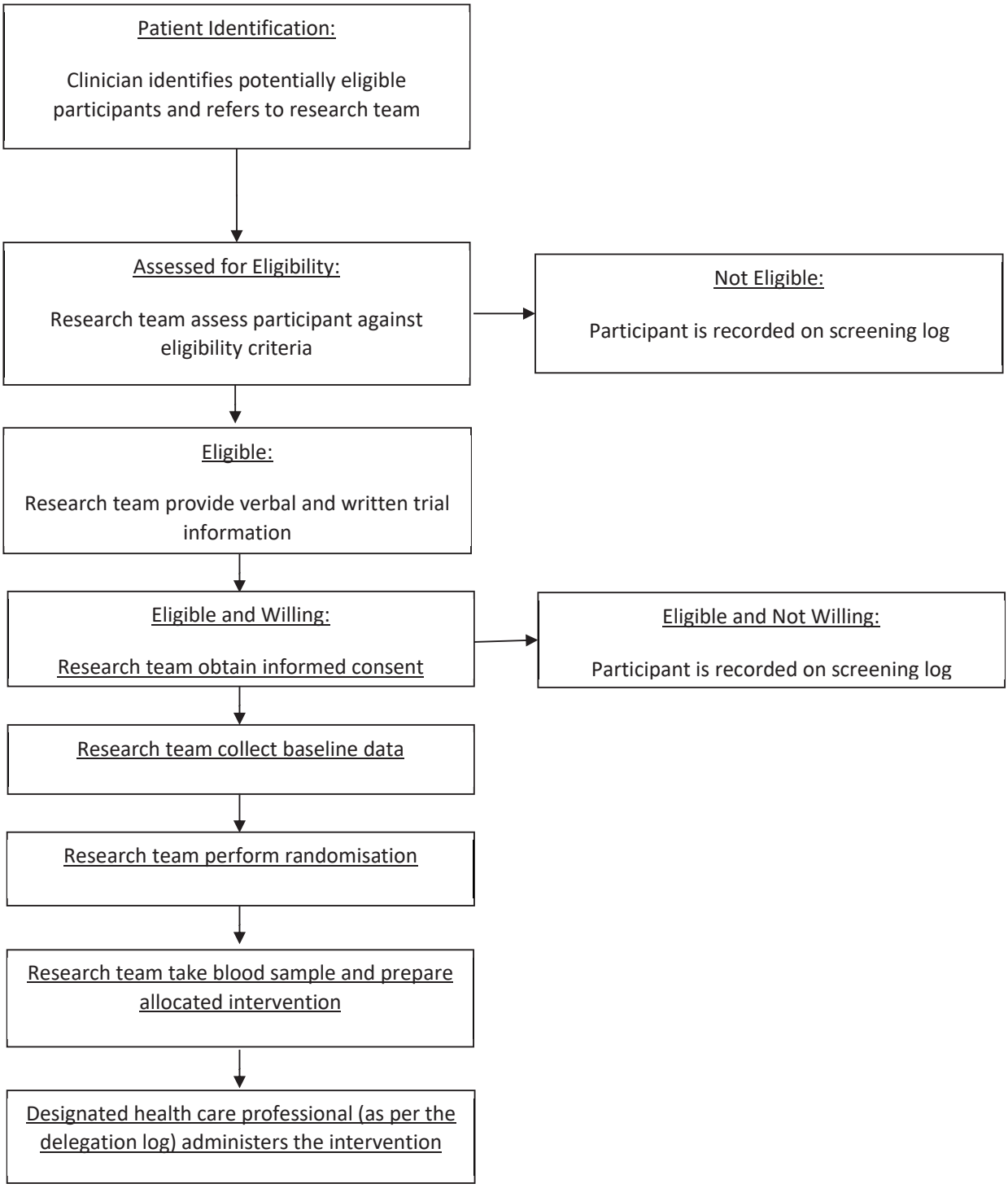
clinical practice. Alternatively, if patients would like to leave the clinic with the information and make a decision at a later date of their choosing, they will be free to do so. The definition of 'sufficient time' is at the discretion of the patient being approached to take part. Timing and appropriateness of obtaining consent in this setting will be closely monitored by the TMG and reviewed by the independent TSC.

New information:

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.

Figure 1: Flow diagram of identification, consent and randomisation procedures



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, 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 by computer using a minimisation algorithm with a random element and stratification by centre and laterality (one or both Achilles tendons affected) following a call to a secure, centralised, telephone-based randomisation service. Minimisation is appropriate because of the relatively small number of participants expected in each strata (stratified randomisation with permuted blocks would not perform sufficiently well). The randomisation service will be available Monday-Friday, 9am-5pm each day to facilitate the inclusion of all eligible patients.

The randomisation system will allocate each patient a unique trial number. The Trial Office will send a confirmation fax/email to the research site containing the randomisation details. A member of the research team 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:

Warwick Clinical Trials Unit
Telephone: +44 (0)24 7615 0402 (Mon-Fri, 9am-5pm)
Fax: +44 (0)24 7615 1586

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.

For the purposes of the trial patients are recommended to refrain from receiving additional treatments (beyond advice and rescue analgesia) for the six month trial duration. If patients do receive additional treatments, they will not be withdrawn (unless they explicitly withdraw consent, as above). However all additional treatments will be recorded on follow up questionnaires administered to participants.

Participants who withdraw will not be replaced in the trial and a corresponding CRF will be completed by the Trial Manager.

All of the outcome questionnaires can be completed over the phone, 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 message templates to be used and 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. Replies from participants will be stored on the WCTU mobile phone to help with future communication with participants and then deleted at the end of the study. When not in use the WCTU mobile phone is stored within a locked cupboard within the trial office.

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

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, RA and relevant designated health care professionals at each site 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 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 designated health care professionals at each site.

Training and delivery of both the PRP and placebo injection will be provided by the lead applicant. The PI at each site will identify relevant health care professionals to be trained and will record those who have completed training on the delegation log. Only those listed on the delegation log are able to prepare and administer trial interventions. Any delegation updates will be sent to the study coordinating centre.

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 study specific 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 health care professional, 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.

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. In either case, the patient will be asked not to seek any additional treatment, as is the case for unilateral presentations.

Research follow up will be at 2 weeks through a telephone call and postal questionnaires will be administered at three and six months after randomisation.

Technical Failure

In the unlikely event that the project specific centrifuge system fails once blood has been drawn for PRP preparation/Placebo preparation the patient will be allocated to the placebo arm and analysed as a protocol violation.

2.6.4 Compliance

Quality assurance checks will be carried out by a member of the trial team to assess compliance with the above intervention preparation and delivery. The appointed researcher will be supplied with a checklist of the intervention and placebo procedures and each participating site will be checked against this. These checks will be done face to face and remotely using relevant digital technology.

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.

Additional quality assurance procedures to verify the quality of the PRP preparation (in attempt to be in line with new reporting guidelines for biologics in orthopaedics [14]) which will involve a sample of research nurses from up to six participating trial sites to prepare PRP samples from healthy volunteers (up to 10 at each site). Healthy volunteers will be recruited from the selected trial sites through advertisement in routinely distributed newsletters and posters. All volunteers will receive a screening phone call to be considered and only excluded for the following reasons (which reflect the ATM eligibility criteria):

- Presence of systemic conditions (including: diabetes, rheumatoid arthritis, peripheral vascular disease)
- Pregnant and/or breastfeeding
- Use of anticoagulant therapy (warfarin, dabigatran, heparin); NOTE - Low dose Aspirin use (or equivalent) is not an exclusion
- Are unable to adhere and consent to procedures

A purposive sample of participants who express an interest will be provided with a participant information sheet and invited to participate. Participants will be offered a £50 voucher to cover expenses and inconvenience caused. Following consent procedures, healthy volunteers will provide two blood samples of up to 10 ml. Sample one will be kept as a whole blood control sample for analysis and sample two will be processed by the trial research nurses to produce a PRP sample for analysis. Samples will be anonymised and transported via courier to an independent test lab which will conduct cell counts of whole blood and PRP preparations. Red cell, platelet and white cell counts

(with full differential count) using a blood counter will be undertaken. All samples will be destroyed after analysis.

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 designated health care professional who will deliver the appropriate intervention. The designated health care professional 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 TM 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 TM 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

For the purposes of reporting background characteristics, 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

For the purposes of reporting background characteristics, 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:** telephone follow up	**3 m (± 1 m) after randomisation: postal follow up**	**6 m (± 1m) after randomisation: postal follow up**
Written informed consent	✓			
Baseline data Form	✓			
Randomisation	✓			
Intervention delivery	✓			
Pain score	✓	✓	✓	✓
VISA-A	✓		✓	✓
EQ5D-5L	✓		✓	✓
Adverse events	✓	✓	✓	✓
Serious adverse events	✓	✓		

4. SAFETY REPORTING AND ADVERSE EVENT MANAGEMENT

4.1 Definitions Safety

4.1.1 Adverse Events and Serious Adverse Events

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.

An AE is considered a 'Serious Adverse Event' (SAE) if it is an untoward medical occurrence 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 SAEs that occur between randomisation and two week after receiving the trial intervention will be reported. At each participating site, the Principal Investigator (PI) will be asked to comply with procedures for reporting SAEs to the Trial Manager (TM) within 24 hours of becoming aware of an event – in line with Warwick SOPs. 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. Those events that are considered to be unrelated to the trial intervention (whether expected or not) will also not need to be reported to the local REC. 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. Events will be followed up until the event has resolved or a final outcome has been reached. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

4.1.2 Expected Adverse Events

PRP is prepared from autologous blood and has been reviewed by NICE interventional procedure panel and deemed inherently safe. There are currently no reported serious adverse events in the literature.

Adverse events related to the study treatment and do not require time critical reporting to the trial coordinating centre but are collected as part of standard data collection include:

- 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
- Allergic reaction

At each postal questionnaire follow up participants will be asked if they have had any adverse events and how they were managed. 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 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 TM 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 trial 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 15% loss to follow-up, this amounts to 240 patients in total.

This scenario is somewhat conservative, as it assumes that a simple unadjusted analysis will be used to compare group mean VISA-A scores at 6 months. In reality, in the main study analysis the baseline VISA-A score will be used as a covariate in the regression analysis. The pilot data suggested a significant positive association between baseline and 6 month VISA-A scores; Pearson correlation coefficient ≈ 0.6. Assuming approximate normality for both baseline and 6 month VISA-A scores, and a correlation coefficient of 0.6, the overall power to detect a difference between group means of 12 increases to 98% in the adjusted analysis. Therefore, if the true difference between groups is smaller than anticipated we will still have good power to reject the null hypothesis. For instance, by simulating from the appropriate multivariate normal distributions, if the difference between groups were (i) 10 (effect size = 0.38), then the power would be 92%, (ii) 9 points (effect size = 0.35), then the power would be 86% and (iii) 8 points (effect size = 0.31), then the power would be 77%. Therefore, in summary, the proposed sample size gives us good power (~90%) for moderate effect sizes of the expected magnitude, and also reasonable power (~80%) for much smaller effect sizes.

6.2 Statistical Analysis Plan

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 assess randomisation balance and 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 primary efficacy measurement will be the mean difference in VISA-A at six months follow up between the two treatment groups. The analysis will be performed on an intention-to-treat basis using linear regression to adjust for design factors (centre and laterality), age, sex and baseline VISA-A score. Centre will be included in the model as a random effect 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. Appropriate diagnostic plots will be used to check the underlying model assumptions. In addition, early functional status will be assessed and reported at three months. Unadjusted analyses will also be presented to enable to impact of the above adjustments on the estimate of treatment effect to be assessed. 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.

Providing sufficient complications (events) occur within each class of important complication (e.g. infection) to enable meaningful time to event analyses to be performed, time to the development of complications will be also be compared between the treatment groups and presented graphically using Kaplan-Meier curves.

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. Stratification of the randomisation by laterality will ensure approximate balance in those with bilateral presentation between the treatment groups.

It seems likely that some participants may not provide complete data for VISA-A score at baseline or six months follow up due to lack of completion of individual data items, voluntary withdrawal 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 it is judged appropriate, missing items in the VISA-A scores will be imputed. The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used 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.

Further details will be given in the Statistical Analysis Plan, which will be prepared separately and agreed with the Data Monitoring and Ethics Committee before the first substantive data analysis. Any subsequent amendments to this initial statistical analysis plan will be clearly stated and justified. There are no plans for early stopping of the study so statistical stopping rule have not been developed.

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

Patient recruitment is planned to conclude on 31st May 2020, however, if the target of 240 patients in total is achieved before this date then recruitment will finish as appropriate.

Following the completion of patient recruitment, a period of 6 months is required to complete the patient follow up tasks along with a further 2 months to allow for result analysis and report compilation. It is therefore estimated that the trial will end February 2021, however, this is subject to change due to being dependent on recruitment rates.

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 with the TSC shortly before the study commences, again after the first 50% of patients have been recruited and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and 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 are no statistical rules for early stopping of the study due to efficacy. Early stopping should only be considered on the grounds of safety and/or feasibility.

(2) The statistical analysis plan for the final analysis of the study will be reviewed by the DMC prior to the first substantive analysis of the data.

(3) After each meeting at which analysis of any study data is presented, 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 recommendation to the TSC is advisory

only. It is the responsibility of the independently chaired TSC to determine whether the trial should continue recruiting to the planned sample size, or be curtailed early.

(4) At the first DMC meeting, which will be held jointly with the TSC, procedures for monitoring patient safety will be discussed and agreed. This decision will be 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 TM 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 TM will take responsibility for organising training sessions.

• Quality assurance checks: In addition to standard quality assurance checks, in keeping with Warwick SOPs, a member of the team with appropriate level of knowledge/experience will 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. A 'plain English' summary of the study findings will be produced which will be made available in the trial hospitals and to patients involved in the trial. In addition, we will publicise the work through multimedia such as websites including Patient.co.uk and work with NHS Choices to prepare patient information.

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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