Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Achilles Tendinopathy Management

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	(●) Yes	( ) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which review bodies are you applying to?

- [ ] HRA Approval
- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

( ) Yes (•) No

If yes and you have selected HRA Approval in question 4 above, your study will be processed through HRA Approval.

If yes, and you have not selected HRA Approval in question 4 above, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

(•) Yes ( ) No

If yes, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before submitting other applications. If you have selected HRA Approval in question 4 above your study will be processed through HRA Approval. If not, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Achilles Tendinopathy Management

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Dr	Rebecca	Kearney
Post	Clinical Lecturer		
Qualifications	PhD: Medicine MSc: Trauma and Orthopaedic Surgery PGC: Medical Education PGA: Musculoskeletal Trauma: Image Recognition PGA: Extended Scope Practice PGA: Joint and Soft Tissue Injection PRINCE2 Practitioner Award BSc: Physiotherapy		
Employer	University of Warwick		
Work Address	Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick Coventry		
Post Code	CV4 8UW		
Work E-mail	R.S.Kearney@warwick.ac.uk		
* Personal E-mail			
Work Telephone	02476153156		
* Personal Telephone/Mobile			
Fax	02476151586		

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior*

consent.
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Dr	Jane	Prewett
Address	Warwick Clinical Trials Unit, Gibbet Hill Campus		
	University of Warwick		
	Coventry		
Post Code	CV4 8UW		
E-mail	wmssponsorship@warwick.ac.uk		
Telephone	02476122746		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	
Protocol Version:	1.0
Protocol Date:	24/08/2015
Funder's reference number:	20831
Project website:	

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):
ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Pain in the back of the heel affects 150,000 people annually leading to walking difficulties. The most common cause is Achilles tendinopathy (disease of an Achilles tendon). Tendons are split into two areas based on composition, 1, the mid-substance containing dense fibrous connective tissue and 2, the tendon-bone insertion, containing many different cell types as it makes its transition to bone where it is attached. Tendinopathy in the mid-substance of Achilles tendon occurs due to the failure of the tendon to repair properly. As a result, the condition can cause debilitating pain. Achilles tendinopathy is managed with advice, painkillers, specific exercises, electrotherapy, injections or surgery, but there is no single best treatment. An Arthritis Research UK group has identified a new type of injection as potentially helpful. This new treatment involves taking a small sample of the participant's own blood, which is spun to separate out the components of the blood. The component, plasma contains a high number of platelets that play an important role in the repair processes within tendons. It is the platelet rich plasma that is to be injected into the painful tendon of the participant. The clinical trial plans to test whether platelet rich plasma injection help increase healing and reduce pain in patients with painful Achilles tendons, by trialling the platelet rich injection against injecting the participant with a placebo imitation injection. Participants will be asked to provide information about their pain, ability to perform activities and complications. This information will be collected at 3 month and 6 month intervals.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

There are minimal risks involved with this study. One of the main risks for the participant is with receiving an injection. There are no known risks specific to the plasma injection which is taken from the patient's own blood, but assessment of the number of complications in each group is a secondary objective of this trial. Adverse events that are known risks of injections are: infection, bleeding, swelling, skin discolouration and possible allergic reaction. These will be recorded but do not need to be reported to the coordinating centre. All participants experiencing serious adverse events will be followed up as per protocol until the end of the trial. All serious adverse events will be entered onto the serious adverse event reporting form and faxed to a dedicated fax machine at Warwick Clinical Trials Unit within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. Serious adverse events that are deemed unexpected and related to the trial will be notified to the sponsors and Research Ethics Committee within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.
Informed consent will be taken by suitable qualified members of the research team who have a full understanding of the ethical principles behind informed consent and capacity. The trial will be conducted in full compliance 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.
Participants will also be asked to complete two short questionnaires (VISA A and EQ 5DL) at regular intervals (baseline, 3 months, 6 months) asking questions about their pain and quality of life. Patients will be given a private room in which to complete these questionnaires at baseline and will be free to leave any questions they do not want to answer. In order to minimise burden to patients, the completion of questionnaires will be done at the patients baseline appointment, which will be in line with their standard clinical care and at home (postal questionnaires), therefore patients will not have to make additional trips to the hospital if they were to partake in the trial.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation

- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The Victorian institute of sport assessment- Achilles (VISA-A) questionnaire tests three significant domains of dysfunction; pain, function and activity.
The principal research question aims to quantify and draw inferences on observed differences in the results from the Victorian institute of sport assessment- Achilles (VISA-A) questionnaire between the trial treatment groups (platelet rich plasma injections verses a placebo injection) at six months after treatment.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

1) To quantify and draw inferences on observed differences in Victorian institute of sport assessment- Achilles (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.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Pain in the back of the heel affects 150,000 people annually leading to walking difficulties. The most common cause is Achilles tendinopathy. Achilles tendinopathy is managed with advice, painkillers, specific exercises, electrotherapy, injections or surgery. Recently, an Arthritis Research UK Think Tank reviewed the literature, guidelines, clinical and patient experiences in relation to these treatments: the top priority for further research was the use of platelet rich plasma injections. Platelet rich plasma injections are prepared from autologous blood that is centrifuged to separate out the plasma fraction that is high in platelets. Platelets contain a high number of growth factors that play an important role in the repair processes within tendons. Within the NHS, the national advisory body (National Institute for Health and Care Excellence) have stated that these new injections are safe, but found that there is no conclusive evidence that they work. At the moment some patients in some hospitals are offered the injections but in other areas they are not available. We have completed a feasibility study to evaluate these platelet rich plasma injections in Achilles tendinopathy. We now propose a placebo controlled randomised trial to quantify and draw inferences at six months on observed differences in a patient reported outcome measure (VISA A) between a group treated with a platelet rich plasma injection and a group treated with a placebo injection. The aim of this will be to provide the national advisory body with robust evidence to decide if this injection treatment should or should not be routinely available to all patients with debilitating Achilles tendon pain. This guidance affects every NHS practice across the UK.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

This is a randomised, single-blinded, placebo-controlled, multi-centre phase III clinical trial comparing Platelet Rich Plasma (PRP) injection to placebo (imitation) injection in adults with Achilles tendon pain.

To be eligible for the trial, patients must be able to provide written informed consent, be over 16 years old, with pain in the mid-substance of the Achilles tendon for longer than 3 months. Tendinopathy must be confirmed by ultrasound or

MRI. This is standard practice in NHS trusts.

Patients deemed eligible to take part in the trial, according to the protocol will be approached to be invited to the study. After time to consider, written informed consent will be obtained. Participants will be asked to complete two questionnaires at baseline; VISA-A and EQ5D-5L.

Patients will be randomised to receiving either platelet rich plasma injection or placebo (imitation) injection. Participants will not be made aware of this allocation until their participation within the trial has ended and that they have requested for this information. Participants within both arms of the trial will receive a local anaesthetic. Blood will be taken from the participant in order to create the platelet rich plasma treatment. Participants receiving the PRP injection will receive an injection into the Achilles tendon. Participants receiving the placebo imitation injection will also receive an injection but this injection will be into the skin, rather than into the tendon. Patients randomised to the placebo arm of the trial will still have blood taken but this will be disposed of. This is to ensure participants are blinded to their treatment allocation.

Participants will be asked to complete two postal questionnaires ; VISA-A and EQ5D-5L, at 3 months and 6 months post randomisation. Completed questionnaires are to be posted back to the trials unit using free post envelopes provided.

Patients will receive follow up appointments as standard practice, at 2 weeks post-treatment and 6 months.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
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 application. 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. Karen Keates is subsequently a lay representative for this application. UNTRAP will support the training and development needs of Karen Keates, through on going provision of appropriate training events and development of good practice partnership working, through implementing agreed codes of conduct.
There will be patient and public involvement (PPI) at trial steering group meetings. PPI representatives have actively collaborated on the development of the application. They will be members of the trial management group and will ensure that the on-going research is appropriately communicated to patients and public through newsletters and posters. On completion of the research they will play a key role in contributing to the reporting of the study and dissemination of its findings. On completion of the research, Karen Keates 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.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [ ] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [x] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 16	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

• Provision of written informed consent
• 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.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

• 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.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Gaining Written Consent	1	0	20 min	The principle investigator or delegated individual at individual hospital sites
Victorian Institute of Sport Assessment - Achilles (VISA-A) questionnaire	3	0	5 min	Participant will complete the VISA-A questionnaire at baseline in the hospital with the option of using a quiet room. 3 month the VISA-A questionnaire (posted to the patient)will be completed by the participant in their home. 6 month the VISA-A questionnaire may be completed in clinic at their appointment or posted to the participant who will be complete the questionnaire in their home.
Quality of life questionnaire	3	0	5 min	Participant will complete the EQ5D-5L quality of life questionnaire at baseline in the hospital with the option of using a quiet room. 3 month EQ5D-5L quality of life questionnaire (posted to the patient)will be completed by the participant in their home. 6 month EQ5D-5L quality of life questionnaire may be completed in clinic at their appointment or posted to the participant who will be complete the questionnaire in their home.
Follow up appointments	2	2	10 min	Follow up appointments will take place at 2 weeks and 6 months. These appointments are standard clinical appointments patients would ordinarily receive as standard practice.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
MRI or ultrasound to confirm diagnosis	1	1	30 min	MRI Technologist or Sonographer. Clinician would confirm diagnosis using results from the MRI or ultrasound.
10 ml whole blood drawn	1	0	5	A suitably qualified member of the research team.

from antecubital fossa (regardless of randomisation)			min	
Local anaesthetic (2% lignocaine)	1	0	1 min	trained principal investigator at site
Platelet rich plasma (PRP) injection or placebo injection (dependent on randomisation)	1	0	1 min	The trained principal investigator or a suitably qualified member of the research team will administer the intervention. The PRP injection will be administered into the tendon but the placebo imitation injection will be administered under the skin but not in the tendon.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

6 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

There are minimal risks involved with this study. One of the main risks for the participant is with receiving an injection. There are no known risks specific to the plasma injection which is taken from the patient's own blood, but assessment of the number of complications in each group is a secondary objective of this trial. Adverse events that are known risks of injections are: infection, bleeding, swelling, skin discolouration and possible allergic reaction. These will be recorded but do not need to be reported to the coordinating centre. All participants experiencing serious adverse events will be followed up as per protocol until the end of the trial. All serious adverse events will be entered onto the serious adverse event reporting form and faxed to a dedicated fax machine at Warwick Clinical Trials Unit within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. Serious adverse events that are deemed unexpected and related to the trial will be notified to the sponsors and Research Ethics Committee within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings. Patients are followed up at 2 weeks and 6 months post-treatment and clinically assessed for any complications.

Participants will also be asked to complete two short questionnaires (VISA A and EQ 5D-5L) at regular intervals (baseline, 3 months, 6 months) asking questions about their pain and quality of life. Patients will be given a private room in which to complete these questionnaires at baseline and will be free to leave any questions they do not want to answer. In order to minimise burden to patients, the completion of questionnaires may be done at the patients baseline appointment and 6 month follow up appointment, which will be in line with their standard clinical care appointments and at home (postal questionnaires at 3 months and 6 months (if patients prefer)), therefore patients will not have to make additional trips to the hospital if they were to partake in the trial. Postal questionnaires will include a free post envelope to make the return of questionnaires as easy as possible.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

The Platelet rich plasma (PRP) injection is not widely available to patients outside of the study. Therefore, one potential benefit could be that by participating in the research the patient may be randomised to receiving this intervention. The PRP injection may reduce the pain of patients, however, the benefit of these injections will be evaluated within this trial so these cannot be confirmed.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

The intervention is given to participants once only, therefore, written consent will only be obtained once from patients and reaffirmed before the intervention is administered.
Since written informed consent will be obtained once from the patient, consent will be reaffirmed each time the patients participates in research data collection at follow up appointments. Implied consent will apply when fully or partially completed questionnaires are returned from participants, unless participants contact the research team to inform us of their withdrawn consent.

A26. What are the potential risks for the researchers themselves? *(if any)*

Researchers are at risk of needle stick injury as with any use of needles. Researchers may be at risk of contracting blood related infections if contact is made with patients blood, therefore, relevant training and relevant immunisations will be given in line with local trust policies.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Eligible patients will be identified from tendon/ foot and ankle clinics by the local Principal Investigator, foot and ankle specialist consultants or registrars. The local Principal Investigator, foot and ankle consultants or registrars will consult the patient as part of their standard referral to the service.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:
Eligible patients will be identified from tendon/ foot and ankle clinics by the local Principal Investigator, foot and ankle specialist consultants or registrars only, who will be part of the patients care team.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

Potential participants will be approached by the local principal investigator (PI), Foot and ankle consultants or registrars, who will be part of the patients care team at tendon clinics. The PI, consultant or registrar will approach the patient asking whether they would like to discuss the research project with the research associate, research nurse or suitably qualified member of the research team to inform the patient of the study. If the patient expresses an interest in being approached about the trial, they will be introduced to the suitably qualified member of the research team who will discuss the trial in detail with the patient. The patient will be given a patient information sheet and the suitably qualified member of the research team will go through the patient information sheet with the patient. This person will be available to answer questions. The PI, consultant or registrar will also be available for questions should the patient want to discuss this further.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Patients will be provided with a verbal explanation of the study and a written information sheet. Patients will be given sufficient time to consider the information, ask any questions and have these answered satisfactorily. Written informed consent will be taken by a suitably qualified member of the research team who will have a full understanding of the consent process and capacity. If patients are willing to take part they will be asked to provide written informed consent by completing an informed consent form.

If you are not obtaining consent, please explain why not.

N/A

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Patients will be given at least 24 hours to consider taking part in the study.
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).

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

○ Yes
○ No
◉ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

All patients will be asked if they are involved in any other trials currently or have been in the recent past. Patients will only be excluded from the trial if other studies could interfere with the research outcomes in the current study or add further risks.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

In the event of a patient not being able to fully understand the explanation of the trial in English, an interpreter will be asked to translate the information to the patient as per standard NHS procedure.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

In the event of new information becoming available, investigators will contact patients and explain the new information. Patients will have the opportunity to withdraw from the study at any time, however, should they wish to continue, further consent will be obtained once the patient has had time to consider an updated version of the Patient Information Sheet which has been approved by the ethics committee.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers

☐ Private company computers

☐ Laptop computers

Further details:
All information will be entered onto a secure database set up by the University of Warwick Clinical Trials Unit, that only authorised personnel will have access to. Case Report Forms, consent forms and the trial master file will be kept in locked filling cabinets in designated archive rooms in the University of Warwick's Clinical Trials Unit, to which only authorised personnel have access.

A37. Please describe the physical security arrangements for storage of personal data during the study?

The personal data will be kept in locked filing cabinets within locked rooms in accordance with GCP and the data protection act, in the Clinical Trials Unit, Warwick Medical School. These filing cabinets will only be accessible by the Achilles Tendinopathy Management (ATM) trial team only. The IT systems comply with appropriate data security standards and staff accessing these systems are trained to ensure data security standards are maintained. All trial databases will be password protected and accessible by the GCP-trained ATM trials team only.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

Apart from initial randomisation and for purposes of sample tracking, any communication between researchers regarding patients, or patient data exchanged between research offices will be pseudoanonymised, to protect patient identity. The patient will be referred to by a unique trial number (TNO), initials and date of birth. NHS number will be collected but not used for identification of the patient when communicating between research offices.

All staff involved with the running of the trial have been trained in Good clinical Practice and in the appropriate stewardship of personal information. The Clinical Trials Unit will be required to maintain the confidentiality of all patient data and will not produce or disclose any information by which patients could be identified. Patients will be reassured that their confidentiality will be respected.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participants will consent to providing the trial management team with their contact details and a next of kin to enable 3 and 6 month questionnaires to be sent to the participants in the post.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Data analysis will be undertaken by the University of Warwick Clinical Trials Unit Statistical Team.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Dr	Rebecca	Kearney
Post	Clinica Lecturer		
Qualifications	PhD, PGCE, MSc, BSc		
Work Address	Warwick Clinic Trials Unit		
	Gibbet Hill Campus		
	Coventry		
Post Code	CV4 7AL		
Work Email	r.s.kearney@warwick.ac.uk		

Work Telephone 02476 573156
Fax

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

As per GCP guidelines, once the trial has come to an end and the analysis has taken place, trial documentation will be held for approximately 10 years. It is the responsibility for the investigator to ensure the data is stored securely by a third party and is easily retrieved if required.
All electronic patient-identifiable information will be held on a secure, password protected database accessible only to essential personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of Warwick Medical School.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◉ Yes ○ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
Patients may receive a £5 gift voucher on their return of questionnaires as a thank you gesture for their support.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

(●) Yes ( ) No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

(●) Yes ( ) No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

(●) Yes ( ) No

Please give details, or justify if not registering the research.
UKCRN
ISRCTN database
University of Warwick website

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [x] Publication on website
- [ ] Other publication
- [x] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [ ] Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Identifiable data will not be used during the analysis of trial data. The data will be pseudonymised to facilitate the analysis of the data and no identifiable data will be published, only anonymised data.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
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.
The results will be made available once the final report is complete.An "End of trial letter" will be sent to patients making reference to the location of the results (likely to be directed to a website containing a lay summary of the results) and participants will be offered further information to be sent to them about the results of the trial if participants would like these.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- ☐ Independent external review
- ☐ Review within a company
- ☑ Review within a multi−centre research group
- ☑ Review within the Chief Investigator's institution or host organisation
- ☑ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The research team are lead authors on a Cochrane review of injection management for Achilles tendinopathy. This work is currently ongoing; 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. Although the trial was small, it did exclude the predetermined important difference in the primary outcome measure. Funded by the Chartered Society of Physiotherapy, our research group led and delivered a feasibility study. 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.
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.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☑ Review by a statistician within the Chief Investigator’s institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Dr	Nick	Parsons
Department	Senior Research Fellow		
Institution	University of Warwick		
Work Address	Warwick Clinical Trials Unit		
	Gibbet Hill Campus		
	Coventry		
Post Code	CV4 7AL		
Telephone	02476 150540		
Fax			
Mobile			
E-mail	nick.parsons@warwick.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The primary outcome measure is the comparison of VISA-A questionnaire at six months after treatment, between the two treatment groups (Platelet rich plasma injection verses placebo) 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.

A58. What are the secondary outcome measures?*(if any)*

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 generic quality of life questionnaire will be an important secondary outcome measure for this trial.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	240
Total international sample size (including UK):	0
Total in European Economic Area:	0

Further details:
N/A

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

There is no consensus on a minimum clinically important difference (MCID) regarding the VISA-A score. However, previous studies support that the MCID lies between 10 and 12 points and that this is in keeping with comparable patient reported outcomes in musculoskeletal medicine. Therefore a MCID of 12 points for this study represents a conservative estimate. Given our best estimate of the population standard deviation of 26 from previous pilot work, this equates to an effect size of 0.46 (12/26), which we would consider to be moderate.
Our previous pilot study enabled assessment of the distributional properties and the population variability of the

primary outcome measure, the VISA-A score, in the selected population. We have not used the estimated effect size from the pilot study for the main study, principally as this was not planned. The main reason for this was that this was a very small study, and as such was unlikely to provide much useful evidence on the likely size of the clinically meaningful difference in this population. From the 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). 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.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
The patient will be randomised to either the intervention or the placebo injection, on a 1:1 basis, stratified by centre only. The treatment group will be allocated using a computer based randomisation. The randomising investigator at site can either fax or call the randomisation service, of which are secure methods of transferring information.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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 differences between treatment groups (Platelet rich plasma injections and placebo) at 6 months 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.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Prof	Matthew	Costa
Post	Professor of Orthopaedic Trauma		
Qualifications	PhD, FRCS Tr & Orth, MB BChir		
Employer	University of Oxford		
Work Address	The Kadoorie Centre		
	John Radcliffe Hospital		
	Oxford		

Post Code	OX3 9DU
Telephone	
Fax	
Mobile	
Work Email	Matthew.costa@ndorms.ox.ac.uk

Title	Forename/Initials	Surname
Dr	Nick	Parsons

Post	Senior Research Fellow in Medical Statistics
Qualifications	PhD and MSc in Statistics, BSc (1st Class) Physics & Applied Mathematics
Employer	University of Warwick
Work Address	Warwick Clinical Trials Unit Gibbet Hill Campus Coventry
Post Code	CV4 7AL
Telephone	02476150540
Fax	
Mobile	
Work Email	nick.parsons@warwick.ac.uk

Title	Forename/Initials	Surname
Mr	Jonathan	Young

Post	Consultant, Trauma and Orthopaedic Department,
Qualifications	FCRS (Orth), Masters Trauma and Orthopaedics, MRCS, MB ChB
Employer	University Hospitals Coventry & Warwickshire NHS trust
Work Address	Clifford Bridge Road Coventry
Post Code	CV2 2DX
Telephone	02476965096
Fax	
Mobile	
Work Email	jsyoung59@doctors.org.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	University of Warwick
Given name	Jane
Family name	
Address	Prewitt
Town/city	Warwick Clinical Trials Unit, Gibbet Hill Campus
Post code	CV4 7AL
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	wmssponsorship@warwick.ac.uk

Is the sponsor based outside the UK?

◯ Yes ◉ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

☑ Funding secured from one or more funders

☐ External funding application to one or more funders in progress

☐ No application for external funding will be made

What type of research project is this?

◉ Standalone project

◯ Project that is part of a programme grant

◯ Project that is part of a Centre grant

◯ Project that is part of a fellowship/ personal award/ research training award

◯ Other

Other – please state:

Please give details of funding applications.

Organisation	Arthritis Research UK
Address	Research Directorate
	Copeman House, St Mary's Court
	St Mary's Gate, Chesterfield
Post Code	S41 7TD
Telephone	
Fax	
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: £484,405

Duration

Years: 4

Months: 4

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Arthritis Research UK Clinical Studies

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (•) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (•) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Mrs	Ceri	Jones
Organisation	University Hospitals Coventry and Warwickshire		
Address	Research, Development and innovation department		
	Clifford Bridge Road		
	Coventry		
Post Code	CV2 2DX		
Work Email	ceri.jones@uhcw.nhs.uk		
Telephone	02476966196		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/09/2015

Planned end date: 31/12/2019

Total duration:

Years: 4 Months: 3 Days: 31

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial (1)

This is the last questionnaire to be sent to participants at the 6 month time point.

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 6

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	6
☐ NHS organisations in Wales	0
☐ NHS organisations in Scotland	0
☐ HSC organisations in Northern Ireland	0
☐ GP practices in England	0
☐ GP practices in Wales	0
☐ GP practices in Scotland	0
☐ GP practices in Northern Ireland	0
☐ Joint health and social care agencies (eg community mental health teams)	0
☐ Local authorities	0
☐ Phase 1 trial units	0
☐ Prison establishments	0
☐ Probation areas	0
☐ Independent (private or voluntary sector) organisations	0
☑ Educational establishments	1
☐ Independent research units	0
☐ Other (give details)	0
Total UK sites in study:	7

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

This study is being conducted under the auspices of the University of Warwick according to the current guidelines for Good Clinical Practice. Participating institutions will be monitored by trials office staff to confirm compliance with the protocol and the protection of patients' rights.

All clinical investigators taking part in the trial will be asked to attend a start-up meeting/initiation visit for training on study procedures and data collection methods. At each centre the principal investigator will and a suitable member of the research team at site will undertake a training programme delivered by the lead applicant, Dr Rebecca Kearney or delegated qualified person. This will ensure standardised delivery of both trial arms. Training will be documented. A research physiotherapist, independent of the research team at site, may be asked to observe the intervention, for quality assurance purposes.

No patients will be recruited into the trial until all regulatory approvals are in place and training conducted.

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. Quality assurance checks will be undertaken by Warwick Clinical Trials Unit (WCTU) to ensure integrity of randomisation, study entry procedures and data collection. Study staff will be in regular contact with site personnel to check on progress and any queries that they may have. WCTU trials team may conduct monitoring visits at participating institutions in accordance with the trials monitoring plan. Investigators will allow the monitors access to source documents as requested. Institutions may be barred from further recruitment in the event of serious and persistent non-compliance.

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

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

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

All serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and faxed to a dedicated fax machine at Warwick Clinical Trials Unit within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and possibly related to the trial interventions will be notified to the Research Ethics Committee (REC) and sponsor within 15 days. All such events will
be reported to the Trial management group at their next meeting.

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 DMEC, therefore they may decide that a narrow window of opportunity does exist to assess treatment efficacy. If so, they are at liberty under the DMEC charter to make recommendations and suggestions to the Trial Management and Steering Committees at end stage of the study.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

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. We will report any serious adverse events as described above.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- ☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

◉ Yes ○ No

If Yes, please give details of the compensation policy:
The University of Warwick has a public and products liability policy which provides cover for 'negligent harm' and the activities here are included within that coverage subject to terms, conditions and exceptions of the policy.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

Participants blood withdrawn from the the antecubital fossa- centrifuged to isolate the platelet rich plasma.

2. Who will collect the samples?

The suitably trained person or principal investigator will extract the blood from the patient.

3. Who will the samples be removed from?

☑ Living donors
☐ The deceased

4. Will informed consent be obtained from living donors for use of the samples? *Please tick as appropriate*

In this research?

◉ Yes ○ No

In future research?

○ Yes ○ No ◉ Not applicable

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

◉ Yes ○ No

Please give further details:
Platelet rich plasma (approximately 3ml) isolated from the participants blood and injected into their painful Achilles Tendon. Isolation will happen via centrifugation of the blood sample. This will be a one time event only. No material will be stored. Human tissue will be disposed in accordance with the human tissue act following the injection treatment.

7. Please explain what licensing arrangements apply to the procurement, processing, distribution or import of the tissues and cells to be used in the research.

Please consult the guidance notes on this question. If either you or a collaborating organisation requires a licence from the Human Tissue Authority under the Quality and Safety Regulations, please confirm that the licence has been obtained or applied for.

Procurement
NHS trusts that will be working on this research project hold individual HTA licences for the procurement of whole blood into plasma containing platelets. This licence will also cover the insertion of these platelets back into the participants body, into their Achilles tendon. Any unused blood products will be disposed in accordance with the Human Tissues Act, immediately after the intervention has been administered. HTA Regulations allow human tissue held for a specific research project approved by a recognised research ethics committee (or where approval is pending) to be stored on premises without an HTA licence. If REC approval is granted for this research project,

copies of the HTA licences may not be required but can be provided if REC committee wishes to view these. As the sponsor, the University of Warwick holds a research HTA license, however, no human tissue will be procured within the University of Warwick so may not be required to be seen by REC committee also.

If applicable, a copy of the HTA licence should be enclosed or provided when available.

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*
○ Yes ◉ No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*
○ Yes ◉ No

In a form in which the donor could be identifiable to researchers?
○ Yes ◉ No

9. What types of test or analysis will be carried out on the samples?

Experimental Group (randomised to receiving the Platelet Rich Plasma injection) : The whole blood extracted from the participant will be spun in a centrifuge to separate out the platelet rich plasma. The component containing red blood cells and other blood components will be discarded from the syringe. One injection of the prepared platelet layer (approximately 3ml) will be administered back into the same participant for which the sample had been taken. The platelet rich plasma injection will be injected into the painful Achilles tendon using a peppering technique at the site of pain. This technique involves a single skin portal and then five penetrations of the tendon.
No other samples will be extracted so no other test or analysis will be carried out following this event.

10. Will the research involve the analysis or use of human DNA in the samples?

○ Yes ◉ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

○ Yes ◉ No

12. If so, will arrangements be made to notify the individuals concerned?

○ Yes ○ No ◉ Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Samples will not be stored. Unused blood and components will be destroyed in accordance with the Human Tissues Act.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☑ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

Samples will not be stored therefore this is not applicable.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Investigator identifier	Research site		Investigator Name	
IN3 ☐	◉ NHS site ○ Non-NHS site		Forename	David
			Middle name	
	Country: England		Family name	Loveday
			Email	DAVID.LOVEDAY@nnuh.nhs.uk
			Qualification (MD...)	MBBS FRCS
	Organisation name	NORFOLK AND NORWICH UNIVERSITY HOSPITALS NHS FOUNDATION TRUST	Country	UNITED KINGDOM
	Address	COLNEY LANE COLNEY NORWICH NORFOLK		
	Post Code	NR4 7UY		
IN5 ☐	◉ NHS site ○ Non-NHS site		Forename	Chris
			Middle name	
	Country: England		Family name	Blundell
			Email	Chris.Blundell@sth.nhs.uk
			Qualification (MD...)	MBBS FRCS
	Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	Country	UNITED KINGDOM
	Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD SOUTH YORKSHIRE		
	Post Code	S5 7AU		
IN4 ☐	◉ NHS site ○ Non-NHS site		Forename	Jonathan
			Middle name	
			Family name	Young

Country: England

Email	jsyoung59@doctors.org.uk
Qualification (MD...)	MBBS FRCS
Country	UNITED KINGDOM

Organisation name	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST
Address	WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY WEST MIDLANDS
Post Code	CV2 2DX

IN6 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	Jitendra
Middle name	
Family name	Mangwani
Email	jmangwani@hotmail.com
Qualification (MD...)	MBBS FRCS
Country	UNITED KINGDOM

Organisation name	UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST
Address	GWENDOLEN HOUSE GWENDOLEN ROAD LEICESTER LEICESTERSHIRE
Post Code	LE5 4QF

IN7 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	Mike
Middle name	
Family name	Carmont
Email	mcarmont@hotmail.com
Qualification (MD...)	MBBS FRCS
Country	UNITED KINGDOM

Organisation name	SHREWSBURY AND TELFORD HOSPITAL NHS TRUST
Address	MYTTON OAK ROAD SHREWSBURY SHROPSHIRE
Post Code	SY3 8XQ

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- (●) Chief Investigator
- ( ) Sponsor
- ( ) Study co-ordinator
- ( ) Student
- ( ) Other – please give details
- ( ) None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Rebecca Kearney on 05/01/2016 10:19.

Job Title/Post:	Clinical Lecturer
Organisation:	Warwick University
Email:	r.s.kearney@warwick.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mrs Jane Prewett on 11/01/2016 19:27.

Job Title/Post:	Deputy Director, R&IS
Organisation:	University of Warwick
Email:	jane.prewett@warwick.ac.uk