UK STAR: UK Study of tendo Achilles Rehabilitation – multicentre randomised clinical trial

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Abbreviations

AE – Adverse Event
ATRS – Achilles Tendon Rupture Score
CI – Chief Investigator
CRF – Clinical Reporting Form
DSMC – Data & Safety Monitoring Committee
EQ-5D – EuroQol
HE – Health Economy/Economist
HTA – Health Technology Assessment
MCAR – Missing completely at random
MCID – Minimal Clinically Important Difference
NHS – National Health Service
OCTRU – Oxford Clinical Trials Research Unit
PI – Principal Investigator
QA – Quality Assurance
RCT – Randomised Controlled Trial
REC – Research Ethics Committee
RF – Research Fellow
SAE – Serious Adverse Event
SAP – Statistical Analysis Plan
SD – Standard Deviation
STAR – Study of Tendo Achilles Rupture
SWAT – Study Within A Trial
TMG – Trial Management Group
TSC – Trial Steering Committee
QALY – Quality Adjusted Life Year

N.B. The terms functional bracing and walking boot are equivalent and are used synonymously throughout the protocol, CRFs and patient documentation.

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2. Synopsis

Study Title	*UK STAR UK Study of tendo Achilles Rehabilitation – multicentre randomised clinical trial*	
Internal ref. no. / short title	UK STAR	
Study Design	Multi-centre, multi-surgeon, parallel, two arm, randomised controlled trial	
Study Participants	Participants of 16 years and older, who have sustained a rupture of the Achilles tendon which will be treated non-operatively.	
Planned Sample Size	A minimum of 330, maximum of 550	
Planned Study Period	01/04/2016 – 31/05/2019	
	Objectives	Outcome Measures
Primary	To quantify and draw inferences on observed differences in Achilles Tendon Rupture Score between the trial treatment groups at 9 months after injury.	Achilles Tendon Rupture Score
Secondary	1. To quantify and draw inferences on observed differences in Achilles Tendon Rupture Score between the trial treatment groups at 8 weeks, 3 and 6 months after the injury. 2. To identify any differences in health-related quality of life between the trial treatment groups in the first 9 months after the injury. 3. To determine the complication rate between the trial treatment groups in the first 9 months after the injury. 4. To investigate, using appropriate statistical and economic analytical methods, the resource use, costs and comparative cost effectiveness between the trial treatment groups.	• *Achilles Tendon Rupture score* • *EQ-5D-5L* • *Resource use* • *Complications*

3. Background

The Achilles tendon is the largest tendon in the human body and transmits the powerful contractions of the calf muscles that are required for walking and running. When the tendon ruptures, it is painful and has an immediate and serious detrimental impact on daily activities of living [1]. In the longer-term, tendon rupture results in prolonged periods off work and time away from sporting activity: average time away from work is between 4 and 8 weeks and time away from sport is between 26 and 39 weeks [1]. This results in lost income and restricted daily activities in the early phase and reduced physical activity, with associated negative health and social consequences, in the long-term. For high-level sportsmen it is frequently a 'career-ending' injury.

Achilles rupture affects over 11,000 people each year in the UK, and the incidence is increasing as the population remains more active into older age [2]. It affects all age groups in a bi-modal distribution; with the first peak in patients aged 30-40 years and the second 60-80 years [2]. The first peak in incidence is often associated with participation in sport, such as football and racquet sports, whereas the second peak often occurs during normal daily activities such as climbing stairs [2]. However, all Achilles ruptures are associated with a pre-existing 'tendinopathy' which is attributed to failures in the protective/regenerative functions which respond to repeated microscopic injury [3 4].

Historically, the main question in relation to the management of patients with a rupture of the Achilles tendon has been whether or not to perform a surgical repair of the tendon. In 1981, Nistor *et al* [5] designed and published the first Randomised Controlled Trial (RCT) to address this clinical question.; this study was followed by a series of RCTs that were pooled in a meta-analysis by the Cochrane review group in 2004 [6]. The results suggested that surgical repair reduced the risk of re-rupture but came with an increased cost and a greatly increased risk of other complications, most of which were associated with infection and wound healing. There was little data on functional outcome at the time of this review.

Traditionally, patients have been treated in plaster casts after rupture of the Achilles; with the cast immobilising the foot and ankle while the tendon heals. However there are potential problems with this approach. Firstly there is the immediate impact on mobility for a period of around eight weeks. Secondly, there are the complications and risks associated with prolonged immobilization: muscle atrophy, deep vein thrombosis and joint stiffness [7 8]. Finally, there are the potential long-term consequences which include prolonged gait abnormalities, persistent calf muscle weakness and an inability to return to previous activity levels [9]. Functional bracing, involving immediate, protected weight-bearing in a brace, was designed to address these issues.

In patients having a surgical repair, seven RCTs [1 10-15] were conducted, directly comparing plaster casts with early movement and/or weight-bearing in a 'functional brace'. The results favour functional bracing in terms of re-rupture rate, functional outcome and quality of life measures. Therefore, in the first guideline (2009) produced on this topic, the American Academy of Orthopaedic Surgeons recommended functional bracing for patients having surgical repair of their tendon. [16]

What about patients managed non-operatively?
Whilst there are now clear guidelines for rehabilitation for patients who have a surgical repair, it has become evident that there is no clarity with regard to the use of functional bracing in non-operatively managed patients.

Does functional bracing provide improved function and quality of life if the tendon is not surgically repaired? Or, in the context of a tendon that has not been stitched together, does a plaster cast provide greater protection and therefore improved healing? Does functional bracing facilitate faster return to work and is this cost effective? Or, is the tendon more vulnerable to re-rupture in a brace with the subsequent risk and cost of reconstructive surgery?

The latest trials comparing surgical repair and non-operative treatment have found no difference in functional outcome [17 18]. Since surgery carries considerable costs, in terms of operating theatre time as well as surgical costs, and carries considerable risks to the patient in terms of complications [6], there is an increasing trend towards non-operative treatment. However, some surgeons have been reluctant to advocate non-operative treatment because of concerns about the lack of evidence to guide early rehabilitation for this group of patients [19]; specifically whether functional bracing is safe and effective if the tendon is not surgically repaired.

We supplemented the 2004 Cochrane review [6] with an updated literature search and found that in total only 2 studies [20 21] have been performed comparing the use of functional bracing with plaster casts for patients managed non-operatively following rupture of the Achilles tendon. Both studies suggested potential benefits from bracing. However, the data from the studies should be interpreted with caution due to small patient numbers (90 in total), patients having received different functional bracing regimes, and minimal reporting of outcomes.

The gap in the evidence was recognized in the recent American Academy of Orthopaedic Surgeons Guideline 2009 [16], which concluded that "*For patients treated non-operatively, we are unable to recommend for or against the use of immediate functional bracing for patients with acute Achilles tendon rupture*". With the incidence of Achilles tendon rupture on the rise, and in light of the large personal and societal cost associated with the injury, this gap in the evidence is a clear priority. Indeed, a recent Arthritis Research UK multidisciplinary 'Think Tank' (ARUK Birmingham 2013) on tendon injuries reported that rehabilitation following non-operative treatment of acute Achilles tendon injury was "the top research priority" in this area.

Some patients may still choose surgical repair of their rupture Achilles tendon, but it is likely that non-operative treatment will become increasingly popular. Therefore, now is the right time to conduct a trial of functional bracing versus plaster casts for patients with an Achilles tendon rupture treated non-operatively.

3.1 Pre-pilot data

We have completed four phases of pilot and preparatory work to establish the following:

1. Initial pilot study [1]. We randomised 48 patients having non-operative treatment for an acute rupture of the Achilles tendon to either functional bracing or plaster cast. This trial showed that patients and clinicians had equipoise for this question and were happy to take part. However, the trial identified that while plaster casting was a mature intervention, the important facets of the complex intervention which is functional bracing were inadequately defined, and that this needed to be addressed before a larger trial was performed.
2. Defining the functional bracing intervention. Our group and collaborators performed a series of reviews and experiments to define the optimal functional bracing regime [22-24]. The rehabilitation strategy proposed in this application is the summation of that work which identified: the optimal

type of orthosis (brace), the optimal foot position within the orthosis and the duration of application of the orthosis.

3. The acceptability and safety of this newly defined regime has now been tested in a further single-centre pilot RCT and qualitative recruitment investigation (ISRCTN68273773).
4. The number of eligible patients. We performed a UK-wide survey of orthopaedic trauma clinicians [19], with regards to the acceptability of the trial interventions and the number of eligible patients seen in each centre. This clearly showed that clinicians are enthusiastic about the study and that the number of eligible patients is large enough for a full trial and indeed rapidly increasing as non-operative management of Achilles tendon rupture becomes more and more common.

A full-scale trial of these interventions is now feasible and required to guide patient care.

3.3 Good Clinical Practice

The trial will be carried out in accordance with Medical Research council (MRC) Good Clinical Practice and applicable UK legislation using the following protocol.

3.4 Consort

The trial will be reported in line with the CONSORT statement using the non-pharmacological treatment interventions extension.

4. Trial design

4.1 Aim

The aim of this project is to improve functional outcome by determining the best rehabilitation strategy for non-operatively managed patients with a rupture of the Achilles tendon.

4.2 Objectives

The primary objective is:
To quantify and draw inferences on observed differences in Achilles Tendon Rupture Score between the trial treatment groups at 9 months after injury.

The secondary objectives are:

1. To quantify and draw inferences on observed differences in Achilles Tendon Rupture Score between the trial treatment groups at 8 weeks, 3 and 6 months after the injury.
2. To identify any differences in health-related quality of life between the trial treatment groups in the first 9 months after the injury.
3. To determine the complication rate between the trial treatment groups in the first 9 months after the injury.
4. To investigate, using appropriate statistical and economic analytical methods, the resource use, costs and comparative cost effectiveness between the trial treatment groups.

4.3 Trial summary

The proposed project is a two-phased study. Phase 1 (Internal Pilot) will confirm the expected rate of recruitment in a large-scale multi-centre randomised controlled trial. Phase 2 (Main phase) will be the proposed multi-centre randomised controlled parallel two-arm superiority trial in a minimum of 22 trauma centres across the UK.

Internal Pilot summary

The pilot will take place in 6 centres over a period of 6 months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the trauma centres over the course of 6 months. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent/withdraw, will be recorded. The pilot will also be used as a basis for testing the systems for collecting outcomes, including measures required for the economic evaluation. The trial will be stopped if the target recruitment during the internal pilot is not achieved. If the trial is stopped, trial patients will remain to receive standard of care treatment and follow-up. If the trial continues into the main recruitment phase, patients from the internal pilot will be included in the main analysis.

Main RCT summary

All adult patients presenting at the trial centres with a primary (first-time) rupture of the Achilles tendon will be screened. The patient, in conjunction with their surgeon, will decide if they have surgery or not, as per standard clinical care. If they decide not to have surgery (non-operative treatment), they will be eligible to take part in the trial. The broad eligibility criteria will ensure that the results of the study can readily be generalised to the wider patient population.
A computer generated randomisation sequence, stratified by centre, will be managed through a secure web-based service. Randomisation will be on a 1:1 basis to either functional bracing or plaster

cast. Both of these rehabilitation strategies are widely used within the NHS and all of the clinical teams in the chosen centres will be familiar with both techniques.
Baseline demographic data and pre-injury functional data using the validated Achilles Tendon Rupture Score (ATRS) will be collected. The patients will also be asked to fill out the EuroQol EQ-5D-5L health-related quality of life questionnaire to indicate their typical pre-injury and current health status. The clinical team will perform a clinical assessment and make a record of any early complications at 8 weeks when the cast/brace is removed and patients will be asked to complete the ATRS. Functional outcome, health-related quality of life, complications and resource use questionnaires will be collected at 8 weeks, 3, 6 and 9 months post-injury.

4.4 Outcome measures

The primary outcome measure for this study is the ***Achilles tendon Total Rupture Score (ATRS)*** [25]***.*** The ATRS is a validated questionnaire which is self-reported (filled out by the patient). It consists of 10 items assessing symptoms and physical activity specifically related to the Achilles tendon. It measures: strength, fatigue, stiffness, pain, activities of daily living, walking on uneven surfaces, walking upstairs or uphill, running, jumping and physical labour. This data will be collected at baseline, 8 weeks, 3, 6 and 9 months post-injury. The ATRS score reaches a plateau between 6 and 9 months after rupture [26]. The validity and reliability of this outcome measure has been previously published [25 27].

The secondary outcome measures in this trial are:
EQ-5D; The EQ-5D-5L is a validated, generic health-related quality of life measure consisting of 5 dimensions each with a 5-level answer possibility. The EQ-5D can be used to report health-related quality of life in each of the five dimensions and each combination of answers can be converted into a health utility score [28]. It has good test-retest reliability, is simple for patients to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.

Complications; all complications will be recorded, from the medical records at the 8 week review and self-reported by the patient thereafter, including: re-rupture, blood clots/emboli, pressure areas/hindfoot pain, falls and neurological symptoms in the foot.
We will use techniques common in long-term cohort studies to ensure minimum loss to follow-up, such as collection of multiple contact addresses and telephone numbers, mobile telephone numbers and email addresses. Considerable efforts will be made by the trial team to keep in touch with patients throughout the trial by means of newsletters etc.

Table 1: Data collection

TIME POINT	DATA COLLECTED	Responsibility
Baseline	Patient demographic and injury information, pre-injury ATRS, pre-injury and contemporary EQ-5D	Hospital Site Staff
8 weeks post randomisation (+/- 1 week)	Complication records, ATRS, EQ-5D, resource use questionnaire	Hospital Site Staff
12 weeks post randomisation (+/- 2 weeks)	ATRS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire	Trial Unit will post, email or text questionnaire pack direct to patient.
26 weeks post randomisation (+/- 2 weeks)	ATRS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire	Trial Unit will post, email or text questionnaire pack direct to patient.
36 weeks post randomisation (+/- 4 weeks)	ATRS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire	Trial Unit will post, email or text questionnaire pack direct to patient.

4.5 Sample size

The primary outcome for this study is the Achilles Tendon Rupture Score (ATRS) [25]. This is a 10-question, patient reported, outcome measure designed for patients with an Achilles tendon rupture. The individual items are converted to a 100 point scale were '0' represents complete disability and '100' is normal function. The minimum clinically important difference (MCID) for the ATRS is 8 points [27]. At an individual patient level, a difference of 8 points represents the ability to walk upstairs or run with 'some difficulty' versus with 'great difficulty'. At a population level, 8 points represents the difference between a 'healthy patient' and a 'patient with a minor disability' [27].

The standard deviation (SD) of the ATRS 9 months after injury in previous work was 20 points [26]; the sample size has also been estimated for a larger and smaller standard deviations to obtain an indication of the sensitivity to changes in this parameter. Taking 20 points as our best estimate of the likely population variability, we have also provided estimates of samples size for differences between 6 and 10 points on the ATRS; these correspond to standardized effect sizes in the range 0.3-0.5 ('small' to 'medium' sized treatment effects). Assuming the distribution of ATRS in the study populations to be approximately normal, which is also consistent with our pre-pilot data, Table 2 shows the total trial sample size with two-sided significance set at 5% for various scenarios of MCID, power and SD. The bold figure of **264** patients represents the most likely scenario, based on our current knowledge, for 90% power to detect the selected MCID; representing a standardised effect size of 0.4.

Table 2: Sample size calculations

	80% Power			90% Power		
MCID	6	8	10	6	8	10
SD						
15	198	112	72	264	150	96
20	350	198	128	468	**264**	170
25	548	308	198	732	412	264

Allowing a margin of 20% loss of primary outcome data, this gives a minimum of **330 patients**. The 20% loss of data will include patients who cross-over between interventions and those who are

lost to follow-up. Therefore, a minimum of 165 patients randomized to each group will provide 90% power to detect a difference of 8 points in ATRS at 9 months at the 5% level. We will review data quality/loss to follow-up during the trial and exceed the minimum of 330 patients if necessary in order to ensure that the trial achieves 90% power.

The internal pilot will specifically inform and test the recruitment rate for the main trial. Recruitment will take place in 6 trial centres over a period of 6 months. The expected rate of recruitment is based upon a pre-pilot study performed at the lead centre and a UK-wide survey. The average recruitment rate for this pre-pilot study was 3 patients per month. The other centres involved in the trial will all be trauma units with similar catchment areas to the lead centre. Experience from previous multi-centre trials has, however, shown that recruitment outside of the lead centre tends to occur at a lower rate. As such, a conservative **recruitment rate of 1 patient per month per centre** is estimated for the 6 month pilot phase. If this recruitment rate is achieved by the end of the internal pilot, the trial will progress to the main phase. We intend to recruit patients from a minimum of 22 centres (including the lead centre). The sample of a minimum of 330 patients will then be recruited over a 16 months period.

Screening logs will be collected throughout the trial to assess the main reasons for patient exclusion as well as number of patients unwilling to take part. Patients will be screened by the Research Associates in the Fracture Clinics at the trial centres.

4.6 Methodology

4.6.1 Screening

Patients with an Achilles tendon rupture are referred, either from the Emergency department or from the community, to an orthopaedic 'fracture' clinic. All adult patients presenting to the clinic within 14 days of a primary (first-time) rupture of the Achilles tendon will be screened by the clinical care team. The patient, in conjunction with their surgeon, will decide if they have surgery or not. If they decide not to have surgery (non-operative treatment), they will be eligible to take part in the trial and will be referred to the research team.

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

4.6.2 Eligibility

Patients will be considered for participation in this study if:

They are aged 16 years or older
They have a primary rupture of the Achilles tendon
They have decided to have non-operative treatment

Patients will be excluded from participation in this study if they:

Present to the treating hospital more than 14 days after the injury, or
There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires; for example, a history of permanent cognitive impairment

The first exclusion criterion relates to patients with 'late presentation', which is not uncommon after this injury. Patients who present late, may have problems with chronic tendon lengthening irrespective of treatment and are frequently offered surgical intervention. The '14 days' has been widely used to define 'acute' rupture, including in our own pilot work.

The second criterion reflects the fact that much of the outcome data is collected by postal or

electronic questionnaire, when help and support will not be available. Also, the primary outcome measure is not validated for proxy reporting.
If a patient taking part in the study were to sustain a contralateral rupture during the trial period, the second rupture would not be included in the study because the result of this intervention would not be independent from the first intervention. However, the patient would remain in the trial, with both previous and future data related to the initial rupture included in the final analysis.

4.6.3 Consent
Informed consent from the patient will be obtained by an appropriately trained and delegated member of the research team. Patients will be provided with verbal and written information about the study. There will be time for the patients to ask questions and to discuss the study with friends and family. If the patient is happy to participate they will be asked to complete an informed consent form. Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants. A revised consent form will be completed if necessary. Patients will be asked to consent to long-term follow-up and data linkage to routine NHS datasets.

4.6.4 Randomisation
The 1:1 allocation to either functional bracing or plaster cast will be made using a secure, centralised, computer-generated allocation sequence and web-based randomisation service. The Research Associate will inform the treating clinical team of the allocated treatment.

Stratification by centre will help to ensure any effect related to the centre itself will be equally distributed in the trial arms. The catchment area will be similar for all of the hospitals; each hospital is a trauma unit dealing with these injuries on a daily basis. While unlikely, it is possible that the clinicians at one centre may be more expert in one or other treatment than those at another centre. Therefore, all of the recruiting hospitals have been/will be chosen on the basis that both techniques are currently routinely available at the centre i.e. the clinical staff are already familiar with both plaster casts and functional bracing.

4.6.5 Post randomization withdrawals
Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives.
Participants have two options for withdrawal;
1) Participants may withdraw from completing any further questionnaires but allow the trial team to still view and record anonymously any relevant hospital data that is recorded as part of normal standard of care; i.e x-rays and further treatment information.
2) or Participants can withdrawal wholly from the study and only data obtained up until the point of withdrawal will be included in the final analysis of the study, thereafter no further data will be collected for that participant.
Once withdrawn, the patient will be advised to discuss their further care plan with their surgeon. Withdrawn participants will not be replaced as the sample size calculation has allowed for loss to follow up.

4.6.6 Blinding
As the type of rehabilitation used is clearly visible, the patients cannot be blind to their treatment. In

addition, the treating clinician will also not be blind to the treatment, but will take no part in the post-operative assessment of the patients. The outcome data will be collected and entered onto the trial central database via questionnaire, by a research assistant/data clerk in the trial central office to reduce the risk of assessment bias.

4.7 Trial treatments

Following randomisation, one group of patients will receive a plaster cast and one group will receive a functional brace. All of the hospitals involved in this trial currently use both plaster casts and functional bracing for patients with both soft-tissue injuries (tendon and ligament) and fractures, so all clinicians/units are familiar with both interventions.

Although the principles of application of both plaster casts and functional bracing are inherent in the technique, there are different types of plaster cast material and functional brace design. Each patient will undergo the allocated intervention according to the protocol below, but the details of the plaster and brace will be left to the discretion of the treating clinician, as per their usual practice. This will ensure that the results can be generalized across the NHS.

4.7.1 Plaster cast

The initial plaster cast will be applied in the 'gravity equinus' position i.e. the position that the foot naturally adopts when unsupported. In this position, with the toes pointing down towards the floor, the ends of the ruptured tendon are roughly approximated. Some units may use ultrasound to assess the approximation of the tendon ends, but this is not routine [19] and so will be left to the discretion of the treating clinician. The patient may mobilise with crutches immediately using their toes for balance (toe-touch), but patients are not able to bear weight on the injured hindfoot. Over the first 8 weeks, as the tendon heals, the position of the plaster cast is changed until the foot achieves 'plantargrade' i.e. the foot is flat to the floor. At this point the patient may start to bear-weight in the plaster cast. The number of changes of plaster cast and the time to weight-bearing will be left to the discretion of the treating clinician, as per their usual practice. The cast will be removed at 8 weeks, as per routine clinical care.

The plaster cast provides maximum protection for the healing tendon, specifically it restricts the upward (dorsiflexion) movement of the ankle which may stretch the healing tendon, but it does not allow the patient to bear weight on the foot immediately.

4.7.2 Functional bracing

A rigid brace will be used in the trial, as opposed to a flexible brace [24]. Initially, two 1-cm heel solid wedges (or equivalent) will be inserted into the brace to replicate the 'gravity-equinus' position of the foot [24]. The patient may mobilise with immediate full weight-bearing within the functional brace. The number of wedges/foot position will then be reduced until the patient reaches 'plantigrade'. Again, the timing of the removal of wedges/change in foot position will be left to the discretion of the treating clinician, as per their usual practice. The brace will be removed at 8 weeks, as per routine clinical care.

The functional brace does not provide the same restriction of movement as the cast, but does allow the patient to bear weight on the foot immediately.

4.7.3 Rehabilitation

When the cast/brace is removed after 8 weeks, we will provide all patients (both groups) with the same standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. This will be based on a published systematic review of current rehabilitation protocols [22]. All of the patients in both groups will be advised to move their toes, ankle and knee joints fully within the limits of their comfort and walking will be encouraged. In this

pragmatic trial, any other rehabilitation input beyond the written physiotherapy advice (including a formal referral to physiotherapy) will be left to the discretion of the treating clinicians. However, a record of any rehabilitation input (type and number of additional appointments) as well as other investigations/interventions will be requested as part of the 8 week, 3 month, 6 month and 9 month follow-up questionnaires.

4.8 Study Within A Trial (SWAT)

4.8.1 Background

Reminders are generally an effective way of increasing response rates to questionnaires and there is some evidence that pre-notification (contacting a participant to say that the trial team will be sending a questionnaire out soon) also has some evidence of benefit, although it is not high certainty evidence [29 30]. This SWAT will attempt to establish whether, for a subset of UKSTAR participants, an email pre-notification enhances retention.

4.8.2 Intervention

The SWAT intervention is a combined thank you and pre-notification email (called: "pre-notification email") sent around 2 weeks after a participant has completed a 3 month or a 6 month questionnaire. Emails are sent to participants who are randomised to receive the intervention and who have supplied an email address. The SWAT will be implemented during the period of follow-up of UKSTAR participants.

4.8.3 Participants

Participants will be included if they have not yet been sent their 6 month or 9 month questionnaire at the time this SWAT is implemented. With a July implementation date, approximately 197 participants will be included.

4.8.4 Randomisation

The allocation to the treatment arm will be random and performed centrally to ensure that participants, investigators enrolling participants, and study office staff who administer follow-ups, cannot foresee allocation. Participants will be randomised on a 1:1 basis to either receiving a combined thank you and pre-notification email or not receiving a pre-notification email.

4.8.5 Outcome measure and analysis

Primary outcome: Proportion of participants contacted who respond by electronic means (email or mobile link). The primary analysis for the SWAT is the difference in response rate by electronic means (email or mobile link) between those receiving the pre-notification email and those receiving no incentive.

The outcome of the SWAT will be for internal trial purposes only and will not form part of the main trial report.

4.8 Adverse event management

Adverse events (AE) are defined as *any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment*. All AEs will be listed on the appropriate Case Report Form for routine return to the 'UKSTAR' central office.

Serious adverse events are defined as any *untoward and unexpected medical occurrence that:*

1. *Results in death*,
2. *Is life-threatening,*
3. *Requires hospitalisation or prolongation of existing inpatients´ hospitalisation*,
4. *Results in persistent or significant disability or incapacity*,
5. *Is a congenital anomaly or birth defect,*

6. *Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed*.

All serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and emailed to a secure NHS.net account accessed only by the research team 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 related to the trial will be notified to the Research Ethics Committee (REC) within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

Some adverse events are foreseeable as part of the proposed treatment, and - even those which meet the definition of "serious" as described above - do not need to be reported immediately to the UKSTAR central office, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. These events are: re-rupture, blood clots/emboli, pressure areas/hindfoot pain, falls and neurological symptoms in the foot.

All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

All unexpected SAEs or SUSARs that occur between date of *consent and 9 month follow-up point* will be reported.

4.9 End of trial

The end of the trial will be defined as the collection of 9 months outcome data from the last participant.

5. Data Management

The Case Report Forms will be designed by the Clinical Trial Manager in conjunction with the trial management team. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Personal data and sensitive information required for the study will be collected directly from trial participants and hospital notes. All personal information received in paper format for the trial will be held securely and treated as strictly confidential. Any personal data will be stored separate from study outcomes. The personal data will be stored in lockable cabinets in secure keycard accessed rooms within the Kadoorie Centre in the John Radcliffe hospital in Oxford. All staff involved in the study share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be entered and stored on a password protected access restricted secure server at the University of Oxford under the provisions of the Data Protection Act and/or applicable laws and regulations.

Patients will be identified by a code number only on the main trial database. Direct access to source data/documents will be required for trial-related monitoring and consent will be obtained from the patients. All paper and electronic data will be retained for at least five years after completion of the trial.

A data management plan will be drafted early in the trial following OCTRU standard operating procedures. It will contain a complete description of the design and production of the data capture tool for collection of participant data at investigator sites, the design and construction of the database to maintain the data electronically, the processing of the data (entry/uploading, cleaning and query management) and the production of the final data set for analysis and data sharing.

5.1 Statistical Analysis

All available data from both treatment arms will be used in data analysis. Reporting of the results will be in accordance with the CONSORT statement using the extension for non-pharmacologic treatment interventions. Descriptive statistics (means and respective standard deviation for continuous variable or frequencies and proportions for categorical variables) will be used to describe the sample demographics, both for the two treatment groups individually and overall sample. The main analysis will investigate differences in the primary outcome measure, the ATRS at 9 months after injury, between the two treatment groups on an intention-to-treat basis. In addition, early functional status will also be assessed and reported at 8 weeks and 3 and 6 months.

The differences between treatment groups will be assessed using a Student t-test, based on a Normal approximation for the ATRS score at 9 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). As discussed earlier, the stratified randomisation procedure should ensure a balance in recruiting centres between test treatments. As any individual clinicians will treat only a small number of patients enrolled in the trial, important clinician-specific effects are not expected in this study. In our pilot work, we did not find evidence that age or gender affected outcome. However, 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. This analysis will also allow the adjustment of other important prognostic variables including baseline ATRS.

Estimates of treatment effects will be presented with 95% confidence intervals for both unadjusted and adjusted analyses. Where severe departure from normality is identified, the first approach will be data transformation. If the data cannot be transformed to normality then the Mann-Whitney U test will be used (in this case, no further adjusted analysis will be made). 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. The fully adjusted analysis of the primary outcome will be used to determine the success or otherwise of the trial.

Secondary continuous outcomes will be analysed using the same methodology for the primary outcomes. Temporal patterns of any complications will be presented graphically and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of important complications (e.g. re-rupture).

Although missing data is not expected to be a problem for this study, the nature and pattern of missing data (missing completely at random – MCAR; missing at random – MAR; or missing not at random – MNAR) will be carefully considered. If judged appropriate (MCAR or MAR), missing data will be imputed using multiple imputation. The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

Any changes to the statistical analysis plan during the trial will be subject to the same review and sign-off procedure with details of changes being included in the new version. Any changes or deviations from the original SAP will be described and justified in the protocol by means of substantial amendment and/or in the final report, as appropriate.

5.2 Health Economic analysis

A prospective economic evaluation, conducted from a NHS and personal social services perspective, will be integrated into the trial design [23]. The economic evaluation will estimate the difference in the cost of resource inputs used by participants in the two arms of the trial, allowing comparisons to be made between the two non-surgical treatment options (plaster cast versus functional bracing) for patients with a primary (first-time) rupture of the Achilles tendon, and enabling costs and consequences to be compared. The economic assessment method will, as far as possible, adhere to the recommendations of the NICE Reference Case [31].

Primary research methods will be followed to estimate the costs of the treatment options, including supplementary interventions (e.g. surgery) and rehabilitation inputs. Broader resource utilisation will be captured through two principal sources: (i) routine health service data collection systems; and (ii) patient questionnaires administered at baseline, 8 weeks and three, six and nine months post-randomisation. Unit costs for health and social care resources will largely be derived from local and national sources and estimated in line with best practice. Primary

research using established accounting methods may also be required to estimate unit costs. Costs will be standardised to current prices where possible. Health - related quality of life will be measured at baseline pre-injury, at the time of consent, 8 weeks and three, six and nine months post-injury using the EuroQol EQ-5D-5L measure; responses will be used to generate quality-adjusted life-years (QALYs). Utility weights will be estimated using recommended algorithms until a national tariff set for the EQ-5D-5L is available [28]. We will in the first instance use self-reports of the EQ-5D measure. Where these data are not available, we will estimate health utilities at each time point using mapping equations between the ATRS score and EQ-5D health outcomes on the basis of existing datasets held by the trial team.

Multiple imputation methods will be used to impute missing data and avoid biases associated with complete case analysis. The results of the economic evaluation will be expressed in terms of incremental cost per QALY gained. We shall use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. One such sensitivity analysis will involve adopting a societal perspective for the economic evaluation, which will incorporate direct costs to trial participants, informal care provided by family and friends, and productivity losses. In the baseline analysis, and for each sensitivity analysis, cost-effectiveness acceptability curves will be constructed using the net benefits approach. Heterogeneity in the trial population will be explored by formulating net-benefit values for trial participants from the observed costs and effects, and then constructing a regression model with an intervention variable and covariates such as age and sex. The magnitude and significance of the coefficients on the interactions between the covariates and the intervention variable will provide estimates of cost-effectiveness of the treatment options by participant sub-group. More extensive economic modelling using decision-analytic methods will extend the target population, time horizon and decision context, drawing on best available information from the literature together with stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values using discount rates recommended for health technology appraisal in the UK.

6. Trial Oversight

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager, based at Nuffield Department of Orthopedic, rheumatology and musculoskeletal Sciences and supported by the OCTRU staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Clinical Trial Manager to undertake training of the research associates at each of the trial centres. The Trial Statistician and Health Economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. A Trial Steering Committee (TSC) and a Data & Safety Monitoring Committee (DSMC) will be set up.

6.1 Trial Supervision

A Trial Steering Committee (with an independent Chairman) and Data & Safety Monitoring Committee (DSMC) will be set up.

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least annually. The remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the trial.

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial.

The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment group and they will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study.

The Trial Management Group (TMG) is made up of the Investigators listed on the front of this protocol, and staff working on the project within OCTRU/ CCTR Trials Group. This group will oversee the day-to-day running of the trial and will meet regularly throughout the lifetime of the study.

6.2 Quality control

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the Host organization, Sponsor or appropriate Regulatory Authorities. A Monitoring Plan will be developed according to OCTRU's SOPS which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

6.3 Insurance and Indemnity Arrangements

The Sponsor has a specialist insurance policy in place - Newline Underwriting Management Ltd, at Lloyd's of London - which would operate in the event of any participant suffering harm as a result of

their involvement in the research. Standard NHS cover for negligent harm is in place for NHS procedures. There will be no cover for non-negligent harm.

6.4 Dissemination

The study monograph will be prepared by the trial management team within three months of completion of the trial. We will simultaneously prepare a manuscript for a high impact peer-reviewed journal, which will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, NICE and hence policy makers. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The results of this trial will substantially inform clinical practice on the clinical and cost effectiveness of the treatment of this injury. The results of this project will be disseminated to patients via patient-specific newsletters and through local mechanisms at all participating centres.

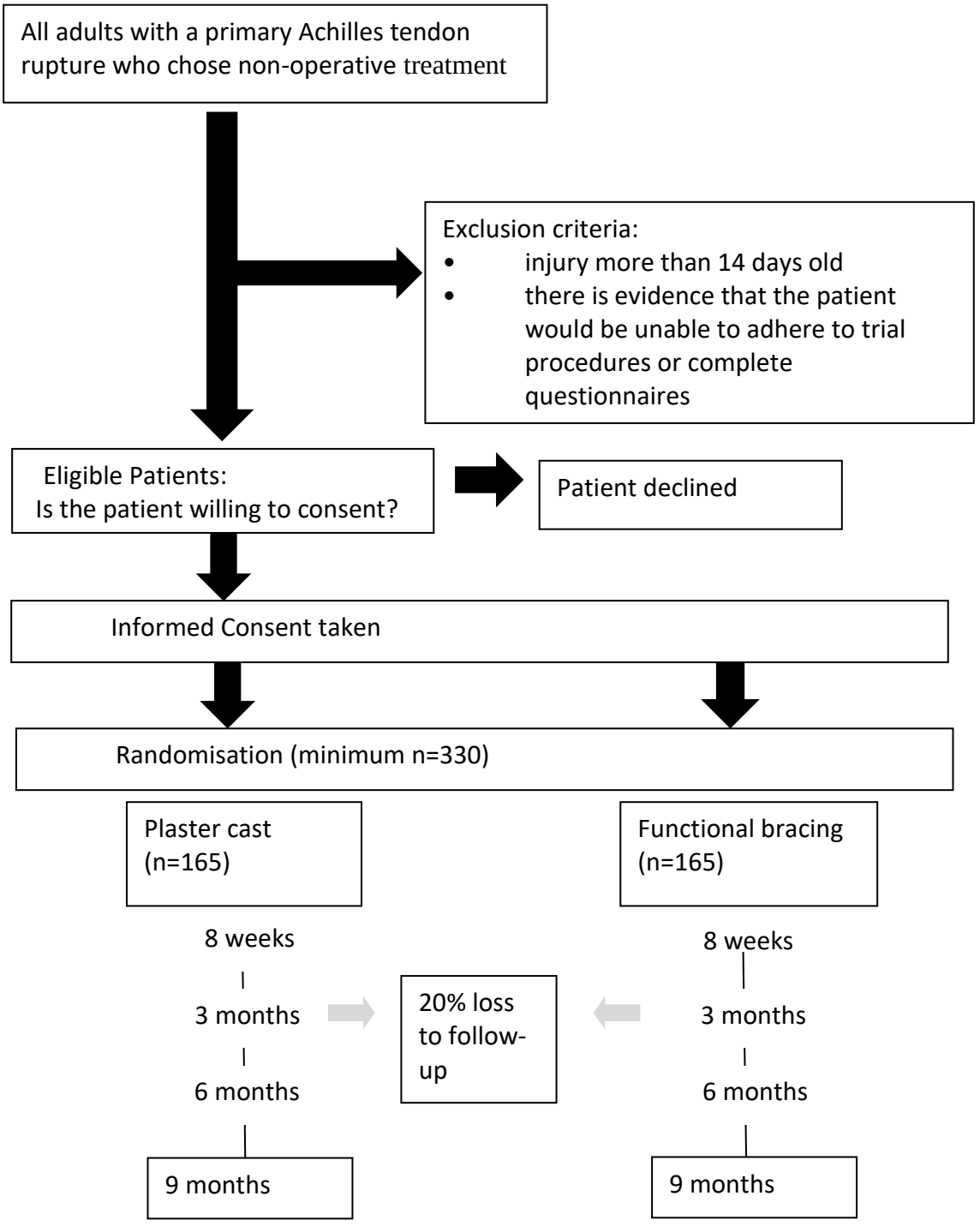
6.5 Project Timetable and Milestones

We propose a 38 months study starting in April 2016. The planned trial timetable is shown below, with key milestones indicated and the responsible parties identified:

Month	By date	Activity	Milestone	Responsibility
-4-0		Ethics submission	REC approval	CI/RF
0-3	April 2016	Start Trial		
		Finalise trial protocol	Protocol final version	TMG
	June 2016	Complete CRF's	CRF final version	CI/Stat/TC
4-10	July 2016	Start recruitment lead centre + pilot centres 1 & 2	1st trial site online 1st TSC/DSMC meeting	TC/CI
	Aug 2016	Start recruitment at pilot centres 3,4,5 & 6	6 pilot sites online	TC/CI
	Dec 2016	Finish pilot recruitment	33 centre months recruitment	TC/CI
	Jan 2017	Decision on progression of trial	Report to TSC and HTA	TMG
11-26	Feb 2017	Start staggered launch 2 centres/month		TC/CI
	July 2017	Start 12/12 follow-up assessments	Initiate follow-up phase	TMG
	Sep 2017	Complete site initiations	All 22 sites recruiting	TC/CI
	Oct 2017	50% total recruitment	170 patients enrolled	
	Nov 2017	Data review first 170 patients	DSMC report	DSMC via TSC to HTA
	Dec 2017		2nd TSC meeting	CI/TC
	May 2018	End recruitment	All patients enrolled	
27-35	Feb 2019	Complete follow-up all sites	All patients completed follow-up	
36-38	April2019	Statistical analysis		Stat
		Health economics analysis		HE
	May 2019	Reporting		
	June 2019	Final report HTA	HTA report	TMG

CI Chief Investigator, RF Research Fellow, TMG Trial management group, TC Trial coordinator, TSC trial steering committee, DSMC Data & Safety monitoring Committee, Stat statistician, HE Health Economist

6.6 Trial flow diagram



7. Protocol Amendments

Amendment Number	Protocol Version	Date of Approval	Reason for change
Amendment 1 (Non-substantial)	1.1	03 May 2016	Correction of typographical errors and clarifications
Amendment 2 (Substantial)	2.0	26 Sep 2016	• Addition of resource use questionnaire at 8 weeks • Update to the statistical analysis section of the protocol so that it reflects the statistical analysis plan for the trial • Clarification regarding the consent process as described in section 4.6.3 of the protocol • Correction of typographical errors and clarifications
Amendment 8 (Non-substantial)	3.0	20 Jul 2017	• Clarification that questionnaires at the 3, 6 or 9 month time points may also be sent electronically to patients via email or text
Amendment 9 (Substantial)	4.0	23 Oct 2017	• Update sample size to a minimum of 330 patients, maximum of 550 patients
Amendment 11 (Non-substantial)	5.0	31 Oct 2017	• Correction of protocol version number from 4.1 to 5.0
Amendment 13 (Substantial)	6.0		• Inclusion of SWAT • Changes to Study personnel • Minor typographical errors corrected.

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