UK Study of **T**endon **A**chilles **R**ehabilitation: A prospective multicentre two-arm individually randomised controlled trial.

Statistical Analysis Plan

Version 2.0 – 04Dec2018

Based on Protocol version 6.0 – 16May2018

Trial registration: ISRCTN62639639

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CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the ***NIHR Health Technology Programme (HTA programme) - funded randomised controlled trial comparing the use of Plaster Cast to Functional Brace in the treatment of adults with Achilles tendon rupture (UKSTAR).*** The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. This document follows the published guidelines regarding the content of statistical analysis plans for clinical trials [1].

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

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1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_29Aug2018	Ioana Marian	UKSTAR_Protocol_V6.0_16May2018	Not applicable as this is the 1st issue
V2.0_04Dec2018	Ioana Marian	UKSTAR_Protocol_V6.0_16May2018	Minor chages in the CONSORT flow diagram and reference to CONSORT PRO extension

2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

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 [2]. 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 [2]. 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 [3]. 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 [3]. 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 [3]. 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 [4, 5].

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 [6, 7]. 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 [8]. Functional bracing, involving immediate, protected weight-bearing in an orthotic, was designed to address these issues.

In patients having a surgical repair, seven RCTs [2, 9-14] 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 [15].

We supplemented the 2004 Cochrane review [16] with an updated literature search and found that in total only two studies [17, 18] 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 [15], 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*". 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?

2.2 Objectives

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

and outcome measures of the trial are described in Table 1. Explicit definitions of endpoints will be detailed later in this document.

Table 1: UKSTAR objectives and outcome measures

	Objectives	Outcome Measures
Primary	To quantify and draw inferences on observed differences in Achilles Tendon Rupture Score (ATRS) between the trial treatment groups at 9 months after injury.	▪ ATRS
Secondary	1. To quantify and draw inferences on observed differences in ATRS 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.	▪ ATRS ▪ EQ-5D-5L ▪ Resource use ▪ Complications

3. STUDY METHODS

3.1 Trial Design/framework

UKSTAR is a 1:1, multi-centre, parallel, two-arm, superiority randomised controlled trial. This study aims to evaluate the use of functional bracing compared to plaster cast for the management of acute Achilles Tendon Rupture (ATR) in adult patients deemed to non-operative treatment. The primary outcome is the ATRS measured at 9 months following injury. Secondary outcomes include complications, quality of life and resource use evaluated at 8 weeks, 3, 6 and 9 months after the injury. The UKSTAR study will take place in a minimum of 22 trauma centres across the UK.

Patients are 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 are 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.

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.

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 'plantigrade' 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.

Functional bracing

A rigid brace will be used in the trial, as opposed to a flexible brace [20]. Initially, two 1-cm heel solid wedges (or equivalent) will be inserted into the brace to replicate the 'gravity-equinus' position of the foot [20]. 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.

3.2 Randomisation and Blinding

Randomisation will be 1:1 block allocation (variable block sizes: 2, 4 and 6 in a 1:2:1 ratio) to either functional bracing or plaster cast 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.

The majority of participants will be randomised during their inpatient admission following their ATR via the randomisation service provided by the Oxford Clinical Trials Research Unit (OCTRU). Full details of the randomisation are available in UKSTAR_RBP_v1.0_26Jul2016**,** stored in the confidential statistical section of the Trial Master File (TMF).

As the type of rehabilitation used is clearly visible, the patients cannot be blind to their treatment. In addition, the treating clinician will also be unblinded 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.

3.3 Sample Size

The primary outcome for this study is the ATRS [21]. This is a 10-question self-reported outcome measure, designed for patients with an ATR. The individual items are converted to a 100-point scale, where '0' represents complete disability and '100' is normal function. The minimum clinically important difference (MCID) for the ATRS is 8 points [22]. 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' [22].

In previous work, the standard deviation (SD) of the ATRS 9 months after injury was 20 points [23]. Assuming a likely population variability of 20, MCID value of 8 and 90% power to detect the selected MCID, there is a requirement of 264 total participants to be randomised. Allowing a margin of 20% loss of primary outcome data to include patients who cross over between interventions and those who are lost to follow-up leads to a requirement of 330 participants. We intend to recruit a minimum of 330 patients from at least 22 centres over a period of 16 months.

Table 2 shows the estimated sample sizes based on 5% two-sided tests, 80% and 90% power, taking into account a larger and smaller SD as well as differences between 6 and 10 points on the ATRS corresponding to standardized effect sizes in the range 0.3-0.5 ('small' to 'medium' sized treatment effects).

Table 2: Sample size

	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

Changes to the sample size

The trial reached its primary recruitment target of 330 participants early and therefore the sample size was recalculated based on a larger population variability equivalent to 25 points SD. As per Table 2 calculations for SD 25, MCID 8 and 20% loss to follow-up 516 participants were required. The maximum number of participants to be recruited for the trial was set at 550. Details on sample size checks are included in SamplesizeCheck_PASS11_14Jan2016 stored in the statistical section of the TMF.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

The Data and Safety Monitoring Committee (DSMC) is a group of independent experts external to the trial who will assess the progress, conduct, participant safety and, if required critical endpoints. The DSMC follows the charter as described in the document UKSTAR_DSMC_Charter_V2.0_09Feb2017 stored in the TMF.

The DSMC will aim to safeguard the interests of trial participants; monitor data quality and completeness; and overview the main outcome measures, including and paying special attention to safety and efficacy. They will also consider emerging evidence from other related trials or research and review related Serious Adverse Events (SAEs) that have been reported. Full details of the interim analyses planned are available in the Interim Statistical Analysis Plan (ISAP) UKSTAR_ISAP_v1.0_05Dec2017 stored in the confidential statistical section of the TMF. Formal comparative interim analyses of the primary outcome is not planned during the trial. The DSMC may advise the chair of the TSC 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.

3.5 Timing of Final Analysis

The timing for the final analysis is the 9 month follow-up after randomisation for all randomised participants and other key time point dates are listed below.

Date of grant activation:	Apr2016
Date of start of recruitment:	Jul2016
Date of expected end of recruitment:	May2018
Date expected end follow-up:	Feb2019
Date expected start of analysis:	Mar2019
Date End of grant:	31May2019

3.6 Blinded analysis

A blinded analysis of data (not separated by treatment arm) will be undertaken prior to the final data lock in order to assess the distribution of variables, missing data distributions and outliers. This analysis may also be used to identify key prognostic variables to be included in the adjusted analysis. The treatment code will be added to the database after the data cleaning has been completed.

3.7 Statistical Analysis Outline

All available data from both treatment arms will be used in data analysis. Reporting of the results will be in accordance with the Consolidated Standards of Reporting Trials for Patient Reported Outcomes (CONSORT) statement using the extension for non-pharmacologic treatment interventions and patient reported outcomes. 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 (ITT) basis. In addition, early functional status will also be assessed and reported at the 8 week and 3 and 6 month follow-up. 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 clinician 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 potential imbalance between treatment groups in patient age, gender and other important prognostic factors.

The fixed effects analysis (linear regression model) will also be generalised 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, age and gender.

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.

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

There is no multiple testing as only a single primary outcome is considered, ATRS measured at the 9 month follow-up. All secondary analyses will be considered as supporting the primary analysis. Significance levels used will be 0.05 and 95% confidence intervals (CI) will be reported.

Interim comparative analyses of primary and secondary endpoints will not be carried out unless requested by the DSMC.

4.2 Definition of Analysis Populations

Intent to treat (ITT) population: all randomised participants included in their randomised groups.

Complier average causal effect (CACE) [24] population: all randomised participants compliant with treatment. Participants are compliant if they wear the treatment they were allocated at randomisation for a period of 6 or more weeks without any cross-over (immediate switch) at baseline or treatment change within this period.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants randomised, receiving intended treatment, completing the study protocol, and analysed for the primary outcome is provided in Figure 1. Details of all who are randomised in error will be reported and these individuals will be excluded from all further analyses.

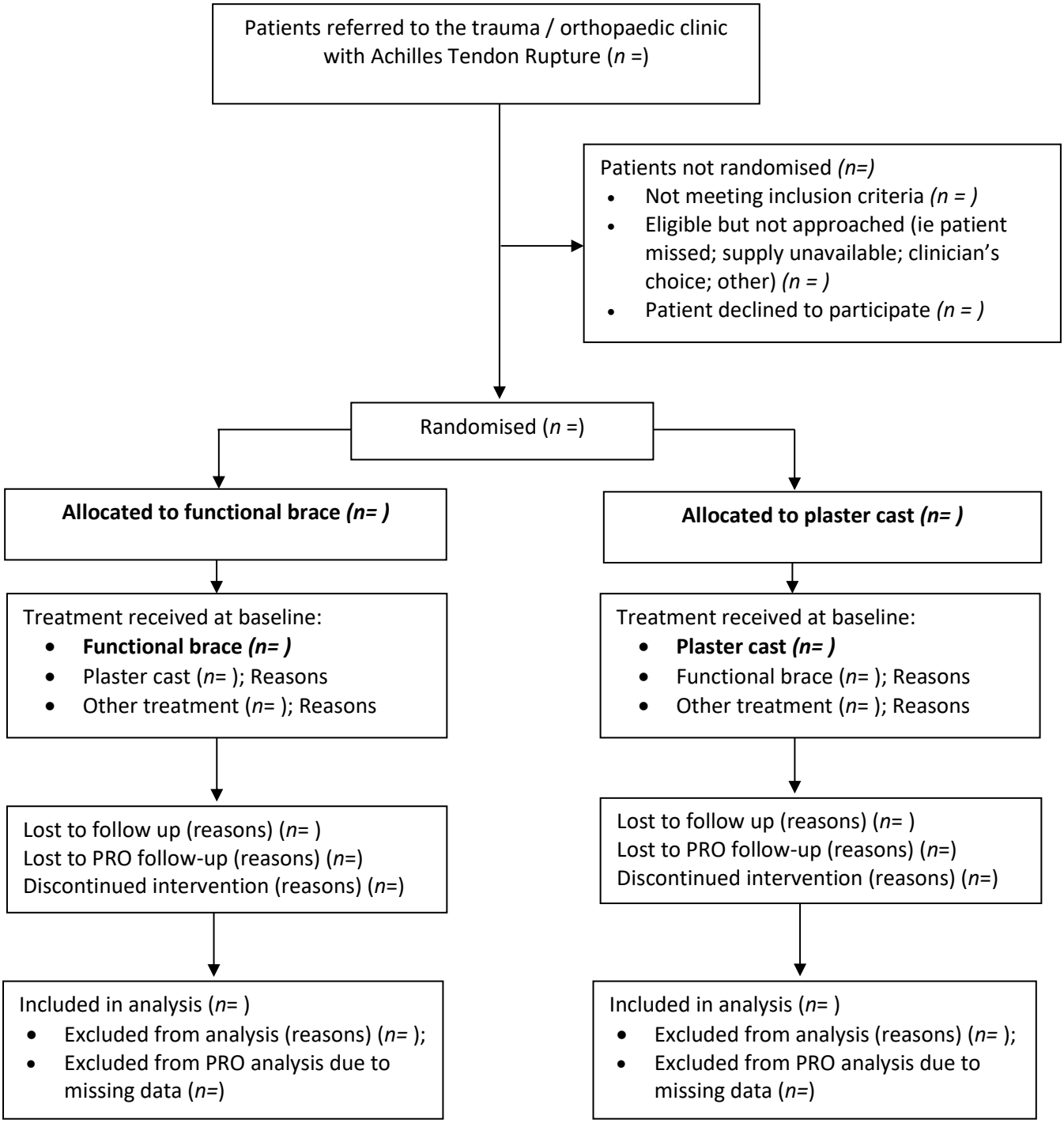

Figure 1: Recruitment flow-chart template of trial participants (based on CONSORT PRO extension [25])

5.2 Withdrawal from treatment and/or follow-up

The number (with percentage) of withdrawals and losses to follow-up over the study period will be reported and compared by treatment arm at each time point. The reasons for losses to follow-up will also be reported as per Table 3. To ensure that there are no differential losses between the groups this will be tested using absolute risk differences (with 95% confidence interval) and a chi-squared test. Any deaths (and their causes) will be reported separately. In the event of a tendon re-rupture following which the participant undergoes surgery, the participant will not be treated as loss to follow-up.

Table 3: Details of loss to follow-up and withdrawals according to intervention group

Follow-up	Functional brace		Plaster cast	
	n	%	n	%
8 weeks				
Completed	XXX	XX	XXX	XX
Withdrawal	XXX	XX	XXX	XX
Reason 1	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX
…	…			
Loss to follow-up	XXX	XX	XXX	XX
Reason 1	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX
…	…			
3 months				
Completed	XXX	XX	XXX	XX
Withdrawal	XXX	XX	XXX	XX
Reason 1	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX
…	…			
Loss to follow-up	XXX	XX	XXX	XX
Reason 1	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX
…	…			
6 months				
…	XXX	XX	XXX	XX
9 months				
…	XXX	XX	XXX	XX

5.3 Baseline Comparability of Randomised Groups

Participant baseline characteristics will be reported by treatment group and will include centre stratification, important prognostic covariates, demographics and baseline values for ATRS and EQ-5D-5L before and after the injury. Numbers (with percentages) for categorical variables and mean (and standard deviation), or medians (with interquartile range (IQR)) for continuous variables will be presented for each treatment group and overall as shown in Table 4 and 5. There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

Table 4: Baseline characteristics according to intervention group and total sample (categorical variables)

	Functional brace		Plaster cast		Total	
	n	%	n	%	n	%
Gender						
Female	XXX	XX	XXX	XX	XXX	XX
Male	XXX	XX	XXX	XX	XXX	XX
Side of injury						
Right	XXX	XX	XXX	XX	XXX	XX
Left	XXX	XX	XXX	XX	XXX	XX
Mechanism of injury						
Fall from height	XXX	XX	XXX	XX	XXX	XX
Fall on steps/stairs	XXX	XX	XXX	XX	XXX	XX
Sports	XXX	XX	XXX	XX	XXX	XX
Walking	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
BMI (kg/m^2)						
Underweight (<18.5)	XXX	XX	XXX	XX	XXX	XX
Normal weight (18.5-24.9)	XXX	XX	XXX	XX	XXX	XX
Overweight 25.0-29.9)	XXX	XX	XXX	XX	XXX	XX
Obese (≥30)	XXX	XX	XXX	XX	XXX	XX
Regular smoker						
Yes	XXX	XX	XXX	XX	XXX	XX
No	XXX	XX	XXX	XX	XXX	XX
Alcohol consumption (units per week)						
0-7 units	XXX	XX	XXX	XX	XXX	XX
8-14 units	XXX	XX	XXX	XX	XXX	XX
15-21 units	XXX	XX	XXX	XX	XXX	XX
More than 21 units	XXX	XX	XXX	XX	XXX	XX
Employment status						
Full-time employed	XXX	XX	XXX	XX	XXX	XX
Part-time employed	XXX	XX	XXX	XX	XXX	XX
Self-employed	XXX	XX	XXX	XX	XXX	XX
Unpaid work	XXX	XX	XXX	XX	XXX	XX
Unemployed	XXX	XX	XXX	XX	XXX	XX
Full-time student	XXX	XX	XXX	XX	XXX	XX
Carer	XXX	XX	XXX	XX	XXX	XX
Retired / looking after home / inactive	XXX	XX	XXX	XX	XXX	XX
Type of employment (if employed)						
Unskilled Manual	XXX	XX	XXX	XX	XXX	XX
Skilled Manual	XXX	XX	XXX	XX	XXX	XX
Unskilled Non-Manual	XXX	XX	XXX	XX	XXX	XX
Skilled Non-Manual	XXX	XX	XXX	XX	XXX	XX
Professional	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
Medical history						
Taking any medication before injury						

No	XXX	XX	XXX	XX	XXX	XX
Yes	XXX	XX	XXX	XX	XXX	XX
Any further diagnosed medical condition						
No	XXX	XX	XXX	XX	XXX	XX
Yes	XXX	XX	XXX	XX	XXX	XX
Medications before injury						
Fluroquinolone Antibiotics	XXX	XX	XXX	XX	XXX	XX
Steroids	XXX	XX	XXX	XX	XXX	XX
DMARDs	XXX	XX	XXX	XX	XXX	XX
Diabetic Medication	XXX	XX	XXX	XX	XXX	XX
Regular Analgesia (e.g. Paracetamol, anti-inflammatory)	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
Previous medical conditions						
Diabetes	XXX	XX	XXX	XX	XXX	XX
Rheumatoid Arthritis	XXX	XX	XXX	XX	XXX	XX
Lower Limb Fracture (last 12 months)	XXX	XX	XXX	XX	XXX	XX
Ligament, tendon or nerve injury to lower limb (last 12 months)	XXX	XX	XXX	XX	XXX	XX
Arthritis	XXX	XX	XXX	XX	XXX	XX
Achilles tendinopathy	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
Study site (See Appendix C)						
Site 1	XXX	XX	XXX	XX	XXX	XX
Site 2	XXX	XX	XXX	XX	XXX	XX
Site 3	XXX	XX	XXX	XX	XXX	XX
Site 4	XXX	XX	XXX	XX	XXX	XX
Site 5	XXX	XX	XXX	XX	XXX	XX
Site 6	XXX	XX	XXX	XX	XXX	XX
Site 7	XXX	XX	XXX	XX	XXX	XX
Site 8	XXX	XX	XXX	XX	XXX	XX
Site 9	XXX	XX	XXX	XX	XXX	XX
Site 10	XXX	XX	XXX	XX	XXX	XX
Site 11	XXX	XX	XXX	XX	XXX	XX
Site 12	XXX	XX	XXX	XX	XXX	XX
Site 13	XXX	XX	XXX	XX	XXX	XX
Site 14	XXX	XX	XXX	XX	XXX	XX
Site 15	XXX	XX	XXX	XX	XXX	XX
Site 16	XXX	XX	XXX	XX	XXX	XX
Site 17	XXX	XX	XXX	XX	XXX	XX
Site 18	XXX	XX	XXX	XX	XXX	XX
Site 19	XXX	XX	XXX	XX	XXX	XX
Site 20	XXX	XX	XXX	XX	XXX	XX
Site 21	XXX	XX	XXX	XX	XXX	XX
Site 22	XXX	XX	XXX	XX	XXX	XX
Site 23	XXX	XX	XXX	XX	XXX	XX

Site 24	XXX	XX	XXX	XX	XXX	XX
Site 25	XXX	XX	XXX	XX	XXX	XX
Site 26	XXX	XX	XXX	XX	XXX	XX
Site 27	XXX	XX	XXX	XX	XXX	XX
Site 28	XXX	XX	XXX	XX	XXX	XX
Site 29	XXX	XX	XXX	XX	XXX	XX
Site 30	XXX	XX	XXX	XX	XXX	XX
Site 31	XXX	XX	XXX	XX	XXX	XX
Site 32	XXX	XX	XXX	XX	XXX	XX
Site 33	XXX	XX	XXX	XX	XXX	XX
Site 34	XXX	XX	XXX	XX	XXX	XX
Site 35	XXX	XX	XXX	XX	XXX	XX
Site 36	XXX	XX	XXX	XX	XXX	XX
Site 37	XXX	XX	XXX	XX	XXX	XX
Site 38	XXX	XX	XXX	XX	XXX	XX
Site 39	XXX	XX	XXX	XX	XXX	XX

BMI- Body Mass Index

Table 5: Baseline characteristics according to intervention group and overall sample (continuous variables)

	Functional brace			Plaster cast			Overall		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Days since injury	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
Age (years)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
Height (cm)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
Weight (kg)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
BMI (kg/m^2)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
Cigarettes (per day)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
Years of smoking	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
ATRS (pre-injury)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
EQ VAS (pre-injury)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X
EQ VAS (post-injury)	XXX	XX.X	XX.X	XXX	XX.X	XX.X	XXX	XX.X	XX.X

BMI- Body Mass Index; SD- Standard Deviation; EQ VAS – EuroQol visual analogue scale

5.4 Unblinding

The patients and treating clinicians will not be blinded to the treatment, as the type of rehabilitation used is clearly visible. Details on blinding are presented in Section 3.2.

5.5 Description of Compliance with Intervention

Following randomisation, one group of patients will receive a functional brace (walking boot) and one group will receive a plaster cast. One aspect of compliance is expected to be cross-over at baseline between treatments and a change of treatment during the follow-up period.. Treatment compliance is defined as accepting the allocated treatment for a duration of six weeks or more following randomisation. The compliance with treatment will be reported by treatment group and summarised where possible with reasons for not receiving the assigned treatment as per Table 6 and 7. Fisher exact test or chi-squared test will be used to test the association between compliance and treatment group. Table 8 presents details on the treatment received.

Table 6: Details of compliance with intervention for each treatment arm

	Functional brace		Plaster cast		Total	
	n	%	n	%	n	%
Intervention received						
Treatment to which was allocated	XXX	XX	XXX	XX	XXX	XX
Different treatment	XXX	XX	XXX	XX	XXX	XX
Cross-over (immediate switch)	XXX	XX	XXX	XX	XXX	XX
Change of treatment (non-immediate switch)	XXX	XX	XXX	XX	XXX	XX
Surgery	XXX	XX	XXX	XX	XXX	XX
Other treatment	XXX	XX	XXX	XX	XXX	XX
Time point when intervention was changed (weeks)[1]						
Baseline	XXX	XX	XXX	XX	XXX	XX
2 weeks	XXX	XX	XXX	XX	XXX	XX
4 weeks	XXX	XX	XXX	XX	XXX	XX
6 weeks	XXX	XX	XXX	XX	XXX	XX
8 weeks	XXX	XX	XXX	XX	XXX	XX
Later than 8 weeks	XXX	XX	XXX	XX	XXX	XX

[1]*median, IQR*

Table 7: Reasons why allocated treatment was changed in each treatment arm and overall

	Functional brace		Plaster cast		Total	
	n	%	n	%	n	%
Reason for cross-over (immediate switch)						
Patient requested to receive another intervention	XXX	XX	XXX	XX	XXX	XX
Clinical decision to offer patient a different intervention	XXX	XX	XXX	XX	XXX	XX
Other reason						
Reason 1	XXX	XX	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX	XXX	XX
…						
Reason for change of treatment (non-immediate switch)						
Patient requested to receive another intervention	XXX	XX	XXX	XX	XXX	XX

Clinical decision to offer patient a different intervention	XXX	XX	XXX	XX	XXX	XX
Other reason	XXX	XX	XXX	XX	XXX	XX
Reason 1	XXX	XX	XXX	XX	XXX	XX
Reason 2	XXX	XX	XXX	XX	XXX	XX
…						

Table 8: Details of treatment received for each intervention arm and overall

	Functional brace		Plaster cast		Total	
	n	%	n	%	n	%
Number of weeks at which patient is allowed to fully bear weight[1]	XXX	XX	XXX	XX	XXX	XX
Baseline	XXX	XX	XXX	XX	XXX	XX
2 weeks	XXX	XX	XXX	XX	XXX	XX
4 weeks	XXX	XX	XXX	XX	XXX	XX
6 weeks	XXX	XX	XXX	XX	XXX	XX
8 weeks	XXX	XX	XXX	XX	XXX	XX
More than 8 weeks	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
Number of weeks at which brace/cast is removed[1]	XXX	XX	XXX	XX	XXX	XX
2 weeks	XXX	XX	XXX	XX	XXX	XX
4 weeks	XXX	XX	XXX	XX	XXX	XX
6 weeks	XXX	XX	XXX	XX	XXX	XX
8 weeks	XXX	XX	XXX	XX	XXX	XX
More than 8 weeks	XXX	XX	XXX	XX	XXX	XX
Other	XXX	XX	XXX	XX	XXX	XX
Number of heel wedges[1]	XXX	XX	N/A	N/A	N/A	N/A
Baseline	XXX	XX	N/A	N/A	N/A	N/A
2 weeks	XXX	XX	N/A	N/A	N/A	N/A
4 weeks	XXX	XX	N/A	N/A	N/A	N/A
6 weeks	XXX	XX	N/A	N/A	N/A	N/A
8 weeks	XXX	XX	N/A	N/A	N/A	N/A
Boot make						
Donjoy	XXX	XX	N/A	N/A	N/A	N/A
Samson	XXX	XX	N/A	N/A	N/A	N/A
Aircast	XXX	XX	N/A	N/A	N/A	N/A
Other	XXX	XX	N/A	N/A	N/A	N/A
The number of plaster changes over 8 weeks[1]	N/A	N/A	XXX	XX	N/A	N/A
VTE prophylaxis[1]	XXX	XX	XXX	XX	XXX	XX
LMWH	XXX	XX	XXX	XX	XXX	XX
Warfarin	XXX	XX	XXX	XX	XXX	XX
Other oral anticoagulant	XXX	XX	XXX	XX	XXX	XX
Duration of treatment[1]	XXX	XX	XXX	XX	XXX	XX

[1]*median, IQR*

5.6 Reliability

To ensure consistency, validation checks of the data will be conducted. This will include checking for duplicate records, checking the range of variable values and validating potential outliers by comparing with CRFs and referring back to sites if necessary. Calculations for derived variables will be checked by hand calculations (where appropriate). This check will be conducted for a minimum of 5% of the available data or 20 participants (whichever is smaller) randomly sampled from the dataset. These checks will also confirm whether the data has been imported into the statistical software correctly and will check any merging of different datasets. Clarification will be sought from the trial office in the case of discrepancies.

For each variable, missing value codes will be checked for consistency and the proportion of missing values per variable will be presented. Patterns of missing data will be explored. Where missing data imputation is used, imputed values will also be verified using the validation techniques described above and sensitivity analyses will be conducted to explore the missing data assumptions.

6. ANALYSIS

6.1 Outcome Definitions

Primary outcome

The primary outcome measure for this study is the *ATRS* [21] at 9 months after injury**.** The ATRS is a validated self-reported questionnaire, which 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. Each item in the ATRS questionnaire varies from 0 (major limitations/symptoms) to 10 (no limitations/symptoms) on an 11-point scale. The final ATRS will be derived from the sum of the 10 questions with a total possible score between 0 and 100. This value reaches a plateau between 6 and 9 months after rupture [21]. The ATRS in this study will be collected at baseline (pre-injury) and at the 8 week, 3, 6 and 9 month follow-up. Where individual ATRS items are missing a total score will be calculated from the available items as long as at least half of the ATRS items are present, otherwise the total ATRS score will be treated as missing. The validity and reliability of this outcome measure has been previously published [21, 23].

Secondary outcomes

The secondary outcomes in this trial are *ATRS* (measured at 8 weeks, 3 and 6 months), *EQ-5D-5L*, *complications* and *resource use*.

The *EQ-5D-5L* is a validated, generic health-related quality of life measure consisting of EQ-5D descriptive system with 5 dimensions each with a 5-level answer possibility and EQ-5D visual analogue scale (EQ-5D VAS) a health thermometer scale. The EQ-5D-5L 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 where 1 represents perfect health and 0 indicates death [26]. The Health Thermometer Scale (EQ-5D VAS) takes values between 0 and 100, where 0 represents worst imaginable health and 100 best imaginable health. It has good test-retest reliability and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes. The EQ-5D-5L is collected at 8 weeks, 3, 6 and 9 months after the injury.

Complications are recorded from medical notes at the 8 week review when the cast/brace is removed and self-reported by the patient at 3, 6 and 9 months after injury. Complications include re-rupture, blood clots/emboli, pressure areas/hindfoot pain, falls and neurological symptoms in the foot.

The *resource use* data will be used to conduct a prospective economic evaluation of the difference in the cost of resource inputs used by the participants in the two trial arms from an NHS and personal social services perspective and is collected at 8 weeks, 3, 6 and 9 months after the injury.
A brief overview of the planned assessments and data collection is included in Table 9 and Appendix B.

Table 9: Planned assessments at each time point

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, VTE Prophylaxis, treatment details	Hospital Site Staff
3 months (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.
6 months (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.
9 months (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.

6.2 Analysis Methods

Primary outcome

The primary outcome ATRS at 9 months after randomisation will be calculated and reported for each of the two treatment groups, walking boot and plaster cast. The main findings of the trial will be reported as the difference on the ATRS between the two treatment arms, estimated with a linear mixed effects (LME) regression model, including outcome information from all follow-up points and adjusting for site, age, gender, baseline ATRS and other important prognostic variables. As individual clinicians will treat only a small number of patients, important clinician-specific effects are not expected, but recruiting centre will be included in the model as a random effect factor to adjust for potential cluster differences. Estimates of treatment effects will be presented with 95% confidence intervals (CI). Tests will be two sided and considered to provide evidence for a significant difference if p-values to three decimal places are less than 0.05 (5% significance level).

Where severe departure from normality is identified (i.e. by checking residuals), the first approach will be data transformation or the use of a different metric such as change from baseline to attain normality. If the data cannot be transformed to reflect normality, then the Mann-Whitney U test will be used (in this case, no further adjustments will be made) and the medians and IQRs will be reported for each treatment arm.

An unadjusted analysis will be undertaken to assess the differences between treatment groups using a Student t-test, based on a Normal approximation for the ATRS score. Estimates of treatment effects will be presented with 95% CIs for both unadjusted and adjusted analyses as per Table 10. The ITT fully adjusted analysis of the primary outcome will be used to determine the success or otherwise of the trial. Sensitivity analyses will be conducted to explore different analysis populations and missing data approaches as detailed in Section 6.3 and 6.4.

Table 10: Analysis of primary outcome ATRS at 9 months (ITT population)

	Functional brace		Plaster cast		Difference (95% CI)		P
	Mean (SD)	n	Mean (SD)	n	Unadjusted	Adjusted*	
Primary outcome ATRS	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	XXX

**adjusted for site, age, gender, baseline ATRS and other important prognostic variables*

Supplementary analysis

In order to explore recovery in the two treatment groups over time, a further analysis of the ATRS will be conducted. This will summarise longitudinal data collected at all four time points to a single value, the area under the curve (AUC) [27] and will facilitate comparison of the ATRS between treatment groups over time. Parameter estimates from the mixed effects models described earlier will be used to calculate AUCs for each treatment group from baseline to the 9 month follow-up. This will provide an overall estimate of recovery over time in each group. Larger ATRS scores are associated with fewer limitations/difficulties related to the injured Achilles tendon, therefore larger AUCs will be suggestive of improved function. AUCs for each treatment group and their difference calculated using a t-test will be presented together with their associated 95% CI (see Table 11). The *lincom* command in Stata may be used to calculate AUC for each group. This analysis will also be conducted for EQ-5D score and EQ-5D VAS.

Table 11: AUC analysis of ATRS and EQ-5D-5L (ITT population)

	Functional brace	Plaster cast		
	AUC (95% CI)	AUC (95% CI)	Difference (95% CI)	P
ATRS	XXX (XX, XX)	XXX (XX, XX)	XXX (XX, XX)	X
EQ-5D score	XXX (XX, XX)	XXX (XX, XX)	XXX (XX, XX)	X
EQ-5D VAS	XXX (XX, XX)	XXX (XX, XX)	XXX (XX, XX)	X

Secondary outcomes

Continuous secondary outcomes (ATRS and EQ-5D-5L) will be evaluated and analysed on an ITT basis using the methodology described for the primary outcome above. Results will be reported at each intervening time points as per Table 12.

Table 12: Analysis of continuous secondary outcomes (ITT population)

	Functional brace		Plaster cast		Difference (95% CI)		
	Mean (SD)	n	Mean (SD)	n	Unadjusted	Adjusted*	P
ATRS							
8 weeks	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
3 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
6 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
EQ-5D score							
8 weeks	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
3 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
6 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
9 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X

EQ-5D VAS							
8 weeks	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
3 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
6 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
9 months	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X

**adjusted for site, age, gender, baseline covariate and other important prognostic variables*

Complications in each of the treatment arms will be reported as numbers (with percentages) and compared at 8 weeks, 3, 6 and 9 months using a Fisher's exact or chi-squared test (see Table 13). The results will be reported with their associated 95% CI and p-values for comparison between the two treatment groups. The population for this analysis will be ITT (see Section 4.2). Complications may be further grouped for analysis.

Table 13: Analysis of complications (ITT population)

	Functional brace		Plaster cast		Odds Ratio	
	n	%	n	%	(95% CI)*	P
8 weeks						
Overall	XXX	XX	XXX	XX	XX	XX
Tendon re-rupture	XXX	XX	XXX	XX	XX	XX
DVT	XXX	XX	XXX	XX	XX	XX
PE	XXX	XX	XXX	XX	XX	XX
Falls						
Fall - no injury	XXX	XX	XXX	XX	XX	XX
Fall - injury sustained	XXX	XX	XXX	XX	XX	XX
Other complications (following treatment)						
Complication 1	XXX	XX	XXX	XX	XX	XX
Complication 2	XXX	XX	XXX	XX	XX	XX
…	…					
Pressure areas/hindfoot pain / neurological symptoms in the foot (on the day)						
Pain under the heel	XXX	XX	XXX	XX	XX	XX
Numbness around the foot	XXX	XX	XXX	XX	XX	XX
Pressure sores	XXX	XX	XXX	XX	XX	XX
Other complications (on the day)						
Complication 1	XXX	XX	XXX	XX	XX	XX
Complication 2	XXX	XX	XXX	XX	XX	XX
…	…					
3 months						
Overall	XXX	XX	XXX	XX	XX	XX
Tendon re-rupture	XXX	XX	XXX	XX	XX	XX
Blood clots/emboli					XX	XX
Blood clots in the leg	XXX	XX	XXX	XX	XX	XX
Blood clots in the chest	XXX	XX	XXX	XX	XX	XX
Falls						
At least one fall	XXX	XX	XXX	XX	XX	XX
Injury from fall	XXX	XX	XXX	XX	XX	XX
Pressure areas/hindfoot pain / neurological symptoms in the foot (on the day)						

Pain under the heel	XXX	XX	XXX	XX	XX	XX
Numbness around the foot	XXX	XX	XXX	XX	XX	XX
Pressure sores	XXX	XX	XXX	XX	XX	XX
Other complications (in the past 4 weeks)						
Complication 1	XXX	XX	XXX	XX	XX	XX
Complication 2	XXX	XX	XXX	XX	XX	XX
…	…					
6 months	XXX	XX	XXX	XX	XX	XX
…	…					
9 months	XXX	XX	XXX	XX	XX	XX
…	…					

**adjusted for site, age, gender, baseline covariate and other important prognostic variables*

6.3 Missing data

The patterns of data availability for primary and secondary outcomes from baseline to end of follow-up, will be summarised for the two treatment groups (functional brace and plaster cast) as well as reasons for missingness where known. The nature and pattern of missing data (missing completely at random – MCAR; missing at random – MAR; or missing not at random – MNAR) will be explored.

The primary outcome ATRS is expected to have low levels of item missingness. Validation rules will ensure that data are entered in the correct format, within valid ranges, minimising the chance of missing data. Where ATRS item responses are missing and at least half of the items are present, a pro-rata estimation of the ATRS score will be imputed based on the average (mean or median values, depending on the data distribution for the overall group) of the available ATRS item responses. The extent of pro-rata estimation will be reported for each treatment group.

Missing continuous primary and secondary outcomes may be imputed using multiple imputation (MI) where the MAR assumption holds, allowing sufficient generality to include baseline variables thought to be important predictors.

6.4 Sensitivity Analysis

Primary outcome

Sensitivity analyses to examine the robustness of conclusions to different assumptions will be conducted for the CACE population defined in Section 4.2 and using multiple imputation for missing forms, where appropriate. Further sensitivity analysis for the definition of compliance with treatment will evaluate outcome data for the population compliant with treatment for 2 weeks or more, and 4 weeks or more. The results will be reported as illustrated in Table 14.

Table 14: Sensitivity analysis of primary outcome ATRS at 9 months (CACE population)

Duration complying with treatment	Functional brace		Plaster cast		Difference (95% CI)		P
	Mean (SD)	n	Mean (SD)	n	Unadjusted	Adjusted*	
6 weeks or more	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
4 weeks or more	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X
2 weeks or more	XXX (XX)	XX	XXX (XX)	XX	XXX (XX, XX)	XXX (XX, XX)	X

**adjusted for site, age, gender, baseline covariate and other important prognostic variables*

Secondary outcomes

The secondary outcome EQ-5D-5L analysis described in Section 6.2 will be repeated for the compliant (CACE) population as defined in Section 4.2. Results will be presented as per Table 12.

6.5 Pre-specified Subgroup Analysis

There are no planned subgroup analyses for any of the follow-up primary or secondary outcomes.

6.6 Supplementary/ Additional Analyses and Outcomes

No supplementary analysis are planned.

6.7 Harms

Serious adverse events (SAEs) are defined as *any untoward and unexpected medical occurrence that is fatal, life-threatening, requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or 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 meetings.

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. A comparison of SAEs between the functional bracing and plaster cast groups will be assessed by examination of 95% confidence intervals for the difference in incidence. The analysis will be conducted for the ITT population as defined in Section 4.2.

6.8 Health Economics and Cost Effectiveness (where applicable)

The statistician is not undertaking this analysis. A separate health economics analysis plan (HEAP) will be written by the trial health economist and all cost effectiveness analysis will be undertaken following that plan by the health economist.

6.9 Meta-analyses (if applicable)

There is no planned meta-analysis in this study

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome and key secondary outcomes a statistician not involved in the trial will independently repeat the analyses detailed in this SAP, by using different statistical software (if possible). The results will be compared and any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Final Statistical Report). If necessary this will include derivation of the primary (ATRS at 9 months) and key secondary outcomes (ATRS at 8 week, 3, 6 and 9 month follow-up; EQ-5D-5L and complications) from raw data.

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report.

9. REFERENCES

Provide references for nonstandard statistical methods

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Current UKSTAR Data Management Plan location: Z:\KC_UKSTAR\UKSTAR eTMF V3.0\Data Management\Data Management Plan\UKSTAR_DMP_V3.0_17May2018.docx**.**

Trial Master File and Statistical Trial Master File:

- UKSTAR TMF location: Z:\KC_UKSTAR
- UKSTAR Statistical TMF location: N:\OCTRU CONFIDENTIAL\STATS\OCTRU Trials - Funded\UK-STAR

Standard Operating Procedures to be adhered to:

- STATS-001 Statistical Analysis Plan
- STATS-003 Statistical Programming and Analysis
- STATS-005 Final Statistical Report
- STATS-007 Trial Results Analysis
- GEN-002 Document Control

APPENDIX A: GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ATR	Achilles Tendon Rupture
ATRS	Achilles Tendon Rupture Score

AUC	Area Under the Curve
BMI	Body Mass Index
CACE	Complier Average Causal Effect
CI	Confidence Interval
CONSORT PRO	Consolidated Standards of Reporting Trials for Patient Reported Outcomes
CRF	Clinical Reporting Form
CSM	Centre for Statistics in Medicine
DSMC	Data and Safety Monitoring Committee
DMSP	Data Management and Sharing Plan
EQ-5D-5L	EurQol (5 levels)
EQ VAS	EQ Visual Analogue Scale
HEAP	Health Economics Analysis Plan
HTA	Health Technology Assessment
ISAP	Interim Statistical Analysis Plan
ITT	Intention to Treat
IQR	Interquartile Range
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
MCID	Minimum Clinically Important Difference
MI	Multiple Imputation
NHS	National Health Service
NIHR	National Institute for Health Research
OCTRU	Oxford Clinical Trials Research Unit
PP	Per-protocol
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
STAR	Study of Tendo Achilles Rupture
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
QALY	Quality Adjusted Life Year

APPENDIX B: CRFS AND QUESTIONNAIRES

Visit schedules and time point for diaries, forms and questionnaires are provided in Table 16 below. The questionnaires used to measure the primary outcome (ATRS) and some of the secondary outcomes (EQ-5D-5L) are also provided here and their coding regimes indicated.

Table 16. UKSTAR visit schedule and time points for diaries, forms and questionnaires

	Baseline	Randomisation	8 weeks	3 months	6 months	9 months

Baseline questionnaire	✓					
Participant contact details form	✓					
Randomisation form		✓				
8 weeks questionnaire			✓			
3 months questionnaire				✓		
6 months questionnaire					✓	
9 months questionnaire						✓
*DVT / PE form**	✓	✓	✓	✓	✓	✓
*Protocol deviation form**	✓	✓	✓	✓	✓	✓
*SAE form**	✓	✓	✓	✓	✓	✓
*Death notification form**	✓	✓	✓	✓	✓	✓
*Withdrawal form**	✓	✓	✓	✓	✓	✓

*These forms are event dependent and therefore are not included in the following tables.

8 Week Questionnaire

UKSTAR participant study number: S T – ☐☐☐ – ☐☐☐☐

Form 4: 8 Weeks Follow Up

Please complete this form in black ballpoint pen

Form 4: 8 weeks FU

Section A: Randomisation Details

To be completed for all patients.

A1. Which intervention was the patient randomised to?

Walking Boot ☐ Plaster Cast ☐

A2. Did the patient *initially* receive the intervention they were randomised to?

Yes ☐ No ☐

If no please indicate reason below

Patient declined to receive allocated intervention ☐

Clinical decision to offer patient a different intervention ☐

Other ☐

If Other, Details: _____

Section B: Patients treated in a Walking Boot

The following section should be completed for:

- *Patients who were **randomised to and received** a **walking boot** as per randomisation. (Includes those who changed treatment at a later date).*
- *Patients who, on rare occasions, were **randomised to a plaster cast** but were **switched immediately** to a **walking boot** following randomisation.*

B1. Date of initial appointment when patient was put into walking boot:

D D / M O N / Y Y Y Y

B2. Date of 8 week follow up appointment:

D D / M O N / Y Y Y Y

B3. How many heel wedges did the patient have at each of the following time points?
(Please select one box only for each time point)

	3 Wedges	2 Wedges	1 Wedge	No Wedges
Baseline	☐	☐	☐	☐
2 weeks	☐	☐	☐	☐
4 weeks	☐	☐	☐	☐
6 weeks	☐	☐	☐	☐
8 weeks	☐	☐	☐	☐

UKSTAR Form 4: 8 Weeks FU 02 of 18 Version 2.0 24Oct2016

UKSTAR participant study number: S T – ☐☐☐ – ☐☐☐☐

Form 4: 8 weeks FU

B4. After how many weeks was the patient allowed to fully weight bear? ***(Please select one box only)***

Baseline	☐	6 weeks	☐
2 weeks	☐	8 weeks	☐
4 weeks	☐	Still not allowed	☐
Other	☐		

If Other, Details: _____

B5. After how many weeks was the walking boot removed?

2 weeks	☐	8 weeks	☐
4 weeks	☐	Still not removed	☐
6 weeks	☐	Other	☐

If Other Details: _____

B6. What brand of walking boot did the patient receive? ***(Please select one box only)***

Donjoy	☐	Aircast	☐
Samson	☐	Other	☐

If Other Details: _____

B7. During treatment did the patient then switch from the walking boot to another intervention?

Yes ☐ No ☐

If Yes please indicate reason below

Patient requested to receive another intervention ☐

Clinical decision to offer patient a different intervention ☐

Other ☐

If Other Details: _____

If the answer to question B7 is "No" please continue to section D.

B8. When was the intervention changed? ***(Please select one box only)***

2 weeks	☐
4 weeks	☐
6 weeks	☐
8 weeks	☐
Other	☐

If Other Details: _____

UKSTAR Form 4: 8 Weeks FU 03 of 18 Version 2.0 24Oct2016

UKSTAR participant study number: S T – ___ – ____

Form 4: 8 weeks FU

B9. **What was the intervention changed to?**

Plaster Cast ☐
Other ☐
If Other Details: _____

Section C: Patients treated in a Plaster Cast

The following section should be completed for:

- *Patients who were **randomised to and received a plaster cast** as per randomisation. (Includes those who changed treatment at a later date).*
- *Patients who, on rare occasions, were **randomised to a walking boot** but were **switched immediately** to a **plaster cast** following randomisation.*

C1. **Date of initial appointment when patient was put into plaster cast:**

D D / M O N / Y Y Y Y

C2. **Date of 8 week follow up appointment:**

D D / M O N / Y Y Y Y

C3. **How many plaster cast changes took place over the 8 weeks?**

0 ☐ 3 ☐
1 ☐ 4 ☐
2 ☐ 4+ ☐

C4. **After how many weeks was the patient allowed to fully weight bear? *(Please select one box only)***

Baseline ☐ 8 weeks ☐
2 weeks ☐ Still not allowed ☐
4 weeks ☐ Other ☐
6 weeks ☐ If Other, Details: _____

C5. **After how many weeks was the plaster cast removed?**

2 weeks ☐ 8 weeks ☐
4 weeks ☐ Still not removed ☐
6 weeks ☐ Other ☐
If Other, Details: _____

UKSTAR participant study number: S T – ☐☐☐ – ☐☐☐☐

Form 4: 8 weeks FU

C6. **During treatment did the patient then switch from the plaster cast to another intervention?**

Yes ☐ No ☐

If Yes please indicate reason below

Patient requested to receive another intervention ☐

Clinical decision to offer patient a different intervention ☐

Other ☐

If Other, Details: _____

If the answer to question C6 is "No" please continue to section D.

C7. **When was the intervention changed?** ***(Please select one box only)***

2 weeks ☐ 8 weeks ☐

4 weeks ☐ Other ☐

6 weeks ☐ If Other, Details: _____

C8. **What was the intervention changed to?**

Walking Boot ☐

Other ☐

If Other Details: _____

UKSTAR participant study number: S T – ☐☐☐ – ☐☐☐☐

Form 4: 8 weeks FU

Section D: VTE Prophylaxis

The following section should be completed for all patients. If a patient experienced a DVT/PE and received any treatment for this then this should be recorded on a separate Form 5 (DVT/PE form).

D1. : Did the patient receive treatment with VTE prophylaxis?

Yes ☐ No ☐

D2. : If Yes, what type of treatment did they receive? *(Please select one box only)*

LMWH ☐ ⇒ Details: _____
Warfarin ☐
Other oral anticoagulant ☐ ⇒ Details: _____

D3. : If Yes, what was the duration of treatment in weeks?

Weeks ☐

Section E: Complications at 8 week visit

The following section should be completed for all patients.

E1. : Following treatment did the patient suffer any of the following complications?

	No	Yes	
Tendon Re-Rupture	☐	☐ ⇒	If the patient had surgery please send an anonymised copy of the operation note.
DVT	☐	☐ ⇒	Please complete form 5 (DVT/PE form)
PE	☐	☐ ⇒	Please complete form 5 (DVT/PE form)
Fall - no injury	☐	☐	
Fall – injury sustained	☐	☐	
Other	☐	☐	

Other, Details: _____

E2. : Is the patient suffering with any of the following complications today (i.e. at the 8 week visit)?

	No	Yes
Pain under the heel	☐	☐
Numbness around the foot	☐	☐
Pressure sores	☐	☐
Other	☐	☐

Other, Details: _____

Name: *(Print)* _____ Date: DD/MON/YYYY

Signature: _____

UKSTAR Form 4: 8 Weeks FU 06 of 18 Version 2.0 24Oct2016

Achilles Tendon Rupture Score (ATRS) Questionnaire

Today's Date: ☐☐ ☐☐☐ ☐☐☐☐ Participant Number: ☐☐ – ☐☐☐ – ☐☐☐☐

UKSTAR Study of Tendo Achilles Rehabilitation

Achilles Tendon Rupture Score

Please answer the following questions as to how you were **BEFORE YOUR INJURY.**

All questions refer to your limitations/difficulties related to your injured Achilles tendon.

Mark with an X in the box which matches your level of limitation!

1. Are you limited due to decreased strength in the calf/Achilles tendon/foot?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

2. Are you limited due to fatigue in the calf/Achilles tendon/foot?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

3. Are you limited due to stiffness in the calf/Achilles tendon/foot?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

4. Are you limited due to pain in the calf/Achilles tendon/foot?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

5. Are you limited during activities of daily living?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

Today's Date: ☐☐ ☐☐☐ ☐☐☐☐ Participant Number: ☐☐ – ☐☐☐ – ☐☐☐☐

Achilles Tendon Rupture Score (Continued)

Please answer the following questions as to how you were **BEFORE YOUR INJURY.**

All questions refer to your limitations/difficulties related to your injured Achilles tendon.

Mark with an X in the box which matches your level of limitation!

6. Are you limited when walking on uneven surfaces?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

7. Are you limited when walking quickly up the stairs or up a hill?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

8. Are you limited during activities that include running?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

9. Are you limited during activities that include jumping?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

10. Are you limited in performing hard physical labour?

0 = Major limitations/symptoms **10 = No limitations/symptoms**

0	1	2	3	4	5	6	7	8	9	10

EQ-5D-5L Questionnaire

Today's Date: ☐☐ ☐☐☐ ☐☐☐☐ Participant Number: ☐☐ – ☐☐☐ – ☐☐☐☐

UKSTAR Study of Tendo Achilles Rehabilitation **EQ-5D-5L** Please answer the following questions as to how your health state is **TODAY.**

Under each heading, please place a cross in ONE box that best describes your health TODAY.

Mobility
- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

Self Care
- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

Pain/ Discomfort
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

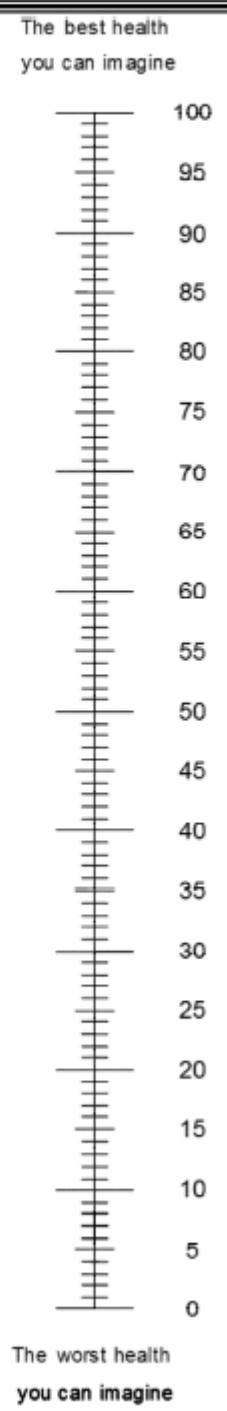
Anxiety/ Depression
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Today's Date: ☐☐ ☐☐☐ ☐☐☐☐ Participant Number: ☐☐ – ☐☐☐ – ☐☐☐☐

EQ-5D-5L (Continued) Please answer the following questions as to how your health state is TODAY.

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Complications Questionnaire

UKSTAR Study of Tendo Achilles Rehabilitation

Complications

1. In the last 4 weeks (since your 8 week check-up visit) did any of the following complications occur?

	Yes	No
A re-tear of the tendon	☐	☐
Blood clot in the leg	☐	☐
Blood clot in the chest	☐	☐
Did you fall?	☐	☐
If you fell did you injure yourself?	☐	☐

2. Thinking about <u>today only</u> are you still suffering with any of the following complications?

	Yes	No
Pain under the heel	☐	☐
Numbness around the foot	☐	☐
Pressure sores	☐	☐

3. In the last 4 weeks (since your 8 week check-up visit) did you experience any other complications?

(Please state) .....

.....

4. If you experienced any other complications how were these treated? Please provide further details below, including any hospital admissions, medications or changes to your treatment plan (e.g. a longer than expected period of time in your plaster cast or walking boot)

.....

.....

.....

	Yes	No
5. Are you still wearing your plaster cast/walking boot?	☐	☐

APPENDIX C: STUDY SITES

Site number	Site name
1	Aberdeen
2	Airedale
3	Alexandra Hospital
4	Burton
5	Cambridge
6	Doncaster and Bassetlaw
7	Dundee
8	East and North Herts
9	Epsom and St Helier
10	George Eliot Hospital
11	Glasgow
12	Hereford
13	Hull
14	Imperial
15	Inverness
16	James Paget University Hospital
17	Kings College Hospital
18	Leeds
19	Luton
20	Maidstone and Tunbridge Wells
21	Mid Yorkshire
22	Milton Keynes
23	Musgrove Park, Taunton
24	North Tees
25	Northern Lincolnshire and Goole
26	Nottingham University Hospitals NHS Trust
27	Oxford
28	Plymouth
29	Rotherham
30	Royal Berkshire Hospital Reading
31	Royal Cornwall
32	Salford
33	Salisbury
34	South Warwick
35	Southampton
36	United Lincolnshire
37	University Hospital Birmingham
38	Whiston Hospital
39	Wythenshawe Hospital, South Manchester