Clinical trial results:
Tendinopathy treatment effects and mechanisms 1 (TEAM 1): A randomised clinical trial of eccentric loading, high volume injection and shock wave therapy for Achilles tendinopathy.

Summary

EudraCT number	2015-000196-27
Trial protocol	GB
Global end of trial date	31 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	9744

Additional study identifiers

ISRCTN number	ISRCTN75305839
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	QMUL - JRMO
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Burtles, QMUL, +44 02078827260, sponsorsrep@bartshealth.nhs.uk
Scientific contact	Burtles, QMUL, +44 02078827260, sponsorsrep@bartshealth.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	22 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2020
Global end of trial reached?	Yes
Global end of trial date	31 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overarching aim is to test the effectiveness and cost effectiveness of Radial Shock Wave Therapy (RSWT) and High Volume Image Guided Injection (HVIGI) when added to usual practice (progressive eccentric loading - EL).

The primary aim will be realised by a three-centre, three-armed randomised clinical trial of EL (usual treatment) compared to EL plus RSWT and HVIGI plus EL. The primary outcome measure will be the Victorian Institute of Sport Assessment – Achilles (VISA-A), a well validated and reliable measure of function and recent pain at twelve months. Subjects will be stratified by activity level.

To identify a clinically meaningful difference between groups of 15 on the VISA-A at a power of 90% and a significance level of 2.5% (Bonferroni correction for multiple comparisons) at the twelve month post treatment follow-up we will recruit 180 participants. Subsequent follow-ups at one and two years will assess long-term treatment effects.

Protection of trial subjects:

Participants had access to trial team contact numbers and email addresses should the need any assistance. Participants were provided with information leaflets and exercise diaries indicating acceptable levels of pain following interventions. Policies and procedures were in place in respect to injections provided within radiology departments.

Radial shock wave therapy (RSWT) is approved for treating Achilles tendinopathy by NICE provided audit is undertaken of effects, and side effects, for every patient. The trial will effectively do this to a greater extent than our current clinical service. Further, our follow-up will be more extensive than the current ASSERT protocol, which the lead researcher helped design.

High volume image guided injection (HVIGI) has not been subject to rigorous evaluation as yet. Two trials have completed but these have not fully reported (in Leeds NCT01583504, and Denmark). It has been subject to 5 published case series with no reports of significant negative effects, and is routine clinical care at the participating sites. The technique was developed at the London Hospital and related sites, and the first reports were delivered by the lead researcher. The MHRA algorithm shows this is a CTIMP, and initial advice from the MHRA is that this trial is a type A CTIMP, as the injectates are being used for a common application. Hydrocortisone acetate or aprotinin have additionally been used in some studies. We will not use these as there are theoretical risks associated and we have emerging evidence from two trials of no difference in effect.

Barts Health NHS trust / QMUL policies and procedures were followed for all untoward events

Background therapy:

Achilles tendinopathy (AT) is common, recurrent, painful and limits the activity of those affected. It causes substantial direct NHS costs and substantial indirect costs due to reduced physical activity participation. There are consequential effects on occupation and exercise for health. Taken collectively, tendinopathies are the second most common problem seen by physiotherapists in the NHS. Tendinopathies are typically slow to respond to conservative treatment, usually consisting of progressive eccentric loading (EL), a form of muscle contraction while lengthening with good evidence. No established interventions have high success rates. We do not know why some people improve and others do not. Surgery often has unsatisfactory outcomes, many side effects and long recovery periods.

The first line of management is usually conservative. An exercise programme that emphasises eccentric loading (EL) is a specific exercise regime where the triceps surae is loaded as it lengthens – rather than

statically or as it shortens. We recently demonstrated that there is strong evidence for application of a three-month EL programme and for shock wave therapy.(1) Further, we found that physiotherapists are typically aware of, and apply, the evidence for this protocol which is now established as best usual care. These interventions typically result in only 60-80% of participants returning to full activity.

Evidence for comparator:

Recent advances have suggested that two intermediate interventions – shock wave therapy (SWT) and high volume image guided injection (HVIGI) – have the potential to improve outcomes for people with tendinopathy. SWT typically involves three treatments, one week apart, and is increasingly accepted into mainstream practise with stage ll clinical trials demonstrating some efficacy. HVIGI has only been subject to evaluation by case series with some encouraging findings of statistically significant and clinically meaningful improvements on well-validated outcome measures.

SWT:

Rompe JD, Furia J, Maffulli N. Eccentric loading versus eccentric loading plus shock-wave treatment for midportion achilles tendinopathy: a randomized controlled trial. The American journal of sports medicine. 2009;37(3):463-70.

HVIGI:

Chan O, O'Dowd D, Padhiar N, Morrissey D, King J, Jalan R, et al. High volume image guided injections in chronic Achilles tendinopathy. Disability and rehabilitation. 2008;30(20-22):1697-708.

Crisp T, Khan F, Padhiar N, Morrissey D, King J, Jalan R, et al. High volume ultrasound guided injections at the interface between the patellar tendon and Hoffa's body are effective in chronic patellar tendinopathy: A pilot study. Disability and rehabilitation. 2008;30(20-22):1625-34.

Humphrey J, Chan O, Crisp T, Padhiar N, Morrissey D, Twycross-Lewis R, et al. The short-term effects of high volume image guided injections in resistant noninsertional Achilles tendinopathy. Journal of science and medicine in sport / Sports Medicine Australia. 2010;13(3):295-8.

Morton S, Chan O, King J, Perry D, Crisp T, Maffulli N, et al. High volume image-guided Injections for patellar tendinopathy: a combined retrospective and prospective case series. Muscles, ligaments and tendons journal. 2014;4(2):214-9.

Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy:

Actual start date of recruitment	01 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 185
Worldwide total number of subjects	185
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	185
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date trial opened to recruitment: 17/12/2015
Date first randomisation: 07/01/2016
Date of last randomisation: 21/12/2018
Target Recruitment: 180
Trial Status: Completed
Number recruited: 185
Number of sites that have recruited: 3

Bartshealth: 171
Homerton University Hospital: 12
Royal Free Hospital: 2

Pre-assignment

Screening details:

Screened for eligibility (n=524),
Excluded (n=339)
- Pre-screen failures - Not meeting inclusion criteria (n=85)
- Screened failures – Not meeting inclusion criteria (n=126)
- Declined to participate (n=72)
- No contact (n=56)

Randomised (185)

Period 1

Period 1 title	Baseline to 12 months (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Independent assessor was blinded to trial arm during final 12 month assessment.

Arms

Are arms mutually exclusive?	Yes
Arm title	EL - Progressive Eccentric Loading

Arm description:

All patients receive a progressive loading intervention with eccentric loading as a key element. A pain monitoring model is used to determine progression of rehabilitation, and patients enter the rehabilitation at the level of difficulty determined by their pain.

Arm type	Active comparator
Investigational medicinal product name	Exercise - Eccentric Progressive Loading
Investigational medicinal product code	
Other name	Exercise Therapy, Loading, Eccentrics, Progressive Loading
Pharmaceutical forms	Not assigned
Routes of administration	External use

Dosage and administration details:

Progressive Loading - 8 supervised exercises sessions over 12 weeks with addition of home exercise programme.

Arm title	EL+SWT

Arm description:

SWT treatment to be administered with settings at 10 Hz with intensity starting at 2.2 bar and increasing, dependent upon patient tolerance levels (pain monitoring model). The treatment duration is 4 minutes, and patients will be provided post-treatment advice as per clinical routine management.

Arm type	Experimental

Investigational medicinal product name	Extracorporeal Shockwave Therapy
Investigational medicinal product code	
Other name	Shockwave
Pharmaceutical forms	Not assigned
Routes of administration	Extracorporeal use

Dosage and administration details:

Key points from SOP: V4.0 TEAM 1 Shockwave Administering SOP 10022020

1.Administering clinician to confirm consent as per departmental guidelines prior to treatment. *Note participant has already consented to treatment prior to randomisation for trial purposes*
2. Explain rationale behind treatment to patient as appropriate.
3. Clinician to ensure the shockwave machine is plugged in and suitable for use. Check the water bottle is empty.
4. Device switched on, first treatment settings 10.0Hz, 2500 pulses, R15 silver probe, Ramp ON and starting from 2.8 Bar
7. Patient to be informed that treatment may be uncomfortable (up to 5/10 on the pain monitoring model is fine) advised to liaise with clinician
11. If well tolerated at 2.8 Bar then dose can be increased incrementally as per pain monitoring model.
13. Patient to be informed that three consecutive weekly appointments required. A one week gap is not ideal but is permissible.

Arm title	EL+HVIGI

Arm description:

Patients are injected with 40 mL of injectable normal saline, mixed with 10 mL of 0.5 % bupivacaine hydrochloride. This is typically administered once, via ultrasound-guided injection to the area immediately adjacent to the primary.

Arm type	Experimental
Investigational medicinal product name	High Volume Image Guided Injection
Investigational medicinal product code	
Other name	HVIGI
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

The preparation and administration of the injection requires the following steps:
- Under sterile conditions and using a giving set;
- Using a 10ml syringe with (for example) a male luer lock fitting and a (for example) a green 21 gauge 40mm needle the local anaesthetic is drawn up;
- Four further 10ml syringes have 10ml each of normal saline drawn up and set aside;
- The local anaesthetic is then attached to a tube with (for example) a female luer lock with a (for example) green 21 gauge 40mm needle also attached;
- The needle is inserted between, but not into, the Achilles and the Kager’s fat pad under ultrasound guidance to ensure needle positioning deep to the main site of maximum pathology, without insertion into the tendon itself;
- The first 10ml syringe is then administered, followed by up to four syringes (as tolerated by patient) of normal saline. If the patient cannot tolerate the full 50mls then this is not classified as a protocol deviation.

Number of subjects in period 1	EL - Progressive Eccentric Loading	EL+SWT	EL+HVIGI
Started	60	62	63
6 Weeks Follow-Up	52 [1]	52 [2]	53 [3]
12 Weeks Follow-Up	48 [4]	46 [5]	55 [6]
6 Month Follow-Up	48 [7]	46 [8]	51 [9]
Completed	56	56	56
Not completed	4	6	7

Consent withdrawn by subject	2	1	-
Did not start intervention after randomisation	2	3	3
Pregnancy	-	-	1
Lost to follow-up	-	2	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Numbers entered at 'started' are the total numbers recruited, subsequent milestone numbers are for those who completed the follow-ups minus those who withdrew or were lost to follow-up. The 'completed' number accounts for all the participants who attended and completed the final 12 month review minus those who withdrew or were lost to follow-up.

Baseline characteristics

Reporting groups	
Reporting group title	EL - Progressive Eccentric Loading
Reporting group description:	
All patients receive a progressive loading intervention with eccentric loading as a key element. A pain monitoring model is used to determine progression of rehabilitation, and patients enter the rehabilitation at the level of difficulty determined by their pain.	
Reporting group title	EL+SWT
Reporting group description:	
SWT treatment to be administered with settings at 10 Hz with intensity starting at 2.2 bar and increasing, dependent upon patient tolerance levels (pain monitoring model). The treatment duration is 4 minutes, and patients will be provided post-treatment advice as per clinical routine management.	
Reporting group title	EL+HVIGI
Reporting group description:	
Patients are injected with 40 mL of injectable normal saline, mixed with 10 mL of 0.5 % bupivacaine hydrochloride. This is typically administered once, via ultrasound-guided injection to the area immediately adjacent to the primary.	

Reporting group values	EL - Progressive Eccentric Loading	EL+SWT	EL+HVIGI
Number of subjects	60	62	63
Age categorical			
All participants were aged 18-64 prior to consent and randomisation			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	60	62	63
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	29	29	21
Male	31	33	42
Activity Level			
Participants were stratified based on activity levels of 'High' or 'Low'			
Units: Subjects			
High Activity	26	24	27
Low Activity	34	38	36

Reporting group values	Total		
Number of subjects	185		
Age categorical			
All participants were aged 18-64 prior to consent and randomisation			
Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	185		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	79		
Male	106		
Activity Level			
Participants were stratified based on activity levels of 'High' or 'Low'			
Units: Subjects			
High Activity	77		
Low Activity	108		

Subject analysis sets

Subject analysis set title	VISA-A Outcome Measure
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary outcome will be VISA-A score and we will test the hypothesis that there is no difference in this between the EL+HVIGI and EL alone arms over the study period using a multilevel model with random effects to account for clustering (recruitment centre) and repeated measures, and adjustment for activity level and VISA-A score at entry to the study. A similar model will be fitted to test the hypothesis that there is no difference in VISA-A score between the EL alone and EL_ESWI treatment arms. Multilevel models will also be used to investigate the effect of patient characteristics on outcomes. Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

Reporting group values	VISA-A Outcome Measure		
Number of subjects	185		
Age categorical			
All participants were aged 18-64 prior to consent and randomisation			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	185		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	79		
Male	106		

Activity Level			
Participants were stratified based on activity levels of 'High' or 'Low'			
Units: Subjects			
High Activity	77		
Low Activity	108		

End points

End points reporting groups

Reporting group title	EL - Progressive Eccentric Loading

Reporting group description:

All patients receive a progressive loading intervention with eccentric loading as a key element. A pain monitoring model is used to determine progression of rehabilitation, and patients enter the rehabilitation at the level of difficulty determined by their pain.

Reporting group title	EL+SWT

Reporting group description:

SWT treatment to be administered with settings at 10 Hz with intensity starting at 2.2 bar and increasing, dependent upon patient tolerance levels (pain monitoring model). The treatment duration is 4 minutes, and patients will be provided post-treatment advice as per clinical routine management.

Reporting group title	EL+HVIGI

Reporting group description:

Patients are injected with 40 mL of injectable normal saline, mixed with 10 mL of 0.5 % bupivacaine hydrochloride. This is typically administered once, via ultrasound-guided injection to the area immediately adjacent to the primary.

Subject analysis set title	VISA-A Outcome Measure
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary outcome will be VISA-A score and we will test the hypothesis that there is no difference in this between the EL+HVIGI and EL alone arms over the study period using a multilevel model with random effects to account for clustering (recruitment centre) and repeated measures, and adjustment for activity level and VISA-A score at entry to the study. A similar model will be fitted to test the hypothesis that there is no difference in VISA-A score between the EL alone and EL_ESWI treatment arms. Multilevel models will also be used to investigate the effect of patient characteristics on outcomes. Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

Primary: VISA-A

End point title	VISA-A

End point description:

The primary outcome will be VISA-A score and we will test the hypothesis that there is no difference in this between the EL+HVIGI and EL alone arms over the study period using a multilevel model with random effects to account for clustering (recruitment centre) and repeated measures, and adjustment for activity level and VISA-A score at entry to the study. A similar model will be fitted to test the hypothesis that there is no difference in VISA-A score between the EL alone and EL_ESWI treatment arms. Multilevel models will also be used to investigate the effect of patient characteristics on outcomes. Where appropriate, a similar approach will be applied to the analysis of secondary outcomes. All analyses will be on an intention to treat basis.

End point type	Primary

End point timeframe:

12 months from date of intervention starting.

End point values	EL - Progressive Eccentric Loading	EL+SWT	EL+HVIGI	VISA-A Outcome Measure
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	56	56	56	
Units: 100				
number (not applicable)	60	62	63	168

Statistical analyses

Statistical analysis title	VISA-A Analysis

Statistical analysis description:

The primary outcome will be VISA-A score and we will test the hypothesis that there is no difference in this between the EL+HVIGI, EL+SWT and EL alone arms over the study period using a multilevel model with random effects to account for clustering (recruitment centre) and repeated measures, and adjustment for activity level and VISA-A score at entry to the study.

Comparison groups	EL+SWT v EL+HVIGI v EL - Progressive Eccentric Loading
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Serious Adverse Events (SAEs) will be recorded in the subjects' notes, the CRF, the sponsor SAE form and reported to the Joint Research and Development Office (JRMO) within 24 hours of the site becoming aware of the event.

Adverse event reporting additional description:

If the AE is not defined as SERIOUS, the AE is recorded in the trial file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

Assessment type	Non-systematic

Dictionary used

Dictionary name	JRMO
Dictionary version	1

Reporting groups

Reporting group title	TEAM-1 - Eccentric Loading

Reporting group description:

All patients receive a progressive loading intervention with eccentric loading as a key element. A pain monitoring model is used to determine progression of rehabilitation, and patients enter the rehabilitation at the level of difficulty determined by their pain.

Reporting group title	TEAM-1 - ESWT

Reporting group description:

SWT treatment to be administered with settings at 10 Hz with intensity starting at 2.2 bar and increasing, dependent upon patient tolerance levels (pain monitoring model). The treatment duration is 4 minutes, and patients will be provided post-treatment advice as per clinical routine management.

Reporting group title	TEAM-1 HVIGI

Reporting group description:

Patients are injected with 40 mL of injectable normal saline, mixed with 10 mL of 0.5 % bupivacaine hydrochloride. This is typically administered once, via ultrasound-guided injection to the area immediately adjacent to the primary.

Serious adverse events	TEAM-1 - Eccentric Loading	TEAM-1 - ESWT	TEAM-1 HVIGI
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	3 / 62 (4.84%)	3 / 63 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer surgery	Additional description: Carcinoma, elective left radial neck dissection plus major flap reconstruction. Tonsillectomy.		
subjects affected / exposed	0 / 60 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Syncope	Additional description: Syncope in gym –Acute coronary syndrome stent required + inpatient stay		

subjects affected / exposed	1 / 60 (1.67%)	0 / 62 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fracture	Additional description: Right Tibial Plateau fracture whilst skiing		
subjects affected / exposed	1 / 60 (1.67%)	3 / 62 (4.84%)	3 / 63 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgery	Additional description: Admitted for planned kidney stone removal		
subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache	Additional description: Headache & Nausea prior to treatment - attended A+E		
subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stroke	Additional description: Right Hemispheric minor stroke and right carotid endarterectomy		
subjects affected / exposed	0 / 60 (0.00%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Fracture	Additional description: Fractured clavicle following trip on a pavement		
subjects affected / exposed	0 / 60 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	TEAM-1 - Eccentric Loading	TEAM-1 - ESWT	TEAM-1 HVIGI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 60 (40.00%)	22 / 62 (35.48%)	28 / 63 (44.44%)
General disorders and administration site conditions			

General AE's - Flu, Low back pain, Colds	Additional description: Combination of AEs reported such as flu, colds, MSK complaints that were deemed non-serious and did not require any medical intervention.		
subjects affected / exposed	24 / 60 (40.00%)	22 / 62 (35.48%)	28 / 63 (44.44%)
occurrences (all)	24	22	28

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2016	substantial amendment to our study, so we can open new sites. These include: minor changes and clarifications to the PIS, ICF and protocol. o the inclusion and exclusion criteria have been simplified and one test removed; o typographical errors amended. A change of PI at the Homerton University Hospital NHS Trust
04 December 2017	Substantial amendment 2 includes the following changes: · Addition of a new site with associated new PI, Mr Haroon Mann o Royal Free Hospital · Protocol: o Correction of an error about the ultrasound confirmation on the previous version. A formatting error meant the ultrasound confirmation moved from being in the inclusion criteria in the submitted version to exclusion criteria section. No patients have had their care or trial status affected as a result. This has been discussed with the sponsor, with the decision being to deal with this in the current amendment. o Minor clarifications to inclusion / exclusion criteria, in order to remove duplications and prevent unnecessary exclusions for irrelevant auto-immune and connective tissue diseases o Changes to site numbers and names, as outlined in the attached NoSA form o Other minor grammatical and formatting changes o Clarification of foreseeable Adverse events o Clarification of the allowed window for assessments o Clarification of the IMP administration · Notification of exercise diary template o Our exercise diary template is included as it was omitted from the previous REC application, as highlighted by an audit · An amended topic guide for the process evaluation interviews is included o This is to more closely match the information we think is important to extract from the process evaluation. · Poster · Two images with associated text are submitted to be used on social media · An amended post injection leaflet is attached, v2.0 · Notification of costs questionnaires Extension of recruitment time to allow target and follow-ups to be reached

01 May 2020	Substantial Amendment 3: The amendment includes the following changes: · Addition of a new statistician Rachael Adcock · Notification of intention to commence data analysis on completion of final participant's 12-month review (primary end-point) instead of 24 month review. · Protocol: o Minor clarification detailing the above change to data analysis plan o Minor clarification of change in 24-month review to remote assessment as per non-substantial amendment (31/03/2020)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported