Acute Rehabilitation following Traumatic anterior shoulder dISlocAtioN (ARTISAN): A Multi Centre Randomised Controlled Trial

STATISTICAL ANALYSIS PLAN

ISRCTN:	ISRCTN63184243
Funding Body:	NIHR HTA
Ethics Approval:	Gwasanaeth Moeseg Ymchwil Research Ethics Committee - 26/07/2018
SAP Version:	2
Date:	25 October 2021
Stage:	Final
Protocol version:	7.0 dated 11 October 2021

Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare products Regulatory Agency
OSIS	Oxford Shoulder Instability Score
PI	Principal Investigator
QOL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASD	Traumatic Anterior Shoulder Dislocation
TMF	Trial Master File
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

2 ADMINISTRATIVE INFORMATION

2.1 SAP revisions

SAP Version	Date and timing of revision	Details of revision
0.1 – 0.2	3 May 19	Working drafts, incorporating DMC comments
1	15 May 19	First final version
1.1	2 Jul 20	Addition of covid-19 sensitivity analysis and validation of app-based data collection. Changes to text throughout for clarity
2	25 Oct 21	Addition of exploratory causal effects models at the request of the DMC. Update to design description and analyses involving 12 month data in line with protocol v7

2.2 Roles and responsibilities

Role	Name and contact
Author of SAP	Dr Helen Parsons
Senior statistician	Dr Helen Parsons
Chief investigator	Dr Rebecca Kearney

3 INTRODUCTION

3.1 Background and rationale

The shoulder is the most frequently dislocated joint; occurring in 8.2 to 23.9 per 100,000 people per year; 95% of these are anterior dislocations. They occur when excessive forces during a traumatic event displace the humeral head frontwards, out of the shoulder socket (glenoid fossa), resulting in the joint surfaces completely losing contact. Traumatic anterior shoulder dislocation (TASD) has a bimodal distribution; males under 25 years during high impact incidents and females over 80 years during low impact incidents. This is an increasing health problem in the second peak because of our aging population.

There is no clinical consensus or high quality evidence on how best to manage TASDs. With increasing numbers, because of an aging population, and need to remain active in older age through continued participation in sporting activities, there is a pressing need for a trial to address this gap in the evidence-base. We will provide high-quality evidence regarding the nature and extent of what physiotherapy is required for the management of patients following TASD.

Full background details may be found in the protocol.

3.2 Objectives

3.2.1 Primary objective

The aim of the study is to test the hypothesis that advice and a course of physiotherapy (ARTISAN programme plus physio) for first time TASD managed non-operatively is superior to a single session of advice (ARTISAN programme alone) at six months using the Oxford Shoulder Instability Score (OSIS).

3.2.2 Secondary objective

Secondary objectives of the trial are:

- To estimate comparative cost-effectiveness (cost/QALY) of the two trial treatments, from an NHS and personal social services perspective.
- To determine the difference in complication rate (e.g. shoulder re-dislocation) in the first 12 months between the trial treatment groups.
- To quantify and draw inferences between the functional status (OSIS) of the trial treatment groups at six weeks, three and 12 months.
- To quantify and draw inferences on observed differences in the functional status (QuickDASH) of between the trial treatment groups at six weeks, three, six and 12 months.
- To quantify and draw inferences on observed differences of health related quality of life (EQ-5D-5L) between the trial treatment groups at six weeks, three, six and 12 months.
- To qualitatively explore participants' experience of receiving the trial treatments and facilitators and obstacles to adhering to them.

4 STUDY METHODS

4.1 Trial design

ARTISAN is a UK multi-centre, two-arm, parallel group, randomised controlled trial with 1:1 treatment allocation and internal pilot.

The study will run in two phases: Phase 1 (Internal Pilot) will confirm the expected rate of recruitment in a large-scale multi-centre randomised controlled trial. Phase 2 (Main phase) will be the proposed randomised controlled trial in trauma centres across the UK.

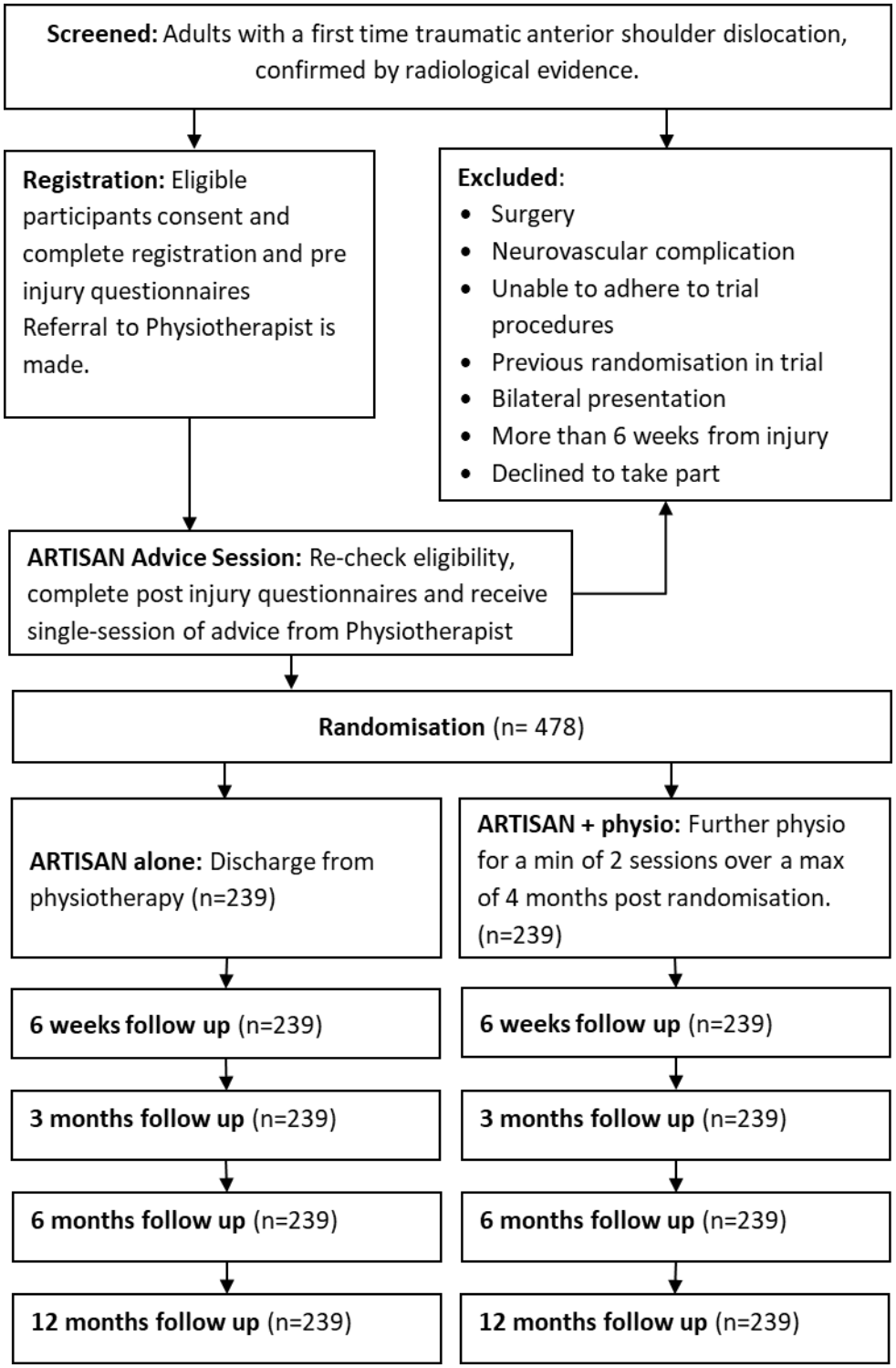
4.1.1 Amendments due to covid-19

The covid-19 pandemic has greatly impacted the ARTISAN study. These effects have included:

- Recruitment
    - study recruitment was paused during lockdown;
    - reduced capacity of site staff to recruit and deliver the study as covid-19 research took priority
    - lockdown and other social distancing measures reduced incidence of shoulder dislocation (e.g. no group sports were taking place)
- Intervention delivery
    - The format of intervention delivery may have changed as the NHS moved to remote delivery of treatment
    - Physiotherapy appointments may have been disrupted
- Study follow up
    - Both patients and staff
    - Covid may have (e.g. no group sports taking place so higher function; anxiety over covid-19 affecting wellbeing and quality of life
    - Study will end data collection in September 2022 as funder unable to grant sufficient resources to extend study further.

Detailed descriptions of the sensitivity analyses to investigate the effects of covid-19 are given in section 7.5.

4.1.2 Trial flow diagram



4.2 Interventions

The following are brief descriptions of the study interventions. Full details can be found in the protocol and the physiotherapy manual, which contains full details of the exercise "menu" covering potential exercises. Briefly, the key components of the recovery are broken into four phases:

- Phase one: education and advice
- Phase two exercises: Moving the shoulder (Table Six)
- Phase three exercises: Strengthening the shoulder (Table Seven)
- Phase four exercises: Returning to sport/advanced exercises (Table Eight)

Adherence to the allocation group will be calculated as defined as in section 5.2.1 below.

4.2.1 Control: ARTISAN alone

At registration, participants will be given a set of self-help resources in the form of a paper booklet and online links to web based materials (Phase One). They will be invited to attend a single session of physiotherapy when an ARTISAN trained physiotherapist which will cover all further phases of recovery for their injury (see above and physiotherapy manual). Exercises will be tailored to the needs of the participant and will include topics such as: pain control; graded exercises to improve function; points of contact if complications occur or expected recovery times are not achieved and returning to sport.

Participants randomised to this allocation group, will not be offered any further physiotherapy by the site.

4.2.2 Comparator: ARTISAN plus physiotherapy

Participants will be given the ARTISAN programme as described above, but will additionally be offered the opportunity of additional follow up physiotherapy sessions at the end of the first physiotherapy/advice session. No minimum number of follow up sessions is required, but only sessions within four months (120 days) after randomisation will be considered study intervention treatment. Session content will cover the same information as the self-help material (see above and physiotherapy manual.

4.3 Randomisation

After the ARTISAN programme has been delivered (see section 4.2.1), registered participants will be randomised into one of the two study groups using a web portal, with telephone back up facilities. Physiotherapists will be asked to confirm that the ARTISAN programme was delivered as per protocol as part of eligibility checks prior to randomisation.

The treatment group will be allocated on a 1:1 basis via a minimisation algorithm with a random element and stratification by participant age (39 years and under *v* 40 years and over), hand dominance (dominant *v* non-dominant).

Allocation concealment will be maintained by an independent randomisation team who will be responsible for generation of the sequence and will have no role in the allocation of participants.

4.4 Sample size

The primary outcome for ARTISAN is the Oxford Shoulder Instability Score (OSIS; see section 7.1).The standard deviation (SD) of the OSIS six months after injury is around 10 points, [1, 2] however, the

literature has predominantly included a younger population. Given that we will recruit a wider range of ages, it is likely that a larger SD is expected for this study. We have estimated required sample size with two-sided significance set at 5% for various scenarios of MCID, power and SD (Table 1). The bolded figure of 191 participants per treatment arm represents the most likely scenario, based on our current knowledge, for 90% power to detect the selected MCID. This corresponds to a small standardised effect size of 0.3.

Table 1: Study sample size. (Figures are per treatment arm)

	MCID	80% power			90% power		
		3	4	5	3	4	5
Stand. Dev	10	176	100	64	235	133	86
	12	253	143	92	338	**191**	123
	14	343	194	125	459	259	166

Allowing a margin of 20% loss during follow-up, this gives a figure of 478 participants in total. Therefore, 239 participants randomised to each group will provide 90% power to detect a difference of 4 points in OSIS at 6 months at the 5% level. [1, 3]

4.4.1 Therapist effects and clustering

This is a rehabilitation trial and the research team recognise the theoretical possibility of therapy effects. All of our recent experience at Warwick CTU of therapist delivered is that therapist effects have minimal or non-existent: BeST, BEAM and SARAH all reported ICC <0.001 or "lower than anticipated" at 12 months. [4, 5, 6] Whilst this does not completely exclude the possibility of such an effect this gives us reassurance that it is unlikely.

To address the possibility that a therapist effect may exist, we will run an interim analysis to estimate the ICC which is described in section 4.7.2.

4.5 Framework

ARTISAN is a superiority study.

4.6 Blinding

The ARTISAN study will not be blinded. This is because the type of rehabilitation used will be immediately clear to both the participant and the treating clinician.

4.7 Statistical interim analyses and stopping guidance

No interim analyses for futility or efficacy are planned in ARTISAN. However, a single interim analysis to estimate therapist effect (section 4.7.2) and a pilot phase (section 4.7.1) are planned. The trial statistician will prepare the interim analyses but will not be blind to the trial results.

The TSC and DMC retain their responsibility and ability to recommend that the trial is stopped on safety grounds at any point in the study.

4.7.1 Internal pilot phase

To ensure the successful delivery of the main phase, ARTISAN contains an internal pilot to evaluate recruitment within six months, amongst 12 pilot sites. The aim of this initial phase will be to determine the number of eligible and recruited participants in the trauma centres over the course of six months from the start of recruitment.

This pilot phase is planned to be approximately 50 participants (around 10% of the total recruitment). No separate analysis of efficacy will be made and these randomised participants will be retained in the full trial analysis.

4.7.2 Interim analysis: therapist effects

An estimate for the study ICC will be calculated, along with its 95% CI. This will be conducted after approximately 200 participants have completed the three month follow up questionnaires whilst recruitment is still open. This is expected to be around month 16 (of 23) of recruitment.

The three month data will be used as if there is a therapist effect present, we expect it would be maximal soon after the end of the treatment phase and for this to attenuate over longer term follow-up. Only values for ICC and the pooled (blinded) study standard deviation will be presented to study team, who will re-visit sample size estimation in light of these additional data. This revised sample size estimate will be discussed with DMC and TSC and if appropriate, we will request permission from the funder to adjust the sample size.

This adaptive design has the additional advantage that we will have actual data on the standard deviation of our primary outcome at three months which will allow us to further refine our sample size estimate.

4.7.2.1 Interim analysis plan

The estimate of the ICC will be via a multi-level mixed-effects model (MLM) without the treatment effect added; 95% confidence intervals will be estimated using bootstrap methods. [7]

Restricting the analysis to pooled data only is suggested best practice as described by the FDA draft guidance for Adaptive Clinical Trials [8] as it ensures control of the overall type I error rate.

4.8 Timing of final analysis

Other than analyses detailed in section 4.7 above, all analyses will take place after the final follow up data are collected. This is anticipated to be in September 2022.

4.9 Timing of outcome assessments

Timing and windows of assessments are given in Table 2.

Table 2: Trial assessments

Assessment point	Pre-Consent	Registration and baseline	ARTISAN (1st physio) session	Six week follow up	Three month follow up	Six month follow up	Twelve month follow up	Interviews
Time after randomisation ± window	-	0 (-6 wks)	0	6weeks (± 2 wks)	3months (±1m)	6months (±1m)	12months (±1m)*	>12 months
Eligibility Check	✓	✓	✓					
Written and verbal information provided	✓							
Consent and registration		✓						
Pre injury baseline CRF		✓						
Phase 1 Advice – Website and booklet		✓						
Post injury baseline CRF			✓					
Physiotherapy control			✓					
Randomisation			✓					
OSIS		✓	✓	✓	✓	✓	✓	
QuickDASH		✓	✓	✓	✓	✓	✓	
EQ5D5L		✓	✓	✓	✓	✓	✓	
Resource use				✓	✓	✓	✓	
Complications				✓	✓	✓	✓	
Interviews								✓

*Follow up window amended for participants recruited after August 21. Final follow up will be brought forward two months so that data can be collected before follow up is ended.

5 STATISTICAL PRINCIPLES

5.1 Confidence intervals and P values

Treatment effects will be presented, with appropriate 95% confidence intervals for all analyses. Unless specified, tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (i.e. a 5% significance level).

5.2 Adherence and protocol deviations

5.2.1 Adherence

Overall, due to the nature of the interventions, adherence will be assumed unless information is given otherwise; either by the physiotherapist delivering the intervention, or by the quality assurance checks performed during study recruitment. Adherence data will be summarised as shown in the dummy tables (see section 9).

Specifically, adherence to the ARTISAN programme (common control intervention, see section 4.2.1) will be recorded on the CRF by the physiotherapist after the patient has been randomised.

Participants randomised to follow on sessions will have attendance at these sessions recorded, along with which exercises were used and the dose delivered (session length for face to face and number of repetitions prescribed for at home). Participants with no follow up sessions recorded will be assumed to have not attended that appointment. However, the quality assurance process will check that an appointment was booked for all appropriate participants. After the internal pilot, participants with at least one session will also be recorded as being discharged or if another appointment was booked.

5.2.2 Protocol deviations

Protocol deviations concerning adherence, visit windows and allocation group cross overs will be presented as shown in the dummy tables (see section 9). Other deviations and violations (etc) will be reported at the request of the TMG, DMC and/or TSC.

6 TRIAL POPULATION

6.1 Screening data

Screening data will be returned to the study administration office by each site on a monthly basis (see protocol). Data will be processed and summarised by the Trial Manager and/or Data Clerk.

6.2 Eligibility

6.2.1 Inclusion criteria

Patients are eligible to be included in the trial if they meet all of the following criteria:

- Primary (first-time) traumatic anterior shoulder dislocation
- Provision of written informed consent
- They are aged 18 years or over

6.2.2 Exclusion criteria

Patients cannot be included if they meet any of the following criteria:

- Have bilateral shoulder dislocation
- Are having first line surgical treatment
- Cannot receive first session of physiotherapy within six weeks of injury
- In the opinion of the assessing clinician there is a neurovascular complication
- They are unable to adhere to trial procedures (e.g. unable to complete questionnaires)
- Have previously been randomised into the ARTISAN study.

6.3 Recruitment

Patients will only have been considered to have been entered into the study once they have been randomised. Patients who are only registered will not be considered part of the trial population.

6.4 Withdrawal/follow-up

Due to the nature of the study interventions, patients may only withdraw from follow up. However, patients may also withdraw from registration prior to randomisation, and this will also be monitored.

Where possible, the reason for withdrawal and/or loss to follow up will be ascertained and reported.

6.5 Baseline patient characteristics

Baseline characteristics will be collected in the pre- and post-injury CRFs will be summarised as shown in the dummy tables (see Table 3, section 9).

7 ANALYSIS

7.1 Outcome definitions

7.1.1 Primary outcome

The OSIS score will be calculated as the sum of item scores. For participants with one or two missing items, the missing items will be replaced with the mean of the other items. For participants with three or more missing items, the total score will be considered missing. [3, 9]

7.1.2 Secondary outcome measures

QuickDASH: The mean score of all completed items is calculated, then transformed to 0-100 score by subtracting one and multiplying by 25. One missing item is allowed, otherwise the total score is considered missing. [10]

EQ5D: The EQ5D utility score will be calculated using same value set as the Health Economic analysis which is detailed in the Health Economic Analysis Plan and protocol.

7.2 Analysis methods

Unless specified, all analyses will be taken under the intention to treat principle.

7.2.1 Primary analysis

The main analysis will investigate differences in the primary outcome measure (OSIS), six months after randomisation, between the two treatment groups. Unadjusted and adjusted regression analyses will be used to estimate the between group difference. This adjusted model will be considered the primary analysis. The model will adjust for the stratification variables, baseline scores and any other clinically important variables. More specifically, adjusted mixed-effects modelling will be used where the recruiting centre will be included as a random effect to allow for possible heterogeneity in participant outcomes due to the recruiting centre.

Since individual clinicians will treat only a small number of participants enrolled in the trial, we do not expect clinician specific effects to be important in this study and hence therapist effects will not be modelled unless shown otherwise by the interim analysis (see section 4.7.2.1). If a therapist effect is found; an adjusted mixed-effects linear regression analysis with a random effect added for each therapist will be reported as the primary analysis.

7.2.2 Secondary analyses

Descriptive statistics of participant reported outcome measure (PROM) data (i.e. QuickDash and EQ-5D-5L) at each time point will be constructed with between group analyses following the method set out for the primary analysis above. Patterns of recovery will also be explored.

Secondary analyses will include chi-squared tests to compare the number of dislocations and other complications between allocation groups. For important complications (e.g. dislocations), Kaplan Meier curves of the time to complication will be constructed. If sufficiently large numbers of these complication groups are observed, Cox regression models will be used to compare the time to complication in each arm. Other secondary functional and quality of life outcomes will also be modelled at each time point as appropriate. Temporal effects will be investigated using a multi-level model of all follow up data.

7.3 Missing data and sensitivity analyses

Whilst every effort will be made to ensure compliance and return of questionnaires, it is inevitable that some data will be missing and likely that cross-overs will occur (i.e. surgeon requesting additional physiotherapy treatment). Careful monitoring of missingness and crossovers will be conducted throughout the study.

7.3.1 Sensitivity analysis due to cross overs

If large numbers of treatment cross-overs from ARTISAN plus physio to ARTISAN alone are observed, and the required assumptions are met, a Complier-Average Causal Effect (CACE) model will be used as a sensitivity analysis. Similar to Per Protocol (PP) methods, CACE models evaluate the average effect of the intervention in participants who comply with their allocated treatment. This preserves randomisation groups and eliminates introducing any potential biases introduced when compliance and adherence are associated with the group allocation.

If large numbers of any other type(s) of treatment cross-overs are observed, a PP analysis will be performed as a sensitivity analysis instead.

7.3.2 Sensitivity analysis due to missingness

It is likely that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the missing-ness will be carefully considered, including whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities available in the statistical analysis software (as stated in section 7.7).

If imputation is undertaken, the resulting imputed datasets will be analysed, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. For example, baseline variables and scores present at other follow up points will be tested for association with missingness at the primary outcome in a stepwise manner. Variables found to be associated will be used as the basis set for the imputation model. 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.

7.3.3 Out of data collection window

Due to the decision to end follow up before all 12 month data can be collected; some participants may not have all data collected, or some data collected outside of the planned follow up window. This is expected to affect approximately 60 participants.

To include as much data as possible, analyses will use all follow data, regardless of when it was collected. However, to investigate temporal effects, a sensitivity analysis using data only collected "in window" will be performed.

7.4 Subgroups

Two pre-specified sub-group analyses will be undertaken to assess whether there is evidence that the intervention effect differs between whether:

- Hand dominance (injured shoulder dominant arm *v* injured shoulder is non-dominant arm)
- Age (younger participants *v* older participants)

The subgroup analyses will follow the methods described for the primary analysis, with additional interaction terms incorporated into the mixed-effects regression model to assess the level of support for these hypotheses.

The study is not powered to formally test these hypotheses, so they will be reported as exploratory analyses only, and as subsidiary to the analysis reporting the main effects of the intervention in the full study population. The subgroups will be presented in the final report regardless of the presence of an interaction effect.

7.4.1 Age cut point

To reflect the uncertainty in the exact break between "young" and "old" patients, prior to starting the subgroup analysis, we will inspect the age distribution of the participants. Hence, we will check our age cut off at the age which best separates the observed older and younger age distributions. If the cut point is found to be different to the randomisation stratification boundary (greater than 10 years difference), this new boundary will be used as a sensitivity analysis.

Specifically, if possible, a Gaussian Mixture Model with fixed support size (k=2) will be fit using an expectation maximisation algorithm [11] such as "normalmixEM" in the mixtools package [12]. The cut point will be defined as when the probability of membership in either distribution is 50%.

7.5 Other analyses

7.5.1 Effects of covid-19

As part of the response to the covid-19 epidemic, the NHS reduced or stopped routine follow appointments. As such, many participants, particularly in the ARTISAN plus physiotherapy allocation group, may have had disrupted physiotherapy, particularly by appointments being cancelled or being unavailable. Trial follow up may also have been affected by both trial staff and participants being unable to access postal services and participant anxiety levels may increase during the lockdown period in 2020. Furthermore, as the lockdown eases, more appointments may be offered virtually (e.g. by telephone or video conference).

Data collected before and after the lockdown started will be compared as a sensitivity analysis to explore these effects. The number of participants who may have had their treatment affected will also be calculated (i.e. those participants randomised approximately four months prior lockdown). The number and manner (where possible) of follow up physiotherapy appointments or contacts will also be summarised.

7.5.2 Validation of data collection via mobile app

As part of the response to the covid-19 lockdown, the trial management have added the option of participants returning data via mobile phone app. Descriptive statistics of participants using each

method of response will be constructed i.e. those responding via paper (postal questionnaires) and app (electronic). Rates of missing data for each method will also be calculated.

To explore if the OSIS (primary outcome) differs between paper and app questionnaires, correlations and agreement between the OSIS and other outcomes (e.g. QuickDASH and EQ5D) will be calculated for each method. Plots of recovery overtime for participants who used each method (paper, app and if appropriate, mixed responses) will be constructed to aid visual interpretation.

If sufficient uptake of the app occurs, psychometric methods will be used to estimate bias arising from the different response methods. For example, the response type will be examined for differential item functioning [13].

If any systematic differences are found during this exploration of the data, these differences will be considered as part of the primary analysis (see section 7.2.1)

7.5.3 Exploratory analyses of further contact with physiotherapy outside the trial

During the trial, a larger than expected proportion of participants have reported further contact with physiotherapy services outside of the study. To investigate this, data will be scrutinised for common patterns of contact (e.g. no contact, contact with NHS services alone, contact with private services alone) and descriptive statistics constructed for each behaviour pattern identified.

Some limited statistical modelling may also be conducted. For example, defining the intervention as the *receipt of at least one further physiotherapy contact* (or not) and a CACE model fit; or statistical models of participant behaviour and its interaction with allocation group may be constructed. All these analyses will be considered exploratory as the trial has not been powered to investigate these differences and has collected limited data for this purpose.

7.6 Harms

All expected and unexpected Serious Adverse Events (SAEs) as described in the protocol will be reported as shown in the dummy tables (see section 9). Expected, related SAEs and Adverse Events (AEs) will be reported as outcomes.

7.7 Statistical software

The study will be analysed using R (www.r-project.org) using R studio (www.rstudio.com) and Stata (Stata Corps).

Scripts will be written and stored in the Statistical Master File.

8 References

The study will be analysed as laid out in WCTU SOPs.

The electronic Trial Master File can be found at: M:\WMS\CTU\Rehabilitation\ARTISAN. This includes the most recent version of the Data Management plan, which gives details of data collection methods.

The Statistical Master File can be found at: M:\WMS\CTU\Statisticians\Helen Parsons\ARTISAN. All sensitive and confidential material is encrypted and access is limited to the Trial Statistician(s) and their nominated access back up (see: M:\WMS\CTU\Statisticians\PGP user tracker for user details).

8.1 Bibliography

[1] J. van der Linde, D. van Kampen, L. van Beers, D. van Deurzen, C. Terwee and W. Willems, "The Oxford Shoulder Instability Score; validation in Dutch and first-time assessment of its smallest detectable change," *Journal of Orthopaedic Surgery and Research,* vol. 10, no. 1, p. 146, 2015.

[2] J. Moser, K. Barker, H. Doll and A. Carr, "Comparison of two patient-based outcome measures for shoulder instability after nonoperative treatment," *Joutnal of Shoulder and Elbow Surgery,* vol. 17, no. 6, pp. 886-892, 2008.

[3] J. Dawson, K. Rogers, R. Fitzpatrick and A. Carr, "The Oxford shoulder score revisited," *Archives of orthopaedic and trauma surgery,* vol. 129, no. 1, pp. 119-23, 2009.

[4] S. Lamb, R. Lall, Z. Hansen, . E. Castelnuovo, E. Withers, V. Nichols, F. Griffiths, R. Potter, A. Szczepura, M. Underwood and BeST trial group, "A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial," *Health Technology Assessment,* vol. 14, no. 41, pp. 1-253, 2010.

[5] UK BEAM Trial Team, "United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: effectiveness of physical treatments for back pain in primary care," *BMJ,* vol. 329, no. 1377, 2004.

[6] S. Lamb, E. Williamson, P. Heine, J. Adams, S. Dosanjh, M. Dritsaki, M. Glover, J. Lord, C. McConkey, V. Nichols, A. Rahman, M. Underwood, M. Williams and SARAH Trial Team, "Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial," *Lancet,* vol. 385, no. 9966, 2015.

[7] C. Roberts and S. Roberts, "Design and analysis of clinical trials with clustering effects due to treatment.," *Clinical Trials,* vol. 2, pp. 152-162, 2005.

[8] FDA, "Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry," [Online]. Available: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. [Accessed 02 07 2020].

[9] F. R. C. A. Dawson J, "The assessment of shoulder instability. The development and validation of a questionnaire.," *J Bone Joint Surg Br,* vol. 81, no. 3, pp. 420-6, 1999.

[10] C. Kennedy, " The DASH and quickDASH outcome measure user's manual," *Institute for Work & Health,* 2011.

[11] P. Schlattmann, Medical Applications of Finite Mixture Models, Springer, 2009.

[12] T. Benaglia, D. Chauveau, D. Hunter and D. Young, “mixtools: An R Package for Analyzing Finite Mixture Models,” *Journal of Statistical Software.,* vol. 32, pp. 1-29, 2009.

[13] F. Bartloucci, S. Bacci and M. Gnaldi, Statistical Analysis of Questionnaires: a unified approach based on R and Stata, CRC Press, 2016.

9 TEMPLATE TABLES

Table 3: Baseline characteristics

Characteristic		ARTISAN programme	ARTISAN + physiotherapy	All participants
Gender (n, %)	Male			
	Female			
Age at randomisation in years (mean, SD)				
Age group	39 and under			
	40 and over			
Injured arm	Dominant			
	Non-dominant			
Mechanism of injury (n, %)	Sports			
	Non-sports			
Concurrent injury (n, %)	Yes (any)			
	Head			
	Chest			
	Abdomen			
	Pelvis			
	Spine			
	Legs			
	Injury to opposite arm			
	Injury to same arm			
BMI (mean, SD)				
Concomitant medication (n, %)	Systemic steroids			
	Pain medication pre-dislocation			
Concomitant illness (n, %)	Inflammatory arthritis			
	Diabetes			
Smoking status	Yes (n, %)			
	If yes, no. per week (mean, SD)			
	For how many years (mean, SD)			
Alcohol units per week (n, %)	0-7 units			
	8-14 units			
	15-21 units			
	>21 units			
Ethnicity (n, %)	White			
	Asian/Asian British			
	Mixed			
	Black/African/Caribbean /Black British			
	Other ethnic group			
Employment	Full time employed			
	Part time employed			
	Self-employed			
	Retired/looking after home/inactive			

	Unpaid work			
	Unemployed			
	Full time student			
	Full time carer			
Trial allocation preference	ARTISAN + physio			
	ARTISAN alone			
	No preference			

Table 4: Summary PROM data (unadjusted)

Outcome measure	**Time point**	**ARTISAN programme** (mean, SD)	**ARTISAN + physiotherapy** (mean, SD)	**All participants** (mean, SD)
OSIS	Pre injury			
	Post injury			
	Six weeks			
	Three months			
	Six months			
	12 months			
QuickDASH	Pre injury			
	Post injury			
	Six weeks			
	Three months			
	Six months			
	12 months			
EQ5D	Pre injury			
	Post injury			
	Six weeks			
	Three months			
	Six months			
	12 months			

Table 5: ARTISAN physiotherapy

		ARTISAN programme (n, %)	**ARTISAN + physiotherapy** (n, %)	**All participants** (n, %)
Time taken to deliver ARTISAN session (mins) (mean, SD)				
ARTISAN session given as per protocol (therapist report)				
Attended one or more ARTISAN follow up physiotherapy sessions				
No of follow up physiotherapy sessions attended (Median, IQR)				
Duration of follow up session (mins) (mean, SD)*				
Session types attended (n)	Individual			
	Group			
Grade of physiotherapist delivering follow on session (n, % of therapists)	Grade 5			
	Grade 6			
	Grade 7			
	Grade 8			
Time taken for attendance for follow sessions (days from 1st follow on to last) (median, IQR)				
Time from randomisation to 1st follow on session (days) (median, IQR)				
Time from randomisation to last follow on session** (days) (median, IQR)				

*protocol states each session may be up to 30 minutes

**protocol states follow up sessions must be given within 4 months (here, 120 days) from randomisation

The table below is a list of all the options given in the "exercise menu" in the Physiotherapy Manual. Other exercises may also be prescribed and will be added to this table as needed

Table 6: ARTISAN follow up physiotherapy exercises - Phase 2, range of movement exercises

Exercise	Times given at sessions (n)	Times prescribed for home (n)	Reps prescribed (median, IQR)
ROM1: Flexion in lying			
ROM2: Flexion with a stick			
ROM3: Flexion with a table			
ROM4: Flexion with a gym ball			
ROM5: Flexion with a wall			
ROM6: Flexion with a pulley			
ROM7: Abduction in lying			
ROM8: Abduction with a stick			
ROM9: Abduction with a table			
ROM10:			
ROM11: Abduction with a gym ball			
ROM12: Abduction with a wall			
ROM13: Abduction with a pulley			
ROM14: External rotation in lying			
ROM15: External rotation with a stick			
ROM16: Rotation with a table			
ROM17: Rotation with a gym ball			
ROM18: Internal rotation with a stick			
ROM19: Internal rotation with a towel			
ROM20: Extension with a stick			
ROM21: Pendula exercises			
ROM22: Other ROM exercise			

Table 7: ARTISAN follow up physiotherapy exercises - Phase 3, strengthening exercises

Exercise	Times given at sessions (n)	Times prescribed for home (n)	Reps prescribed (median, IQR)
Strength1: Thera-band extension			
Strength2: Thera-band external rotation (standing)			
Strength3: Thera-band external rotation (sitting)			
Strength4: Thera-band internal rotation (standing)			
Strength5: Thera-band internal rotation (sitting)			
Strength6: Thera-band flexion (stable surface)			

Strength7: Thera-band flexion (standing)			
Strength8: Thera-band abduction			
Strength9: Scapula setting			
Stregnth10: Glenohumeral control			
Strength11: Standing weight drop			
Stength12: Lying weight drop			
Strength13: Other strength exercise			

Table 8: ARTISAN follow up physiotherapy exercises - Phase 4, return to sport advice

Exercise	Times given at sessions (n)	Times prescribed for home (n)	Reps prescribed (median, IQR)
Adv1: floor push ups			
Adv2: Wall push ups			
Adv3: Gym ball push ups			
Adv4: Gym ball weight transfer			
Adv5: Gym ball proprioception			
Adv6: Proprioception			
Adv7: Sport specific drills			
Adv8: Falling press up, waist level			
Adv9: Falling press up, standing height			
Adv10: Other advice			

Table 9: ARTISAN follow up physiotherapy exercises – additional physiotherapy modalities

Exercise	Times given at sessions (n)	Times prescribed for home (n)	Reps prescribed (median, IQR)
PM1: Acupuncture			
PM2: TENS			
PM3: Ultrasound			
PM4: Pulsed Shortwave Diathermy			
PM5: Physiological mobilisation (e.g. Maitland)			
PM6: Accessory mobilisation (e.g. Maitland)			
PM7: Mobilisation With Movement (e.g. Mulligan)			
PM8: Taping techniques			
PM9: Hydrotherapy			
PM10: Myofascial release techniques/soft tissue mobilisation			
PM11: Muscle energy techniques			
PM12: Other modality			

Table 10: Patient reported physiotherapy

		ARTISAN programme (n, %)	**ARTISAN + physiotherapy** (n, %)	**All participants** (n, %)
Additional NHS physiotherapy visits	Yes (n, %)			
	If yes, number attended (median, range)			
Telephone NHS physiotherapy contact	Yes (n, %)			
	If yes, number made (median, range)			
Private physiotherapy sessions	Yes (n, %)			
	If yes, number attended (median, range)			

Table 11: Complications

Time point	**Complication**	**ARTISAN programme** (n, %)	**ARTISAN + physiotherapy** (n, %)	**All participants** (n, %)
Six weeks; Three months; Six months; 12 months	Shoulder surgery			
	Unscheduled hospital appointment			
	Broken/fractured shoulder			
	Re-dislocation of shoulder			
	Frozen shoulder			
	Hospitalisation for other reason			

Table 12: Summary of SAEs reported

SAE		**ARTISAN programme**	**ARTISAN + physiotherapy**	**All participants**
All reported SAEs				
SAEs per participant	1			
	2 or more			
Death (n, % of SAEs)				
Life threatening (n, % of SAEs)				
Hospitalisation or prolongation of existing hospitalisation (n, % of SAEs)				
Persistent or significant disability or incapacity (n, % of SAEs)				
Other reason (n, % of SAEs)				
Relatedness to intervention (n, % of SAEs)	Related			
	Unrelated			
If related, was the SAE expected (n, % of related SAEs)	Expected			
	Unexpected			