HEALTH ECONOMICS ANALYSIS PLAN

Acute Rehabilitation following Traumatic anterior shoulder dISlocAtioN (ARTISAN): A multi-centre randomised controlled trial

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2 Administrative information

This document describes the planned analysis of economic data within the ARTISAN trial. This Health Economics Analysis Plan (HEAP) should be read in conjunction with the ARTISAN Trial Statistical Analysis Plan and Trial Protocol which provide in detail: trial design and methods, amendments, documentation, oversight, roles and responsibilities, and the statistical plan of analysis of clinical and patient outcome measures.

3 Background

Shoulder dislocation is common in the population occurring in about 23.9 per 100,000 people [1]. Traumatic anterior shoulder dislocation (TASD) is the displacement of the humeral head from the shoulder socket. TASD has a bimodal distribution, typically in males under 25 years old often during high impact incidents, and females over 80 years old during low impact incidents [1]. Although rehabilitation may reduce re-dislocation and restore functionality to the injured shoulder, there currently no available evidence to support the effectiveness of physiotherapy in managing TASD [2]. Given the burden and costs associated with physiotherapy, the research aims to investigate the clinical and cost effectiveness of additional physiotherapy sessions in the management of TASD.

4 Trial Design

ARTISAN is a UK multi-centre randomised controlled trial of two parallel treatment arms following anterior shoulder dislocation. Randomisation is stratified by participant age (< 40 and ≥40 years old). Participants over the age of 18, able to provide informed consent with traumatic acute shoulder dislocation managed without surgical intervention are included in the study. Participants in the control arm are given a single session of advice while participants in the intervention arm will be given a single session of advice and at least one course of physiotherapy. A total of 478 participants will be recruited and randomly allocated to treatment.

The primary objective is to evaluate differences in in the Oxford Shoulder Instability Score (OSIS) between patients who receive a single session of advice and physiotherapy with a single session of advice. OSIS is a self-completed questionnaire containing 12 questions with the descriptive level of the attributes based on both frequency and severity of symptoms with a possible score of 0 (best function) to 48 (worst function) [3].The secondary objectives are to determine health-related quality of life and estimate the comparative cost effectiveness of the two trial treatments using the EQ-5D-5L; to evaluate differences in the functional status the trial treatment groups using QuickDASH; and to determine differences in complication rate in the first 12 months between the trial treatment groups. Measurements will be taken at baseline, during the first physio session, six weeks, 3 months, 6 months and 12 months after randomisation.

5 Objective

The health economic objective is to estimate the comparative cost-effectiveness of the two trial treatment groups using resource use and quality of life data from baseline to 12 months follow-up. Analysis is by intention-to-treat, presenting resource use, cost and quality of life findings by trial arm. Attention will be paid to completeness of data, identifying issues and potential remedies.

6 Economic Evaluation

In accordance with this HEAP, a prospective economic evaluation of the ARTISAN trial will be conducted from a NHS and personal social services perspective [4] following intention-to-treat principles. Using data from the ARTISAN trial and following TASD, a within-trial patient cost-effectiveness analysis will be conducted comparing advice with advice and physiotherapy. Treatment effects will be summarised at the patient level as overall cost and quality adjusted life years (QALYs). As follow-up continues for 1 year only, costs and benefits will be undiscounted.

6.1 Resource use and costs

Resource use in each arm of the trial will be captured with the case report forms (CRFs) at scheduled clinical visits and contacts. Data will be collected on health and social service use, time off work and out of pocket expenses during the period between randomisation and 12 months after randomisation. Resource use data will be collected at each follow-up time point. The cost of advice, common to both trial treatment groups, will be estimated from statistics obtained from Personal and Social Services Research Unit (PSSRU) [5]. The national average cost of a one-to-one physiotherapy session is (at the tiem of writing) £54. The cost of advice and additional physiotherapy sessions will be adjusted for physiotherapist grade and time spent.

Individual patient costs will be estimated in UK pounds sterling as the sum of resources used weighted by their reference costs, reflated to the latest common year base available. Costs of inpatient stays (in days) and outpatient visits will be estimated using the National Schedule of Reference Costs (NSRC) [6]. Community health contacts will be costed using unit costs provided by PSSRU [5]. Lost earnings will be estimated from published national average weekly earnings [7]. Medication will be costed using national Prescription Cost Analysis (PCA) averages by therapeutic [8]. Aids and adaptations will be costed using statistics from the PSSRU [5].

6.2 Outcomes

Generic health-related quality-of-life (QoL) will be assessed using the EuroQol questionnaire: a patient-completed two-page questionnaire consisting of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L includes five questions addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at five levels: from no to extreme problems. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis [9] [10], providing a single health-related index including 0 (death) and 1 (perfect health), where negative scores are possible for some health states. Patients who die during the study are subsequently scored zero at later scheduled follow-up visits for both cost and EQ-5D score and are included as observed data. The EQ VAS reports self-rated health on a vertical, visual analogue scale where 100 denotes 'best imaginable health state' and 0 denotes 'worst imaginable health state'. Quality of life measures are captured within trial CRFs during clinic visits or contacts at baseline, 6 weeks, 3 months, 6 months, and 12 months. Using the trapezoidal rule, the area-under-the-curve (AUC) of health status scores will be calculated, providing patient-level QALY estimates for the cost-effectiveness analysis. Similarly EQ-VAS will be integrated discretely over time. Since AUC estimates are predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates will be adjusted for baseline scores within regression analyses.

6.3 Analysis

Follow-up of trial participants is problematic particularly over long periods and some incompleteness of data is anticipated. Consequently, the base case analysis will use multiple imputation, to account for missing data. The base case analysis will present the imputed within trial incremental cost and QALY quality-adjusted life years (QALYs) gained, adjusted for trial covariates. Supportive sensitivity analyses will include participants with complete data and explore the impact of imputation.

Imputation will be conducted according to good practice guidance [11]. Multiple imputation provides unbiased estimates of treatment effect if data are missing at random: this assumption will be explored in the data, for example by using logistic regression for missingness of costs and QALYs against baseline variables [12]. A regression model will be used to generate multiple imputed datasets (or 'draws') for individual treatment groups, where missing values are predicted. Outcome measures and costs (at each time point) will contribute as predictors and imputed variables. The trial's age stratification variable will be included as a predictor in the imputation. Each draw provides a complete dataset, which reflects the distributions and correlations between variables. Predictive mean matching drawn from the five nearest neighbours (knn=5) will be used to enhance the plausibility and robustness of imputed values, as normality may not be assumed. The imputation model will use fully conditional (MCMC) methods (multiple imputation by chained equations), which are appropriate when missing and correlated data occur in more than one variable. Each draw will be analysed independently using bivariate regression (see below) and the estimates obtained will be pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule – a method that captures within and between variances for imputed samples [13]. To minimise the information loss of finite imputation sampling, 20 draws will be taken. The distribution of imputed and observed values will be compared visually and statistically to establish the consequences of estimation.

Bivariate regression using seemingly unrelated regression equations will be used to model incremental changes in costs and QALYs. This method respects the correlation of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored and which improve precision [14]. Baseline QOL scores will be included within all models to allow for potential baseline imbalances [15]. Joint distributions of costs and outcomes will be generated using the (non-parametric) bootstrap method, with replicates used to populate a cost-effectiveness plane. Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure) to create a new bootstrap sample from which a change in costs and QALYs are estimated. Using bias-corrected non-parametric bootstrapping, 2000 bootstraps will be taken per model or draw evaluated. Mean estimates will be reported with 95% confidence regions.

The incremental cost-effectiveness ratio (ICER) will be estimated as the difference between treatments in average total costs divided by the difference in average total QALYs. Value-for-money is determined by comparing the ICER with a threshold value, typically the NICE threshold for British studies, of £20k-30k/QALY [4]. This represents the willingness to pay for an additional QALY, and lower values than the threshold could be considered cost-effective for use in the NHS. Base case assumptions will be explored using a range of supportive sensitivity analyses, providing an assessment of the robustness of findings.

The net monetary benefit (NMB) of changing treatment will be reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (upto) the same threshold. NMB estimates will be used to generate cost-effectiveness acceptability curves (CEACs). The CEAC compares the likelihood that treatments are cost-effective as the willingness to pay threshold varies [13].

The expected value of perfect information (EVPI) is the upper limit of the value to a healthcare system of further research to eliminate uncertainty [16]. Findings from cost-effectiveness analyses remain uncertain because of the imperfect information they use. If a wrong adoption decision (to make a treatment available) is made this will bring with it costs in terms of health benefit forgone: the NMB framework allows this expected cost of uncertainty to be determined and guide whether further research should be conducted to eliminate uncertainty. If EVPI findings indicate that further research may be valuable, the analysis will be augmented with an expected value of perfect information (EVSI) analysis, giving guidance on optinal sample size.

Analyses and modelling will be undertaken in Stata 15 SE (or later release if available). Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [17]

Should costs and quality-of-life not converge within one year, more extensive economic modelling using decision-analytic methods may be considered to extend the target population, time horizon and decision context, drawing on best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. If longer term decision modelling is to be undertaken, then costs and outcomes will be discounted at 3.5% after the first year of randomisation in line with NICE reference case [4]

7 Dummy tables

In accordance with the analysis plan, planned tables and figures are described below.

7.1 Table 1: Completeness of data by follow-up visit

	Control[1] n (%, N)	**Intervention[2]** n (%, N)	**Total** n (%, N)
Health status[3]			
EQ-5D Baseline			
EQ-5D 6 weeks			
EQ-5D 3 months			
EQ-5D 6 months			
EQ-5D 12 months			
EQ-5D All visits			
Resource use[4]			
Inpatient			
Outpatient			
Community			
Personal social services			
Aids and Adaptations			
Work absence			

1 Single advice session only
2 Single advice session and at least one physiotherapy session
3 EQ-5D-5L index score
4 Range shown, lowest to highest completion at measurement points

7.2 Table 2: Health status, resource use and cost (complete cases)

	Control		Intervention		Total	
	mean	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
Health status[1]						
EQ-5D Baseline						
EQ-5D 6 weeks						
EQ-5D 3 months						
EQ-5D 6 months						
EQ-5D 12 months						
EQ-5D AUC						
Resource use (all visits)						
Inpatient days						
Outpatient visits						
Community						
GP surgery visits						
GP home visits						
GP telephone contacts						
Practice nurse contacts						
District nurse contacts						
Physiotherapy contacts						
Occupational therapy contacts						
Other community contacts						
Personal social services[2]						
Aids and Adaptations[3]						
Work absence (days)						
Medications						
Cost[4]						
A: Cost (study procedures)						
B: Cost (NHS contacts)						
C: Cost (Personal social services)						
Cost (Total, A+B+C)						

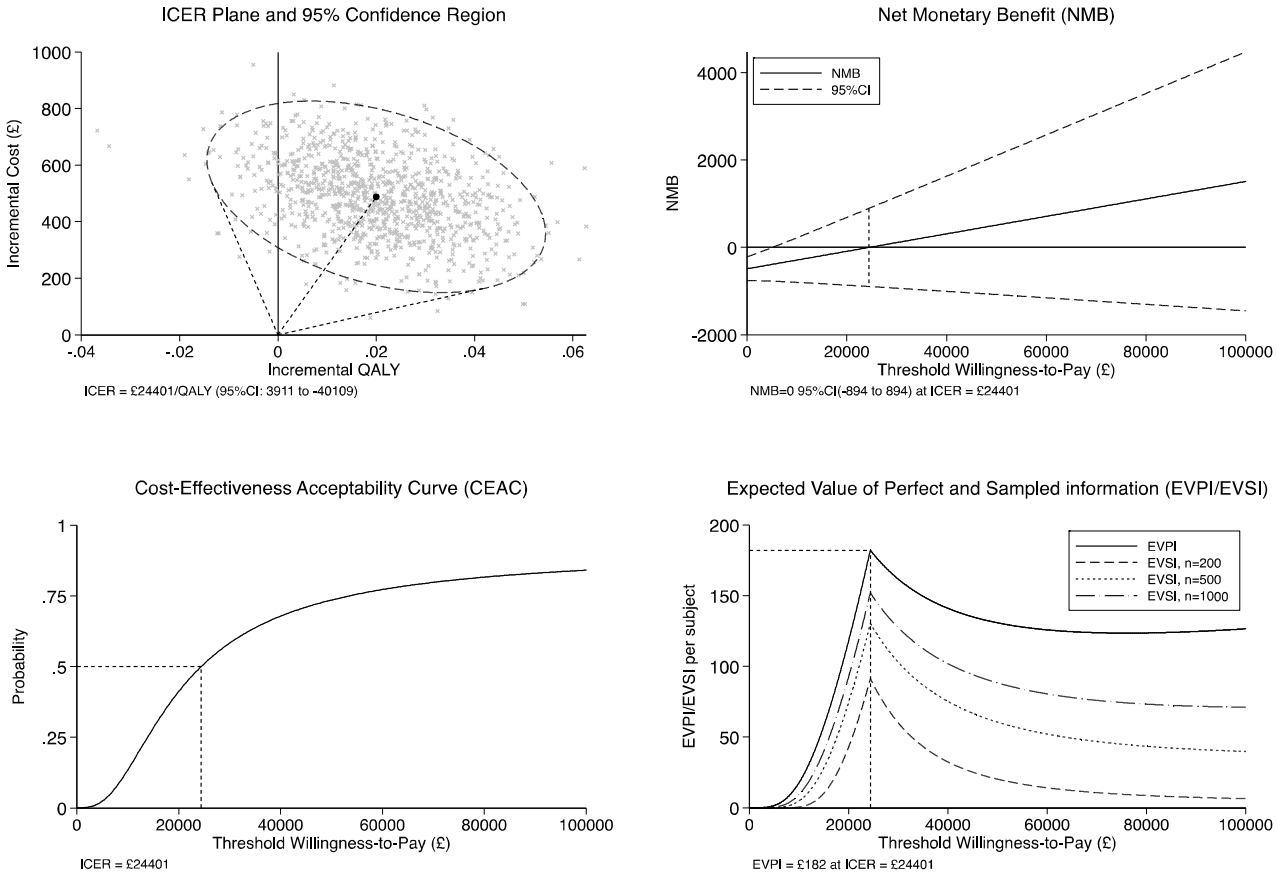
1 EQ-5D-5L index score
2 Includes: meals on wheels, laundry services, social worker, care worker, home helper and other specified contacts
3 Includes: shoulder brace, sling/collar and cuff other specified items
4 Time from work is not include in the analytic perspective, which includes health service and personal social services costs

7.3 Table 3: Cost-effectiveness, cost/QALY (£, 20xx): advice and physiotherapy compared to advice

		Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p[1]	p[2]	NMB[1]	NMB[2]
Base case								
	Imputed costs and QALYs, covariate adjusted							
Sensitivity analyses								
1	Imputed attributable costs and QALYs, baseline EQ-5D adjusted							
2	Complete case attributable costs and QALYs, covariate adjusted							
3	Base case: trial strata sub-groups							
Base case: sub-group analysis								
	Age <40 years of age							
	Age ≥40 years of age							

1 probability cost-effective or net monetary benefit if willing to pay £20,000/QALY
2 probability cost-effective or net monetary benefit if willing to pay £30,000/QALY

7.4 Figures 1-4 Presentation of base case economic analysis (illustrative example)



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