Clinical and cost effectiveness of progressive exercise compared to best practice advice, with or without corticosteroid injection, for the treatment of rotator cuff disorders: a 2x2 factorial randomised controlled trial

Health Economics Analysis Plan

V 2.0 (0.6 Nov 2019)

Based on Protocol version 5.0 (02 Jan 2019)

Trial registration: ISRCTN16539266

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1 INTRODUCTION

This document details the proposed health economics data presentation and health economic analysis for the main paper(s) and final study reports from the HTA-funded multicentre randomised controlled factorial trial to co-test two interventions commonly used in the management of rotator cuff disorders in primary care: progressive exercise delivered by a physiotherapist and corticosteroid injection. 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 cleaning 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. Currently there are no published guidelines regarding the content of the health economics analysis plans for clinical trials.

The health economics analysis plan is also designed to ensure that there is no conflict with the protocol or associated statistical analysis plan and it should be read in conjunction with those documents.

Any deviations from the economic 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 economist, 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 the previous version of HEAP

A summary of key changes from earlier versions of HEAP (Table 1), with particular relevance to protocol changes that have an impact on the health economics analysis will be provided. Include protocol version number and date.

Table 1. Changes from the previous version of HEAP

HEAP version, Issue date	HEAP author	Protocol version, Issue date	Significant changes from previous version together with reasons
V1.0_01Oct2018	May Ee Png	V4.0_14May2018	Not applicable as this is the 1st issue.
V2.0 _06Nov2019	Melina Dritsaki	V5.0_02Jan2019	After consultation with the GRASP project CI, the document was revised from the 1st Version. An introduction was added to reflect the purpose if this document. Key personnel and roles were added. Objectives were defined with a table illustration. Expected time points of the trial were included. Direct medical resource use was described in detail. A section on data reliability was added The proposed analysis was described in a way to fit the factorial design of the study based on the recommended literature. Only the section on health utilities was kept as it was written on the 1st version. The scope of the cost-effectiveness analysis was rephrased in order to reflect the four arms under investigation and their pairwise comparisons. The missing data section was

			clarified and re-written. Originally the within the tables (or inside the table) analysis was defined as the base case analysis with the at-the –margins approach and the regression analysis with and without interactions defined as secondary ones. It was agreed that inside the table analysis is similar to the regression with interactions whereas at the margins is the same as regression without interaction terms. So, the base case analysis was changed to the regression with interactions and the secondary as the regression without interactions. Table 2 was replaced to look the same as the one presented in the SAP Clarifications were added about the theoretical background behind the economic analysis within a factorial design trial in sections

2 BACKGROUND AND OBJECTIVES

2.1 Background

The annual incidence of adults consulting for a shoulder condition in the UK primary care is estimated around 2.4%, with rotator cuff disorders being the most common cause of shoulder pain (Linsell et al, 2005; Lewis, 2009). Rotator cuff disorders can persist for a long period of time while causing pain and affecting an individual's ability to work as well as perform daily tasks and social activities. However, standard care can be highly variable (from primary care to tertiary care services) and there are currently no National Institute for Health and Care Excellence (NICE) clinical guidelines. Standard care can include various combinations of rest, advice, analgesia, non-steroidal anti-inflammatory drugs, physiotherapy, and corticosteroid injections (Hopewell et al, 2017).

2.2 Objectives

The primary objective of the GRASP trial is to assess the clinical effectiveness of an individually tailored, progressive exercise programme compared with best practice advice, with or without corticosteroid injection, in patients with a new episode of shoulder pain attributable to a rotator cuff disorder at 12 months after randomisation. The secondary outcome, which is relevant here, is to evaluate the cost-effectiveness of progressive exercise alone, progressive exercise plus corticosteroid injection, best practice advice alone and best practice advice plus corticosteroid injection ***among patients with a rotator cuff disorder in this 2x2 factorial randomised controlled trial*** from the NHS and personal social services (PSS) perspective.

The statistical analysis plan makes two independent comparisons between corticosteroid injection versus no injection and between progressive exercise and best practice advice based on the assumption that there is no interaction (see Table 2). However, it is recommended that the conclusions of economic evaluations are based on incremental comparison between the individual combinations of factors considered in the trial (Dakin and Gray, 2017), following the established decision rules for mutually-exclusive interventions.(Gray et al., 2011; Karlsson et al., 1996; Drummond et al., 2005)

Table 2. GRASP treatment groups 2x2 factorial design

	Corticosteroid injection	
	No	**Yes**
Individually tailored progressive exercise programme	Group A (ProgEx)	Group C (ProgEx+I)
Best practice advice	Group B (BPA)	Group D (BPA+I)

3. Economic approach/ overview

3.1 Aim(s) of the economic evaluation

An economic evaluation will be conducted as part of the trial design. The aim of the economic evaluation is to address the question ***"what is the cost-effectiveness of progressive exercise alone, progressive exercise plus corticosteroid injection, best practice advice alone and best practice advice plus corticosteroid injection among patients with a rotator cuff disorder"***.

The within-trial economic analysis will be performed using individual patient level data from the GRASP trial. The analytical approach will take the form of a cost-utility analysis. Based on trial evidence, incremental cost-utility ratios will be calculated by taking a ratio of the difference in the mean costs and mean quality-adjusted life years (QALYs) for pairwise comparisons between treatment arms.

The trial is conducted in the UK which has a National Health Service (NHS), providing publicly funded healthcare, primarily free of charge at the point of use. The economic analysis will be from the NHS and personal social services (PSS) perspective.

The economic analysis will compare the costs and consequences of each group over the 12 months after randomisation with no extrapolation beyond the study period of 12 months.

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4. ECONOMIC DATA COLLECTION & MANAGEMENT

4.1 Trial design

GRASP is a multicentre randomised controlled trial using a 2x2 factorial randomised controlled trial. Patients will be randomised to one of the four physiotherapist-led interventions:

1) Group A: Progressive exercise programme (ProgEx): an individually-tailored progressive home exercise programme prescribed and supervised by a physiotherapist involving up to six face-to-face sessions over 16 weeks.
2) Group B: Best practice advice (BPA): one face-to-face session with a physiotherapist and a simpler home exercise programme supported by high quality self-management materials.
3) Group C: Progressive exercise programme (as described above), preceded by a subacromial corticosteroid injection (ProgEx+I).
4) Group D: Best practice advice session (as described above), preceded by a subacromial corticosteroid injection (BPA+I).

704 participants aged 18 and above with a new episode of shoulder pain (within the last 6 months) due to a rotator cuff disorder (e.g. cuff tendonitis, impingement syndrome, tendinopathy or rotator cuff tear) will be recruited from twenty primary care based musculoskeletal services and their related physiotherapy services in the UK over a 2 year period. Participants will be followed up at 8 weeks, 6 months and 12 months after randomisation.
The primary outcome is the SPADI (Shoulder Pain and Disability Index) score at 12 months post randomisation. Secondary outcomes will be collected at 8 weeks, 6 months and 12 months after randomisation.
Expected time points of the trial are shown in the table 3 below:

Table 3. Expected time points of the trial

Event	Date
Grant activation	01 Oct 2016
Trial Open (start of recruitment)	10 Mar 2017 (1st patient recruited)
End of recruitment	30 Apr 2019
Date expected end follow-up	30 Apr 2020
Expected start of final analysis	01 May 2020
End of Grant	31 August 2020

4.2 Software package

All analysis will be carried out using appropriate analytical software such as STATA, R, Microsoft Excel. The relevant package and version number will be recorded in the health economics report.

4.3 Collection of health resource data

Resource use data for the economic evaluation will be collected during the trial period from information gathered in the form of a postal questionnaires sent to participants at 8 weeks, 6 months and 12 months after randomisation into the trial.

The questionnaires will capture both NHS and Personal Social Services perspective (PSS) resource use and costs borne by the patient and their family due to shoulder pain attributable to a rotator cuff disorder. That will include the frequency of use of inpatient care, outpatient care, and community-based health (both private and NHS) that are not part of the GRASP trial. It will also record direct medical costs that are not part of the trial (e.g. medications and steroid injections), direct nonmedical costs (e.g. help with housework/childcare and travel) the latter being excluded from the base case economic evaluation These health resource questionnaires will be completed by the participant covering three survey periods (baseline to 8 weeks, 8 weeks to 6 months and, 6 months to 12 months post-randomisation).

To improve completion rate of the questionnaires, at least one postal reminder will be sent for those who do not respond to the initial postal questionnaire. A web-based version of the questionnaire, telephone and email follow-up will also be used to contact those who do not respond to the postal questionnaire. Telephone and email follow-up will be used to collect a core set of questionnaire items if these have not been fully completed on the returned questionnaire. A small monetary incentive (in the form of a gift voucher) will be sent to all participants along with their 12 month follow-up questionnaire in order to help maximise response rates for the 12 month follow-up.

4.4 Collection of unit cos

4.4.1 Direct medical cost (intervention)

Resources required for intervention delivery include injection (either triamcinolone acetonide (up to 40mg, (Kenalog) or methylprednisolone acetonide (up to 40 mg, Depomedrone)), physiotherapy sessions, information booklets, resistance bands and DVDs. The number and duration of physiotherapy sessions as well as the type of health professional who delivered them alongside his/her salary band, will be provided by trial data. Unit costs of resource use associated with trial interventions will be sourced from the Personal Social Service Research Unit (PSSRU), NHS Digital and British National Formulary (BNF) (Table 4).

Table 4. Resource use associated with trial (example suggested to be included in the final monograph)

Resource item	Progressive exercise	Best practice advice	Progressive exercise + corticosteroid injection	Best practice advice + corticosteroid injection	Unit type	Unit cost (£)	Source
Physiotherapist	✓	✓	✓	✓	hour		
Exercise diary	✓	✓	✓	✓	item		
Action planner	✓	✓	✓	✓	item		
Resistance bands	✓	✓	✓	✓	item		
DVD or online access to exercise videos	X	✓	X	✓	item		
Info booklet	✓	✓	✓	✓	item		
Corticosteroid injection	×	×	✓	✓	each		

Abbreviation: BNF = British National Formulary, PSSRU = Personal Social Service Research Unit

4.4.2. Other direct medical cost

Unit costs of direct medical cost that are not part of the trial such as inpatient care, outpatient care and NHS community care will be sourced from the latest available NHS Reference Cost (Department of Health, 2016) (Table 5).

Private care cost and any other non-NHS/PSS cost (e.g. over the counter medication) will be excluded from the base case economic evaluation, but will be tabulated in the monograph.

The unit cost of medications related to rotator cuff will be sourced using the latest available BNF (MedicinesComplete, 2018) and the Prescription Cost Analysis (PCA) for England. Costs of medications for individual participants will be estimated based on their reported doses and frequencies, when these are available, or based on an assumed daily dose using BNF recommendations. When a dose range is reported as 'as required' or when the quantities are not recorded, we will assume a mean cost for that medication item based on the prescription cost analysis values (net ingredient cost per item), assuming that each prescription lasts 28 days, or for the duration of treatment if that is less than 28 days. If the dose of the medication is missing, we will assume the patient received the same dosage as other trial participants who reported taking the same medication.

4.4.3 Direct nonmedical and indirect costs

Collection of unit costs for direct nonmedical resource items such as help with childcare, travel to appointments, help with housework and any other additional expenses because of shoulder pain incurred by the participant will be obtained directly from the postal questionnaire and tabulated in the monograph, but excluded from the base case analysis as they are beyond the NHS/PSS perspective of the economic evaluation.

4.5 Cost per patient

The cost of NHS health care resource use per patient will be computed by multiplying the frequency of health resource utilisation reported by the participant by the unit cost of each resource item

The base currency of all costs will be the most recent year for which unit cost data are available and expressed in UK pounds (£) (Table 5).

Table 5 Unit cost of NHS health care resource use data over 12 months (example suggested to be included in the final monograph)

Health care resource	Unit Cost, 2018/2019 prices, £	Source
Medication		
Medication prescribed by doctor		
Steroid Injection (not as part of GRASP)		
Primary care (NHS community based services)		
General Practitioner visit		
General Practitioner telephone contact		
General Practitioner home visit		
Practice Nurse		
Physiotherapy (further to GRASP)		
Secondary care (NHS outpatient services)		
Orthopaedic clinic (for shoulder)		
Physiotherapy department (not as part of GRASP)		
Radiology- x-rays		
Radiology-ultrasound		
Radiology- MRI scan		
Accident & Emergency		
Secondary care (NHS inpatient services)		
Inpatient care		

4.6 Health utilities

The participants' questionnaires contain the EQ-5D-5L questionnaire for self-completion at baseline, 8 weeks, 6 months and 12 months post randomisation. The EQ-5D-5L instrument (Herdman et al, 2011) facilitates the generation of a utility score from a person's health related quality of life while reducing the ceiling effect and being more sensitive than its three-level (3L) predecessor (Rabin et al, 2011). A utility score refers to the preference that individuals have for any particular set of health outcomes. As per the NICE position statement, the responses to the EQ-5D-5L will be converted into multi-attribute utility scores using an approved "cross-walk" to the 3L instrument and its established time trade-off utility algorithm for the UK, using the mapping function developed by van Hout et al (2012).

The EQ-5D-5L in the participants questionnaires was not formatted exactly according to the developer's guideline in this trial (instead of having the EQ-5D-5L descriptive system on one page and the EQ Visual Analogue Scale (VAS) on another page, the last question of EQ-5D-5L descriptive system and VAS are on the same page and the VAS is 16.6cm long instead of the recommended 20cm when printed out on paper). However, we do not believe that the participants' results will be significantly affected, as (1) the content of the instrument is not altered, and (2) we are primarily interested in differences in quality of life between the four intervention groups, and all participants will receive the same questionnaire formatted in the same way across each of the follow up time points.

QALYs will be calculated as the area under the curve connecting utility scores reported at different time points. Deceased patients will be assigned a utility of zero from the date of death; we will assume that utility remains constant between the last utility measurement and the date of death.

4.7 Data 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 where possible. As the data are collected electronically, many of these checks will be implemented automatically as part of the data entry procedure. Calculations and processes performed by a computer program, including the construction of derived data, will be checked by hand calculations. This check will be performed for 20 participants 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 (see more details below about handling missing data).

4.8 Missing data

Incomplete data are a particular issue in within-trial health economic evaluations and can result from time-point missingness. Consequently, a base-case analysis will be constructed where missing data are imputed using fully conditional MI-MC (multiple imputation under chained equations) using the STATA command mi impute chained.

Within MI-MC, regression models will be used to impute unobserved costs and utilities at each time point using the baseline covariates (age, gender, EQ-5D), as predictor variables. The imputation model will include a dummy variable for allocation to injection, a dummy variable for allocation to progressive exercise and an interaction term equal to the product of these two variables, following best practice for factorial trials (Dakin and Gray, 2017). Costs and EQ-5D utility scores at each time point will contribute as both predictors and imputed variables. The imputation will be run following the rule of thumb that the number of imputations (M) should be similar to the percentage of incomplete cases.

Multiple imputation will generate M datasets (or 'draws') using predictive mean matching (PMM). PMM provides plausible values when costs and QALYs are non-normally distributed. In line with best practice, the MI model will be validated by comparing the distributions of the imputed data with the observed data.

5 DATA ANALYSIS

5.1 Analysis of resource use, costs and outcome data

Since we will include costs rather than quantities of resources, quantities of resources used will be summarised on an available-case basis, excluding patients with missing data on that resource (Table 6).

Table 6. Intervention resource utilisation (example suggested to be included in the final monograph)

Health care resource	Progress Exercise (n, mean, SD)	Best practice advice (n, mean, SD)	Progress Exercise + corticosteroid injection (n, mean, SD)	Best practice advice+ corticosteroid injection (n, mean, SD)
Physiotherapist				
Exercise diary				
Action planner				
Resistance bands				
DVD or online access to exercise videos	**N/A**		**N/A**	
Info booklet				
Corticosteroid injection	**N/A**	**N/A**		

A breakdown of imputed resource use items will be summarised by trial allocation group over the 12-month follow-up period (Table 7)

Table 7. Resource utilisation over the 12-month follow-up period (example suggested to be included in the final monograph)

Health care resource	Progress Exercise	Best practice advice	Progress Exercise + corticosteroid injection	Best practice advice+ corticosteroid injection
Medication (n, mean, SD)				
Medication prescribed by doctor				
Medication over the counter				
Steroid Injection (not as part of GRASP trial)				
Primary care (NHS community based services) (n, mean, SD)				
General Practitioner visit				
General Practitioner telephone contact				
General Practitioner home visit				
Practice Nurse				
Physiotherapy (not as part of GRASP trial)				
Secondary care (NHS outpatient services) (n, mean, SD)				
Orthopaedic clinic (for shoulder)				
Physiotherapy department (not as part of GRASP)				
Radiology- x-rays				

Radiology-ultrasound				
Radiology- MRI scan				
Accident & Emergency				
Secondary care (NHS inpatient services)				
Inpatient care				
Private care (n, mean, SD)				
Orthopaedic clinic (for shoulder)				
Physiotherapy department				
Radiology-x-rays				
Radiology-ultrasound				
Radiology- MRI scan				
Chiropractor				
Complementary therapist				
Injections				
Non-medical costs (n, mean, SD)				

Mean health care cost by trial arm over the 12-month follow-up period after imputation, will be presented (Table 8).

Table 8. Healthcare cost (UK £) over the 12 month follow-up after multiple imputation (example suggested to be included in the final monograph)

Health care resource	Progress Exercise (n=) Mean (SE)	Best practice advice (n=) Mean (SE)	Progress Exercise + corticosteroid injection (n=) Mean (SE)	Best practice advice+ corticosteroid injection (n=) Mean (SE)
Intervention				
Exercise				
Corticosteroid injection				
8-week follow-up				
Prescribed medication				
Primary care				
Secondary care				
6-month follow-up				
Prescribed medication				
Primary care				
Secondary care				
12-month follow-up				
Prescribed medication				
Primary care				
Secondary care				
Total cost				

EQ-5D scores at each time point (including imputed values) and QALY scores will be presented (see Table 9)

Table 9. EQ-5D scores and QALYs over the 12 month follow-up after multiple imputation (example suggested to be included in the final monograph)

Health outcome	Progress Exercise (n=) Mean (SE)	Best practice advice (n=) Mean (SE)	Progress Exercise + corticosteroid injection (n=) Mean (SE)	Best practice advice+ corticosteroid injection (n=) Mean (SE)
EQ-5D-5L				
Baseline				
8 weeks				
6 months				
12 months				
QALYs				
QALYs at 12 months				
QALYs at 12 months*				

*QALY estimates to be adjusted to control for imbalances in baseline utilities between the interventions of interest

Costs and QALYs will not be discounted because of the one-year time horizon

5.2 Cost-effectiveness analyses

A within-trial cost-utility analysis will be conducted from a NHS and PSS perspective using the GRASP trial data over a 12-month time horizon.

The analysis will adopt intention-to-treat (ITT) principles and incremental cost-effectiveness ratios (ICERs) will be calculated as the difference in mean costs divided by the difference in mean QALYs between the interventions. The NICE (2013) cost-effectiveness threshold of £30,000 per additional QALY will be used to identify which of the following treatments represent best value for money (i.e. has highest net monetary benefit, NMB): (1) progressive exercise; (2) best practice advice; (3) progressive exercise plus corticosteroid injection; and (4) best practice advice plus corticosteroid injection. Measures of uncertainty (standard errors and confidence intervals) will also be reported around the mean costs and QALYs and confidence intervals will be presented around ICERs if they are defined. In addition, NMBs will be estimated for a range of different willingness to pay (WTP) thresholds.

In addition to calculating and reporting ICERs and NMBs, results will also be presented graphically in cost-effectiveness (CE) planes and cost-effectiveness acceptability curves (CEACs) showing the probability that each of the four arms of the study has highest NMB. Standard errors and cost-effectiveness acceptability curves (CEACs) will be generated via non-parametric bootstrapping with 1,000 replicates. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness-to-pay for an additional QALY.

We will make no adjustment for clustering of patients by physiotherapist when analysing costs, QALYs or cost-effectiveness since the randomisation is done on an individual basis, stratified by centre (rather than using cluster-randomisation) and injections and physiotherapy will both be delivered according to a standard protocol.

Findings of this economic evaluation will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of health economic evaluations.

Since GRASP is a factorial trial, it is important to consider the interactions, in other words to examine whether the difference in costs, QALYs or NMB between best practice advice and progressive exercise is affected by the use of corticosteroid injection. In the GRASP trial *clinical* analysis, the endpoints will be analysed "at the margins" assuming no interactions and if interaction terms will only be included in the model if interactions are significant at the 0.05 level. From the economics point of view, this approach is not appropriate as health economics findings are interpreted in terms of the magnitude of ICERs, rather than focusing on hypothesis testing.

Dakin et al., 2017 have extensively discussed challenges and methods about conducting an economic evaluation within a factorial design trial. In particular, interactions may be more likely to arise for QALYs and costs than for clinical endpoints (Dakin et al., 2017). In the case of GRASP, interactions for cost could arise if the injection affected the number of physiotherapy sessions that patients attended. Floor effects for cost and ceiling effects for EQ-5D could also introduce interactions if both treatments were highly effective – particularly since the ceiling effect is pronounced for EQ-5D-5L (Janssen et al., 2013).

Four main approaches have been proposed for analysing factorial trials: 1) at-the-margins analysis 2) regression analysis without interaction terms, 3) inside /within-the-table analysis and 4) regression analysis with interaction term. A recent simulation study (Dakin et al., 2019) has confirmed the earlier theoretical work (Dakin et al., 2017), demonstrating that using at-the-margins analysis or using a regression analysis without interaction terms can give misleading conclusions about which treatment has highest expected net benefit. The simulation study (Dakin et al., 2019) also showed that including all interactions regardless of magnitude and statistical significance minimise the opportunity cost of adopting a treatment that did not in fact have highest net benefits, while including only interactions that were statistically significant performed very poorly.

For the purpose of the GRASP trial, the base case analysis will therefore comprise regression analysis approach with an interaction term, while regression analysis without interaction terms will be used as a sensitivity analysis to assess whether the assumptions about interactions change the conclusions of the analysis. Benefits of using regression analysis in the context of factorial design trial are that it allows for variation in sample size between groups, adjusts for the effect of the other intervention, facilitates adjustment for baseline utility and can predict the mean outcomes for each cell in the factorial design.

Regression analysis with interaction term (base case analysis)

For the reasons explained above, the base case analysis of the economics evaluation of the GRASP trial will be based on regression analysis with an interaction term (Table 10).

Regression analyses predicting both costs and QALYs will be calculated for each bootstrap sample on each imputed dataset. Randomised allocation to corticosteroid and randomisation to exercise will be included as dummy variables and the base case analysis will also include an interaction between these two variables. The OLS regression predicting QALYs will also control for baseline utility to avoid the bias that would otherwise arise from any imbalance in baseline utility between groups. A total of 1000 bootstrap samples will be drawn for each imputed dataset, and means for both incremental costs and incremental QALYs (with associated 95% confidence intervals) will be calculated.

The final step will involve combining estimates from the M imputed datasets using Rubin's rule to generate an overall mean estimate of costs and QALYs, as well as the standard errors. The standard error calculated through Rubin's rules reflects the variability within and across imputations.

For the 2x2 GRASP factorial trial, the regression model predicting costs with an interaction term will take the form below:

$$y_i = \beta_o + \beta_A A_i + \beta_B B_i + \beta_{AB} A_i B_i + \varepsilon_i \qquad (1.1)\ *$$

Where,

Y_i represents the outcome measure (cost or QALY or NMB)

β_A represents the coefficient for treatment effects for exercise

β_B represents the coefficient for treatment effects for the corticosteroid injection

β_{AB} represents the interaction coefficient between exercise and corticosteroid injection

β_o represents the constant term

*Note that the QALY equation will also include baseline utility

Table 10. Results of regression analysis with an interaction term (example suggested to be included in the final monograph)

		Total cost/patient	Total QALYs/patient	NMB/patient	Cost per QALY		
					Versus A	Versus B	Versus C
Treatment effect for Progressive exercise		XXX	XX	XX	-	-	-
(SE)		XX	XX	XX	-	-	-
Treatment effect Best practice advice		XX	XX	XX	--	-	-
(SE)		XX	XX	XX	-	-	-
Interaction (exercise * injection) (SE)		XX	XX	XX	-	-	-
Constant term (SE)		XX	XX	XX	-	-	-
Predicted mean outcome (SE)	A (n=)	XX	XX	XX	-	-	-
	B (n=)	XX	XX	XX	XX	-	-
	C	XX	XX	XX	XX	XX	-

	(n=)						
	D (n=)	XX	XX	XX	XX	XX	XX

A: Progressive exercise
B: Best practice advice
C: Progressive exercise+ Corticosteroid injection
D :Best practice advice+ Corticosteroid injection

Regression analysis <u>without</u> interaction term

Regression techniques with interaction term provide an alternative to at-the-margins analysis, which also assumes no interaction (Dakin, 2017). This analysis will be used as a sensitivity analysis (Table 11).

This approach assumes that interventions are mutually exclusive. In other words, the cost and outcomes of individual tailored progressive exercise programme are assumed to not be affected by whether corticosteroid injection is given or not and vice versa.

Also, regression analysis without interaction term, although similar to at-the-margins approach, makes the prediction of group means and SEs easier (Dakin et at 2017). As interventions are assumed to be mutually-exclusive options, these predictions can help us identify which of the four treatment options (progressive exercise, best practice advice, corticosteroid injection + progressive exercise, corticosteroid injection + best practice advice) maximises NMB and also estimates the cost and effects of each option separately (see Table 12).

For the 2x2 GRASP factorial trial, the regression model for this sensitivity analysis will take the form below:

$$yi = \beta_o + \beta_A\, A_I + \beta_{\ B}\, B_\iota + \varepsilon\iota \qquad (1.2)\ *$$

Where,

Y_i represents the outcome measure (cost or QALY or NMB)

β_A represents the coefficient for treatment effects for exercise

β_B represents the coefficient for treatment effects for the corticosteroid injection

β_o represents the constant term

*Note that the QALY equation will include baseline utility

Table 11. Results of regression analysis without an interaction term (example suggested to be included in the final monograph)

		Total cost/patient	Total QALYs/patient	NMB/patient	Cost/ QALY		
					Versus A	Versus B	Versus C
Treatment effect for exercise		XXX	XX	XX	-	-	-
(SE)		XX	XX	XX	-	-	-
Treatment effect for corticosteroid injection		XX	XX	XX	--	-	-
(SE)		XX	XX	XX	-	-	-
Constant term (SE)		XX	XX	XX	-	-	-
Predicted mean outcome (SE)	A (n=)	XX	XX	XX	-	-	-
	B (n=)	XX	XX	XX	XX	-	-
	C (n=)	XX	XX	XX	XX	XX	-
	D (n=)	XX	XX	XX	XX	XX	XX

A: Progressive exercise

B: Best practice advice

C: Corticosteroid injection + Progressive exercise

D: Corticosteroid injection + Best practice advice

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