REGAIN
REHABILITATION EXERCISE AND PSYCHOLOGICAL SUPPORT AFTER COVID-19 INFECTION

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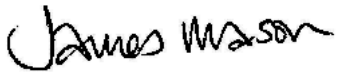
Senior health economist	 James Mason	14th Sep 2022
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The REGAIN Health Economics Analysis Plan

Purpose of health economics analysis plan

The objective of the health economics analysis is to inform decision makers regarding the cost-effectiveness of the 'Rehabilitation Exercise and psycholoGical support after covid-19 infectioN' (REGAIN) intervention compared to usual care. This entails a systematic analysis of both the costs and consequences of the two treatment pathways. The purpose of the health economics analysis plan (HEAP) is to outline the framework of methods that will be used to analyse the health economic components of the trial to ensure the integrity of the cost-effectiveness analysis.

1. Introduction

The REGAIN trial is a multi-centre two-arm randomised controlled trial (RCT) with 12-month follow-up. The trial is designed to assess the effectiveness and cost-effectiveness of an intensive, on-line, supervised, group, home-based rehabilitation programme to support long term physical and mental health recovery in patients with on-going COVID-19 sequelae more than 3 months after hospital discharge. COVID-19 has caused many people to suffer significant adverse health impacts leaving the UK facing a rehabilitation challenge. This has physical, psychological and economic consequences at an individual and societal levels. The REGAIN intervention has the potential to guide recovery and re-entry to economic productivity for those living with the longer-term consequences of COVID-19. Thus, the REGAIN trial aims to test the effectiveness and cost-effectiveness of the intensive rehabilitation programme compared to best-practice usual care. The two arms of the trial are characterised as follows:

> **Usual care/control arm**: A thirty-minute, on-line, one-to-one consultation with a REGAIN practitioner, who is trained and supported by a Health Psychologist during the study. All study participants will be directed to freely available on-line programmes published by NHS England [1].
>
> **Intervention arm**: The intervention arm consists of individual assessment and exercise familiarisation with a trained REGAIN practitioner; a supervised outpatient exercise programme over 8 weeks; psychosocial coaching and education over six weeks; and a guided home exercise plan.
>
> - The *individual assessment and exercise familiarisation* consist of a 1-hour one-to-one appointment with a REGAIN practitioner to assess the patient's current medical status and to discuss goals. This information will be used to inform the exercise prescription level given by the practitioner.
> - The *supervised home-based exercise programme.* This includes one live online group session per week lasting 45 minutes. Additionally, participants will also be asked to complete 1-2 pre-recorded online exercise sessions per week for eight weeks.
> - *Psychosocial and motivation support; and education:* participants will attend six online group sessions each lasting up to one hour.

- *Participant workbooks:* All participants will be provided with a participant workbook containing study information, intervention instructions, space for recording exercise, and psychological learning and worksheets to supplement the psychological support sessions.

1.1. General principles for the primary health economic analysis

We will adopt principles that best meet the requirements of UK decision makers. The methods of economic evaluation will therefore be guided by the National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal [2].

1.1.1 Type of economic evaluation

As recommended, the primary health economic analysis will be a cost-effectiveness analysis with incremental quality adjusted life years (QALYs) as the primary health economic outcome [2]. Following NICE guidance, the EQ-5D-5L will be used for the construction of QALYs (see section 2.1.1) [2].

1.1.2 Perspective

A healthcare and personal social services (PSS) will be adopted as recommended by NICE [2]. We will however consider wider societal costs within a sensitivity analysis.

1.1.3 Time Horizon

The primary health economic analysis will run concurrently to the effectiveness analysis. Economic outcomes will be collected at baseline, and at three, six, and 12 months post-randomisation. The time horizon will therefore be the 12-month period post-randomisation. Should outcomes not have converged after 12 months, we will consider the development of a decision analytic model to extrapolate the cost-effectiveness results over a longer-term time horizon (see section 5.5).

1.1.4 Discounting

Given the trial-based analysis has a time-horizon of 12 months, costs and QALYs will not be discounted. Should longer-term decision modelling be conducted, we will use the 3.5% annual discount rate as recommended by NICE to discount future costs and QALYs [2].

1.1.5 Clustered data structure

Participants are being randomised at the individual level. However, there may be a cluster level effect relating to the centres that each patient is recruited from. We will therefore explore the degree to which clustering occurs within the data using the intra-cluster correlation coefficient (ICC) and then choose appropriate methods (e.g. random effects model) accordingly.

1.1.6 Intention to treat

The health economic analysis will adopt the principle of 'intention to treat' [3]. This means that the health economic analysis will analyse individuals according to the trial arms to which they were randomised.

1.2. Missing data

Missing data is a common occurrence within randomised clinical trials and needs to be addressed within the health economic analysis [4]. Missing data will be explored, and if non-trivial (5% or more in either costs or QALYs) [5], the base case analysis will use multiple imputation (MI) [6] as the preferred method for estimating results in the presence of missing data. MI uses the observed data and samples from the predictive distribution to create multiple datasets [7]. Under the assumption

of missing at random, this provides unbiased estimates, allowing estimate uncertainty to be maintained whilst allowing full use of the available data (see section 5.2).

2. Outcomes

2.1. Primary health economic outcome

As recommended by NICE, incremental quality adjusted life years (QALYs) will be used as the primary outcome for the health economic analysis [2].

2.1.1. Estimating QALYs

QALYs combine both mortality and morbidity into a single measure that can be compared across different contexts within the healthcare service. To calculate QALYs it is necessary to combine a preference-based measure of health-related quality of life with time. In this study, we are using the EQ-5D-5L [8] at four time points (baseline, 3 months, 6 months, 12 months). The EQ-5D-5L is recommended by NICE for use in economic evaluation [2]. The measure contains five dimensions of health, each containing five levels. There exist value-sets [9], [10] that allow the calculation of *health preference (utility)* scores for any given set of responses to the EQ-5D-5L. A utility score is a score on an index scale, where zero equals death, one equals full health and negative scores are possible for some severely ill health states. These utility values can be combined with time to derive QALYs. Although a new UK specific EQ-5D-5L value set exists [9], it has been a subject of controversy [11]. Currently NICE instead recommends [12] the use of the Van Hout et al [10] 'cross-walk' algorithm. This however may change in the interim period between the period of writing and the date of analysis. The choice of value set will therefore be made closer to the date of analysis and will be chosen in accordance with NICE guidelines at the point of analysis.

QALYs for each participant will be calculated by using the EQ-5D-5L utility values at baseline, 3 months, 6 months and 12 months. QALYs will be calculated by linearly interpolating the four time points and calculating the area under the curve using the trapezium rule [13]. QALYs will be calculated for each patient in the trial.

3. Resource use and costing

To calculate costs for use in cost-utility analysis it is necessary to capture information on resources used for both the control and intervention arm. Costs within this trial have the following components:

- Direct intervention costs (e.g. the cost of running the group exercise session)
- Direct healthcare and PSS costs (e.g. outpatient appointments)
- Training costs (e.g. practitioner training)
- Other societal costs (e.g. absence from work)

NICE's guide to methods of technology appraisal recommend costing from an NHS and personal social services (PSS) perspective [2]. The primary analysis will only consider the first three items; broader societal costs will be included within sensitivity analysis. To calculate costs, it is first necessary to capture resource use, and then apply unit costs. The price year for the analysis will be informed by the latest available base year for common costing resources at time of analysis.

3.1. Direct intervention resource use and costs

The REGAIN intervention can be split into three components: i) individual assessment; ii) on-line, home based exercise rehabilitation and iii) psychological support. The control arm however receives only one 30-minute practitioner appointment in conjunction with direction to access freely available

on-line resources. The intervention components and associated resource use are summarised within Table 1 below. This table shows what the components are, how they will be collected and where unit cost sources may be sourced from.

Table 1: Direct intervention resource use and cost sources

Intervention arm			
Resource type	**Resource use**	**How collected**	**Unit costs source**
Individual online assessment	1 hour one to one online appointment with practitioner	Trial team	PSSRU unit costs
Supervised online group exercise session	45-minute group exercise session for eight weeks, 15 mins preparing	Trial team	PSSRU unit costs
Participant workbooks	Professionally produced workbooks	Trial team	Invoice for participant workbooks
Group psychological and motivational support session	Six sessions lasting one hour over the eight-week period	Trial Team	PSSRU unit costs
Equipment: remote facilitation - Zoom/Beam and website hosting	Subscription and website hosting costs	Trial Team	Invoice for subscriptions and hosting
Control arm			
Individual appointment	One telephone/or online appointment with practitioner lasting 30 minutes	Treatment logs	PSSRU unit costs

3.2. Healthcare and social care resource use

In accordance with NICE guidance, we will capture healthcare and PSS costs for both arms of the trial [2]. This will include, inpatient care, outpatient care, community care, accident and emergency admission, medication, and personal social services. The methods for capturing the resource use and the sources for unit costs are outlined in Table 2 below. Most of these resource use items will be captured with the online-administered case report forms (CRFs) at 3, 6 and 12 months and triangulated with medical records, whilst medication will be captured using a concurrent rolling medication log. For participants not responding to requests to complete CRFs online, core data will be collected by telephone.

Table 2: Ongoing costs for both arms – health care costs and social costs

Resource type	**Resource use**	**How collected**	**Unit cost sources**
Inpatient care	Specified within CRFs	CRFs at 3m, 6m and 12m.	NHS Reference Costs and PSSRU. HRG4+ 'Code to Group' [14] used to allocate inpatient care to HRG groups for costing.
Outpatient care	Specified within CRFs	CRFs at 3m, 6m and 12m.	NHS Reference Costs and PSSRU
Accident and emergency care	Specified within CRFs	CRFs at 3m, 6m and 12m.	NHS Reference Costs and PSSRU

Community care	Specified within CRFs	CRFs at 3m, 6m and 12m.	PSSRU and NHS Reference Costs
Medication	Specified within CRFs	CRFs at 3m, 6m and 12m.	Prescription cost analysis [15]
Personal social services	Specified within CRFs	CRFs at 3m, 6m and 12m.	PSSRU unit costs

3.3. Training costs

To deliver the intervention successfully, it is necessary to train intervention practitioners to ensure that both the supervised exercise program and the psychological intervention group sessions are delivered as intended. This requires time for both the trainers and the trainee. These training sessions will be recorded by the trial team.

Table 3: Training resource use

Resource Type	Resource use	How collected	Unit cost sources
Supervised exercise training programme	½ day for both practitioner and trainer	Recorded by trial team	PSSRU unit costs
Psychological intervention training programme	½ day for both practitioner and trainer	Recorded by trial team	PSSRU unit costs

3.4. Wider costs

Within an addition sensitivity analysis, we will also be collecting information related to days lost from work due to long covid and consequences. These will be collected online.

Table 4: Wider costs

Resource type	Resource use	How collected	Unit cost sources
Absence from work	Specified within CRFs	CRFs at 3m, 6m and 12m	ONS salary data.

3.5. Development costs

Within an additional sensitivity analysis, we will also include the costs associated with the development of the intervention materials. These will be estimated by the trail team.

Table 5: Wider costs

Resource type	Resource use	How collected	Unit cost sources
Development cost	Trial team time	Trial team estimate	UoW salary scales

4. Data integrity

Blinded descriptive data will be routinely reported and presented to the data monitoring committee (DMC), this will include the proportion of missingness of the health economic variables. Any data issues (e.g. outliers/high missingness) will be queried and followed up if necessary. The DMCs will provide an opportunity to refine data collection, if necessary. All data will be stored on secure University of Warwick servers in encrypted folders and access will be limited to those approved to use it. Subsequently at the health economic analysis stage, variables will be range-checked and implausible values queried.

5. Statistical analysis

5.1. Descriptive analysis

Resource use, costs and EQ-5D utility scores will be presented descriptively (means and standard deviations) as is good practice, and to inform parameters for future health economic studies. Costs will be calculated for all perspectives outlined previously.

5.2. Addressing missing data with multiple imputation

If missing data for either costs or QALYs is more than 5% we will use multiple imputation to impute data within the base-case analysis. This data will then be used in the incremental analysis of costs, QALYs and the joint cost-effectiveness analysis. A complete case analysis will be included as a sensitivity analysis. Stata [16] will be used to conduct both the multiple imputation and the analysis of imputed data. The 'mi impute chained' command which uses chained equations to generate imputed datasets will be used for each treatment group. Within the imputation regression framework, we will include both costs and EQ-5D-5L at each timepoint as both imputed and predictor variables. Multiple imputation provides unbiased estimates of treatment effect if data are missing at random (i.e., causes of missingness are captured within observed variables). This assumption will be explored in the data using logistic regression of the missingness of costs and QALYs against baseline variables. We will use predictive mean matching drawing from the 5 nearest 'neighbours', this is important for the avoidance of drawing implausible values, e.g., utility values over 1, and 'negative costs'. The number of iterations will be guided by the fraction of missing information [5]. Analysis of multiple draws will be conducted with Stata's MI framework providing estimation adjusted for Rubin's rule. MI estimation models will be bootstrapped to limit parametric assumptions. To minimise the information loss of finite imputation sampling, the Fraction of Missing Information (FMI) will be used to ensure the number of imputed draws exceeds the FMI percentage. We will examine the validity of the imputed data by comparing the distribution of the imputations and observed data both visually and statistically.

5.3. Single end point analysis: incremental costs and incremental QALYs

Before conducting the joint cost-effectiveness analysis, we will examine the impact of the intervention on incremental costs and incremental QALYs in isolation. Differences between the two arms will be assessed using a regression framework. The exact specification will depend upon the nature of the data. For example, should clustering be a concern then multi-level models could be specified. As recommended [13], given the impact of baseline utility values on QALYs accrued, baseline utility will be included within the regression analysis to adjust for any baseline differences in health-related quality of life. Costs will be estimated by combining resource use data with unit costs. Costs for each patient within the trial will be calculated and incremental costs between the two arms will be estimated. Again, a regression framework will be used, and its exact specification will be informed by the nature and distribution of the data. Should missingness exceed 5% we will use the multiply imputed data for this analysis.

5.4. Cost-effectiveness analysis and characterising uncertainty

Methodologically, when conducting a cost-effectiveness analysis there are several potential approaches for analysing costs and QALYs. An optimal approach has several requirements. First, it is necessary to use methods that account for correlation between costs and QALYs. That is, costs and QALYs are likely to be correlated and this needs to be accounted for in the methods chosen. Second, given QALYs accrued are often influenced by baseline utility [13], it is necessary to control for differences in baseline utility. Third, it may be necessary to account for clustering whereby

individuals within clusters are likely more similar to each other, than to individuals within different clusters.

To meet these challenges, it is anticipated that we will use bivariate regression analysis in the form of seemingly unrelated regressions (with bootstrapping) for the joint analysis of costs and QALYs. This framework offers several benefits: first of all it accounts for the existence of correlation between costs and outcomes for patients; second it allows the inclusion of covariates within the analysis, this is particularly relevant for the adjustment of baseline utility with respect to QALYs accrued; third it is generally robust to non-normal distributions; fourth, it can account for clustering either by including clusters as a fixed effect or by running the seemingly unrelated regressions in a multi-level framework . Non-parametric bootstrapping will be used to examine the level of uncertainty by presenting the bootstrapped results on a cost-effectiveness plane, and by generating cost-effectiveness acceptability curves (CEACs). Should there be distributional or computational concerns (e.g. difficulty in fitting a multi-level seemingly unrelated regression model with imputed data in Stata) then we may consider combining costs and outcomes within a (multi-level) univariate net-benefit regression framework.

5.3.1 Characterizing uncertainty for decision makers

CEACs will be used to characterise uncertainty. CEACs show the probability that the intervention is cost-effective compared to the control at different levels of willingness to pay for QALYs and explicitly highlight the uncertainty within the decision problem. To avoid the issues related to uncertainty around cost-effectiveness ratios we will calculate net-monetary benefit for each of the bootstrapped iterations:

$$\Delta NB = \Delta e\gamma - \Delta c$$

In this instance, ΔNB refers to the incremental net monetary benefit, Δe reflects the incremental outcome of interest, incremental QALYs, whilst Δc refers to the incremental costs. The symbol γ refers to the decision maker's willingness to pay per QALY. For each of the bootstrapped cost-effectiveness samples we will calculate the associated net-monetary benefit across a range of levels of willingness to pay (γ). For each γ the proportion of iterations where net-benefit is greater than zero can be used estimate the probability that the intervention is more cost-effective at that willingness to pay. This will be conducted for a range of γ including £20,000 and £30,000 per QALY as specified by NICE and plotted to derive a CEAC [2].

5.3.2. Sensitivity analyses

In addition to the probabilistic sensitivity analysis outlined above we will also consider sensitivity analyses, these will include:

- Costing from a societal perspective
- Complete case analysis (assuming missing data exceeds 5%).
- Trial randomisation strata as specified within the statistical analysis plan
- Downweighing fixed costs to simulate wider rollout
- Inclusion of development costs

5.5. Value of information analysis

We will also conduct a value of information (VoI) analysis to examine the expected value of future research. The VoI analysis will entail the calculation of the expected value of perfect information (EVPI) using data from the cost-effectiveness analysis. EVPI can be conceptualised as the expected gain from eliminating uncertainty within the decision problem, or put another way, the expected loss associated with uncertainty. This is essentially the probability of the decision being wrong

multiplied by the average consequence of being wrong [18]. This allows us to calculate the estimated value of 'perfect knowledge' which is the maximum value society should be willing to pay for additional evidence to reduce uncertainty around whether the intervention or the control is more cost-effective [19]. Using the trial data, we will calculate the per person EVPI using a willingness to pay threshold of £30,000 per QALY, representing the threshold NICE uses in practice [20]. This will be multiplied by the number of potential beneficiaries of the intervention within the NHS along with the technological horizon (years) to estimate population EVPI. Discounting of EVPI will be applied at 3.5% beyond the first year.

5.6. Decision modelling

The primary trial-based analysis will focus on the costs and QALYs accrued during the trial period. There however is potential for costs and benefits to accrue beyond the trial period. If outcomes have not converged by the 12m timepoint we will consider extrapolating the results over a longer time horizon using a decision analytic model. This would involve combining the trial data with external sources to estimate the long-term cost-effectiveness of the intervention. Any costs and benefits accruing after the first year would be discounted at a rate of 3.5% per year and full probabilistic sensitivity analysis would be conducted in line with the NICE reference case [2]. A decision as to the necessity of building a decision analytic model and its specification will be made following discussion between the health economists and the trial team following preliminary analysis of the data. This will be informed by considerations such as the conclusiveness and direction of within trial results. For example, if the control dominates the intervention and extrapolation would only increase the strength of this result then there is little need to extrapolate further as the intervention should be rejected.

6. Dummy Tables

Table 1: Completeness of data by follow-up visit

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

1.EQ-5D-5L index score
2. Range shown (3M-12M)

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

	Control		*Intervention*		*Difference*	
	mean	**(SD)**	**mean**	**(SD)**	**mean**	**(95% CI)**
Health status[1]						
EQ-5D Baseline						
EQ-5D 3 months						
EQ-5D 6 months						
EQ-5D 12 months						
QALYs						
Resource use *(all visits)*						
Inpatient days						
Nursing home days						
Outpatient visits						
A&E Visits						
Community						
GP surgery visits						
GP home visits						
GP telephone contacts						
Practice nurse contacts						
District nurse contacts						
Community Physiotherapy contacts						
Other physiotherapy contacts						
NHS Direct contacts						
Calls for ambulance/paramedic						
Occupational therapy contacts						
Other community contacts						
Personal social services[2]						
Privately funded care home						
Personal expenses						
Work absence (days)						
Medications						
Cost[3]						
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 Time from work is not included in the analytic perspective, which includes health service and personal social services costs

Table 3: Cost-effectiveness results

	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, baseline EQ-5D adjusted							
Sensitivity analyses							
1 Inclusion of societal costs							
2 Complete case analysis							
3 Base case: sub-group analyses specified in the SAP							
4 Downweighing fixed costs to simulate wider roll out							
5 Inclusion of development costs							

[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

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