HEALTH ECONOMICS ANALYSIS PLAN

Trial Title

REMEMBRIN STUDY

Trial Summary

Rehabilitation of Memory following Traumatic Brain Injury – a Phase III Randomised Controlled Trial

Trial Details

ISRCTN: ISRCTN65792154:

Study Coordination Centre: Nottingham Clinical Trials Unit

Chief Investigator: Prof. Roshan Das Nair

Study Statistician: Lucy Bradshaw

Health Economics Lead: Prof. Deb Fitzsimmons

Health Economics Researchers, Dr Shaun Harris, Ioan Humphreys

Revision History

Revision Date	Release	Summary of Changes	Changes Made by
08/2014	1.0	Initial version	DF, IH
03/2016	2.0.	Draft version	SH, IH, DF
07/2016	3.0	Draft version	SH, IH, DF
11/2016	4.0	Draft version	SH, IH, DF
12/2016	4.1	Final Version	SH, IH, DF

Agreement The following people have reviewed the Health Economics Analysis plan and are in agreement with the content.

Name	Title	Date	Version

Acronyms and definition of terms

These are the same as the definition of terms in the SAP. Where additional terms are defined these are written out in full (abbreviation in brackets) for the first time and abbreviation used subsequently.

Health economic analysis plan authorship

This health economic analysis plan (HEAP) was written by Professor Deborah Fitzsimmons, Dr Shaun Harris and Ioan Humphreys. The plan will be finalised prior to data analysis after discussion with the Chief Investigator, statistician and circulation to the TMG. The final version will be signed off by the lead author and health economics lead for the trial, statistician and Chief Investigators. The analysis will be carried out by health economist researcher/modeller (Shaun Harris and Ioan Humphreys) from SCHE with support from Professor Deborah Fitzsimmons with final internal QA check undertaken by a senior health economist within SCHE.

1.0 Introduction and purpose

This health economics plan (HEAP) has been written as a supplement to the trial statistical analysis plan Version 1.0 (19th December 2016). The HEAP outlines the specific methods and procedures to conduct the health economic analysis for the 'REMEMBERIN' study.

This HEAP should be read alongside the SAP[1] and trial protocol[2]. All details in the SAP apply to the HEAP apart from those specific to the economic analyses. Where required, the HEAP will cross reference to the relevant sections in the SAP/trial protocol.

1.1 Compliance with the Trial Protocol and SAP

This HEAP has been revised in accordance with the final trial protocol 5.0 (dated 22 January 2016) and SAP version Version 1.0 (19th December 2016).

1.2 Conduct of the health economic analysis

The HEAP will comply with the methods and procedures outlined in the trial protocol. Throughout the study, the health economics team will work closely with the trial manager and statistician to ensure agreed processes are in place for data management/cleaning as specified in the SAP. Throughout the study, quality assurance checks will be undertaken to ensure the integrity of the data and compliance with the SAP and HEAP.

1.3 Commencement of final health economic analysis

Health economic analyses will **only** commence once the study statistician has confirmed, in writing, to the CI and project lead (health economics) that the data has been locked for analyses. Appropriate data management process will be put in place by the trial team to allow SCHE access to the dataset including ensuring SCHE has the necessary standard operating procedures (SOP) for data management and statistical analyses. Throughout the health economic analysis, quality assurance checks will be undertaken to ensure the integrity of the data and compliance with the SAP and HEAP. Where trial data needs to be further analysed for the health economic analysis, a full log/decision trial) of this will be kept (e.g. syntax files, outputs) and be made available to the trial statistician and CI for checking and approval prior to reporting the final health economics results.

1.4 Introduction to the trial

'REMEMBERIN' is a multi-centre, parallel group, randomised controlled trial (RCT). The study is single blind for the individual goal attainment by the research assistant. Participants will be randomised in clusters of 4-6. Once 4-6 individuals are identified and have consented they are randomly allocated, as a group, to either intervention or usual care on a 1:1 ratio. Participants will be randomised to receive 10 group memory rehabilitation sessions (1.5 hours long, once a week for 10 weeks) or usual care and are followed up for 12 months from randomisation.

1.5 Main research question

The purpose of the REMEMBERIN study is to address the following question:

What is the clinical and cost-effectiveness of memory rehabilitation for military personnel and civilians with memory problems following traumatic brain injury (TBI)?

1.6 Primary trial objective

The primary objective is to determine whether attending a group memory rehabilitation programme is associated with improved management of memory in daily life, as measured on the Everyday Memory Questionnaire – patient version (EMQ-p) when compared to usual care.

1.7 Health Economics objective

The health economics objective is part of the secondary trial objectives:

- To assess the cost-effectiveness of the intervention when compared to usual care
- In addition, net monetary benefit (NMB) will be considered as an alternative to the cost-effectiveness analysis. This, for example, will allow for a wider perspective regarding costs and effects relating to the intervention. NMB will form part of the post-hoc analysis and is not part of the original study protocol. These results will be reported separately.

1.8 Perspective

The health economic analysis will be assessed from the perspective of the UK NHS and personal social services as recommended by NICE 2014 [1].

2.0 Rapid Review of the literature

Prior to commencement of the final health economic analysis a review of the health economics literature will be conducted to inform the report; identify possible candidate models for adaption and data inputs (e.g. utility decrements/gains associated with improvement in everyday memory) to inform the model where additional data [alongside the findings from the trial] are required.

A PICO approach will be used to generate appropriate search terms. PUBMED and the NHS EED will be systematically searched to identify relevant studies (systematic reviews, RCTs and where necessary observational studies); following key principles of PRISMA. Cost of illness studies, costing studies or other partial economic evaluations will be listed but not formally reviewed. In addition, searches to identify literature to inform health–related quality of life (HRQoL)/utility estimates will be undertaken. A summary reporting the economic evidence will be used to inform the background/introduction to the health economic analyses.

If economic modelling proves feasible, the REMEMBERIN trial team will also be consulted to identify suitable sources of evidence on the longer-term effects of memory problems following traumatic brain injury in order to identify a) any appropriate candidate model for use/adaptation and b) candidate inputs for the longer-term evaluation (modelling) to be undertaken.

2.1 Data collection

The data collection required for the health economic analyses has been incorporated into the trial protocol and utilises a variety of methods to collect costs and outcomes.

2.2 Identification and measurement of costs

A number of different data sources will be used to estimate the costs associated with the intervention; compared to usual care (table 1). The focus will be on all health care and personal social services usage.

The costs of providing the intervention will be estimated using standard NHS sources and we will identify the key cost drivers.

Health service resource use in primary care, secondary care and the community will be administered via questionnaires (SUQs) to participants in both arms of the trial at baseline, 6 and 12 months. Questions will relate to all health service contacts (e.g.

hospital appointments, hospital stays, GP contacts, visiting nurse appointments, etc.) and prescription medicines dispensed during the trial period with a three month recall period.

Patient recall has been shown to be a valid method for collecting health service resource use data over this period (i.e. 0-6 months and 6-12 months) and, as clinical records are often fragmented, and sometimes unavailable across different parts of the health service, patient-reported data is likely to remain more readily available and less costly to collect for research purposes [2].

Table 1: Sources of data to inform costing.

Data	Main source	Comments
Implementation costs	Local records and discussion with the trial team	The delivery of the intervention will be established from the REMEBERIN team in order to ascertain the staff time/grade, materials, venue, and consumables associated with delivering the interventions. Relevant records will be obtained (e.g. time sheets and travel records) to assist with the calculation of the staff time and resources associated with the intervention. The different size of groups will be taken into account and if applicable, any costs which may be associated with different sites. The analysis will consider the impact of no-attendance on costs [and any subsequent costs associated with 'catch-ups' for participants]. The trial data on adherence will be used to summarise the costs associated with the delivery of the intervention under the trial conditions. Where relevant, and in discussion with the trial team, possible scenarios will be considered e.g. changes in how the intervention may be given in routine NHS practice, as part of the sensitivity analysis.

Health care utilisation	Service use questionnaire (SUQ), and discussion with trial team.	Data on the resultant costs associated with health care utilisation as a result of the intervention when compared to usual care will be estimated from a service use questionnaire completed by participants at their second assessment (baseline), and at both 6 months and 12 months follow-ups. We will include costs associated with both primary (e.g. GP) and secondary care (e.g. hospital admissions costs), and any prescribed medications. Discussion with the trial team will ensure that appropriate costs are attributed e.g. to ensure that the most relevant HRG codes are used to document hospital admissions and medication usage. If applicable, NHS vs. non-NHS (e.g. private) health care costs will be separated.
Personal social services	Service use questionnaire (SUQ)	Data on the resulting costs associated with contacts with social services as a result of the intervention compared to usual care will be documented from the SUQ.

The resources utilised and associated costs will be summarised. This will be used to compare the costs of the intervention to those associated with usual care and to inform the calculation of incremental costs. The SUQ considers healthcare service usage, considering both those "Because of memory problems" and those "Because of other reasons". For the primary analysis a combined approach considering both usage categories will be undertaken. Due to the structure of the intervention no difference in service usage due to "other reasons" is predicted to be observed between the intervention and control groups. As part of the sensitivity approaches, usage "Because of memory problems" will be separately analysed to determine whether differences arise within this category within the two groups as a result of the intervention.

The sources of costs will be fully referenced to aid transparency of the analysis. Where possible, published unit costs will be used e.g. Personal and Social Services

Research Unit (PSSRU) [4], British National Formulary [5], and NHS reference costs [6] using the most recent published costs - 2014/15 in pound sterling. Where relevant costs cannot be obtained from this year, an inflation calculator (Bank of England) will be used to convert into the correct currency year, reporting both original and inflated values.

Costs will be presented using standard descriptive methodologies (mean, SD, and 95% confidence intervals) or where appropriate the non-parametric equivalent (median and interquartile range).

2.3 Outcomes to inform the economic analysis

The outcome measures used in the trial are summarised in the trial protocol (5.0. 22 January 2016) and SAP. For the economic analysis, the primary outcome measure will be used as part of a cost effectiveness analysis and the EQ-5D as the outcome measure for the cost-utility analysis.

2.4 EQ-5D to derive health utilities

The EQ-5D™ is a standardised instrument for use as a measure of health-related quality of life. The output from the questionnaire provides a simple descriptive profile and a single index value which are used for health economic evaluation to enable estimation of quality adjusted life years. This study will employ the 5-level version of the questionnaire. A descriptive analysis of EQ-5D™ responses taken at second assessment (baseline) then at 6 and 12 months follow-up will provide a comparison of pre-intervention and post-intervention responses and a between groups comparison at these time points. The reported EQ-5D values will then be used to derive utilities based on the UK social tariff [3]. It will also be used to produce estimates of quality adjusted life years (QALYs) gained (or lost) as a result of receiving the intervention, within the study period.

2.5 Framework for the Health Economic Analyses

The health economic analysis framework will consist of:

a. A descriptive summary of resource use and costs associated with the intervention;
b. A descriptive summary of QALYs gained/lost as a result of the intervention;
c. A series of incremental cost-effectiveness analyses and cost-utility analysis (cost per QALY gained)

d. Post-trial economic modelling over a suitable time horizon to assess the longer term cost-effectiveness (cost per QALY gained) of the intervention (this will only be undertaken if the within-trial analysis shows reasonable evidence of cost-effectiveness)

2.6 General analysis considerations

For all analysis, consistent methods will be used to treat cost and outcomes as it would be methodologically unsound to use disparate approaches e.g. use an unadjusted cost with an adjusted outcome. Where appropriate, we will follow the SAP in making adjustments e.g. to take into account the effect of clustering.

2.7 Analysis population

Consistent with the approach outlined in the SAP, participants will primarily be analysed using an intention to treat approach for all the economic outcomes. Moreover, the main analysis population for the 6-month and 12-month outcomes will concern only those participants who complete the questionnaires within 9-months and 15-months from randomisation respectively.

We will use similar methods as those within the SAP, including linear regression models to take into account the impact of covariates. As part of this, the impact of baseline imbalances of costs and HRQoL data whereby not taking into account small but important differences in baseline utilities may impact on the estimation of subsequent QALYs. These will be considered and where required, appropriately considered in the analysis.

2.8 Impact on attendance

As part of exploring the impact of attendance, we will undertake sensitivity analysis to examine the costs and outcomes associated with those who did attend a full course.

2.9 Outliers

Due to the nature of costing data, it is often highly skewed. To take into account the possible impact of skewness in our cost data, the distribution of costs for normality will be examined including the impact of removing extreme outliers from the analysis. Where required, the sensitivity of our results will be checked by considering appropriate transformation [7]. Bootstrapping is expected to be used to derive appropriate 95% confidence intervals around a point estimate of cost per participant

in each of the trial arms. The impact of outliers will be examined in both the costs and outcomes datasets, and where applicable sensitivity analyses will be performed to examine the robustness of results with and without the inclusion of identified outliers.

3.0 Missing data

Missing data related to both costs and outcomes can affect cost-effectiveness results and should be fully considered in the analysis. In line with the SAP, the impact of the observed proportion of missing data (including costs) will be considered.

For outcomes, we will examine the pattern of missing data; particularly on whether it is missing at random or not at random. If data is assumed to be missing at random, suitable multiple imputation methods may be undertaken as detailed in the SAP. If the data is not assumed to be missing not at random, sensitivity analysis will be undertaken to explore the robustness of the results.

In accordance with the SAP missing items from questionnaire responses at baseline and both 6-month and 12-month follow-ups will be imputed using the participant specific mean of the completed responses where 10% or fewer of the items in the questionnaire have not been completed. Therefore, total scores will be calculated where:

- 25 or more of the 28 items are completed on the EMQ
- 27 or more of the 30 items are completed on the GHQ

At baseline, if greater than 10% of the items from the questionnaire are missing, total scores will be imputed using the mean score at each centre for the given time point; these mean scores will be calculated using individual total scores including those where 3 or fewer responses have been imputed as detailed above. In accordance with the SAP, no imputation will be applied to those outcomes with greater than 10% of questionnaire items missing. These simple imputation methods, including the second order imputation of total scores, are consistent with the SAP and are superior to more complicated imputation methods when baseline variables are included to improve the precision of the treatment effect [8].

Should any component of the EQ-5D be missing, the cross-walk model cannot compute a utility score. To maintain consistency with the SAP, missing baseline utility values will be imputed using the centre mean, whereas missing outcome utility values will not be imputed with the primary analysis considering participants with available data at 6-months.

Missing data relating to participant service usage will be treated in accordance with the following rules which consider the manner of incompleteness of the questionnaire:

- If the EMQ is not scoreable the participant is excluded from analysis thus no action for service use required.

- If the EMQ is scoreable and one or more items in service use are completed (values of 0 or greater), questionnaire is assumed fully completed and any missing items will be imputed with a zero (i.e. filled in only those which were relevant).
- If the EMQ is scoreable and all other questionnaires are completed, yet service usage questionnaire is blank then impute service use with zeroes (i.e. not filled in as had no contact)
- If the EMQ is scoreable yet either the GHQ or EBIQ are not scoreable, and the service usage questionnaire is blank, impute service usage using the site mean for the visit number.

3.1 Health Economic analysis

Analyses will be performed using SPSS or Stata version 13 or above. Participants will be analysed as randomised, regardless of adherence with allocation (ITT). No formal adjustment for multiple significance testing will be applied. No per-protocol or sub-group analysis is formally planned.

Incremental cost-effectiveness and cost-utility analyses will be used to estimate cost per improvement in EMQ-P score based on the primary clinical endpoint and cost per QALY gained. Incremental costs and effects will also be presented in disaggregated format with 95% confidence intervals for results. Where simple dominance occurs e.g. the intervention is less costly and more effective, ICERs will not be produced. The reporting of results in the final report will show sufficient information to reproduce the calculations of the ICER.

3.2 Sensitivity analyses

Sensitivity analyses will be undertaken to account for the inherent uncertainty in the parameters in the cost-effectiveness analysis.

One-way deterministic sensitivity analysis will examine the impact of changes in the key parameters on the ICERs by modifying one parameter at a time in plausible ranges (e.g. upper/lower 95% CI value or +/- 30%). Scenario analyses will be used to examine the best case (i.e. where the most optimistic outputs are used) and the worst case (i.e. where the worst outputs are used). A threshold analysis will be conducted to determine what needs to change (e.g. in terms of QALY gains) to affect the base-case finding (e.g. to provide a cost-effective result).

A probabilistic sensitivity analysis (PSA) using bootstrapping will be undertaken to characterise joint uncertainty around parameter estimates. At least 1,000 resamples will be used. Results of the PSA will be expressed as the percentage probability that the intervention is cost-effective. Cost-effectiveness acceptability curves (CEACs) will be generated to depict the probability of the intervention being cost-effective at a variety of willingness-to-pay thresholds.

Generally, NICE considers an intervention cost-effective if one of the following applies:

- The intervention is less costly and more clinically effective than all other relevant alternatives. In this case, no ICER is calculated as the strategy in question dominates the alternatives
- The intervention has an ICER of < £20,000 per QALY compared with the next best alternative. This means that an investment of up to £20,000 in order to achieve an additional QALY is considered cost-effective.

For the cost-effectiveness ICER, it is recognised there is no societal WTP threshold available.

4.0 Longer-term modelling

Given the limitations of the length and scope of clinical trials, modelling exercises are typically proposed to establish relevant economic outcomes from in-trial results [9], [10].

If feasible and indicated by the initial trial results, a decision-analytical model will be developed to assess the longer-term cost-effectiveness of the intervention. Prior to this, and on receipt of the initial analysis of the clinical effectiveness results, a feasibility check of undertaking the modelling will be discussed with the REMEMBERIN team based on a) The intervention has shown sufficient evidence of clinical effectiveness during the trial; b) the trial results (with supporting literature found) provides a realistic estimation of all data inputs attributed to the intervention compared to the control group and c) that the model is able to produce plausible estimates of the longer-term costs and outcomes associated with intervention.

4.1 Model Structure

Given the limitations regarding the length and scope of the ReMemBrIn trial, an exploratory economic model has been proposed to extrapolate the economic outcomes from the in-trial results to a longer term horizon. Evidence presented by Corrigan and Hammond [12] demonstrates that traumatic brain injuries are consistent with the characteristics of chronic conditions with evolving progression of the condition. A Markov model, utilising a finite number of mutually exclusive health states with cycles of 6 months is thus proposed to assess cost and utility outcomes.

Utilising the GHQ total score, based on the GHQ scoring method, the model depicted by Figure 1, comprises a set of three mutually exclusive health states based on GHQ scores, and the absorbing death state, of which a participant can be classified. Specifically, pro-rating to the categories defined by Raj et al. [11] these states are defined as a state of no or mild distress for scores of 0-5, moderate distress for scores 6-17, and severe distress for scores of 18 or higher. In any given cycle, participants are permitted to either remain within the same GHQ based health state, or transition between any two states. Alternatively, participants may transition to the death state; by definition death is an absorbing state and does not permit transition to any other state in subsequent cycles of the model.

The specification of the Markov model represents the potential combination of events which may arise following the intervention. This includes participants experiencing an initial improvement following intervention prior to an exponential worsening of mood, and no initial change prior to improvements/deteriorations. A logic model would be developed outlining the treatment pathways and validated with the trial team before building the model in EXCEL. A provisional structure for the model is represented in figure 1.

4.2 Model assumptions

Key structural parameters and other assumptions, including transition probabilities, and utilities and costs associated with each state, will be agreed with the trial team prior to analysis. The probability of death will be calculated based on trial data and literature estimates of the standardised mortality ratio applied to UK life tables.

4.3 Time Horizon

Following discussion with the REMEMBRIN team, the minimum time horizon for which the model shall be estimated is 5 years, whilst longer-term estimates can be made e.g. horizons of 10 years shall be examined if plausible. A life-time horizon (up

to the age of 100 years) may also be evaluated. Longer term transition probabilities will be informed by the literature and validated by the trial team.

4.4 Population

The trial population would be used for the participant cohort whilst populations of various sizes to represent clinical practice will also be evaluated.

4.5 Data Inputs and Sources

The results of the in-trial evaluation would be used as the primary source of data. Where necessary, the rapid review of the literature (2.0) would identify other relevant data inputs required. Discussion with the main trial team would be used to identify any other additional resources and costs associated with treatment and down-stream effects.

4.6 Discounting

Future costs and benefits would be evaluated at present values which require discounting at the conventional rate of 3.5% p.a.

4.7 Health outcomes

The outcome used in the model would be QALYs i.e. an incremental cost per QALY gained (cost-utility analysis) will be undertaken. Responses from the EQ-5D questionnaire from trial participants will be used to derive QALY's, which thus represent health states. The use of GHQ and EQ-5D results to respectively define and describe health states, of which both are subjective measures, implies that the model will deliver an exploratory analysis of the longer term effects of brain injury.

4.8 Incremental analysis

Incremental cost-utility analysis would be undertaken on the base case as outlined in 2.5 'Framework for the Health Economic Analyses' section above.

4.9 Sensitivity analysis

Sensitivity analysis would be undertaken as outlined in 3.2. For the model, no sub-group analysis would be expected to be undertaken as part of the sensitivity analysis.

For the probabilistic sensitivity analysis, inputs will be computed using standard distributions from Bayesian probability theory based on the values observed from the

trial. Namely, transition probabilities and utilities will be estimated from the beta distribution with a range from 0 to 1; as costs have a zero lower-bound and infinite upper-bound, the gamma-distribution will be used.

Final report tables and figures (for illustration purposes only)

Table 1 Intervention costs of rehabilitation programme

	Intervention Cost Based on x sites, x groups, x sessions (x sessions per group), x participants					
	Resource	**Unit cost**	**Resource Usage**	**Cost**	**TOTAL**	**Unit cost source/Description**
Per Site Training Costs	Training Psychologist Band 8a	£98	2 Hours	£196		PSSRU (2015) Band 5 - Band 8 Page 90
	Training Assistant Psychologist Band (mid-band 5)	£79	2 Hours	£158		PSSRU (2015) Band 5 - Band 8 Page 90
	Cost per Site			**£354**		
	One off training cost (sub total)				**£3,186**	***Based on x sites***
Per Group Costs	Admin Staff (Band 3)	£70	1 Hour per group	£70		PSSRU (2015) Band 3 Page 173 - 174
	Cost per Group			**£70**		
	Total admin cost for groups (sub total)				**£2,450**	***Based on x groups***
Per Session Variable Costs	Assistant Psychologist Band (mid-band 5)	£79	2 Hours per session	£158		PSSRU (2015) Band 5 Page 173 - 174
	Total per Session			**£158**		
	Total cost of sessions (sub total)				**£55,300**	***Based on x sessions***
Per Participant Variable Costs	Cost per manual	£2.20	1 manual per participant	£2.20		Trial Team
	Refreshments	£0.50	£0.50 per particpant per session	£5.00		Team
	Stationary Costs (e.g.Pens, misc)	£1.00	Est. total £1 per participant for all sessions	£1.00		Trial Team
	Total per Participant			**£8.20**		
	Per participant costs (sub total)				**£1,402**	***Based on x participants***
	Overall cost of rehabilitation intervention				**£62,338**	*Sum of total column*
	Cost of rehabilitation per participant				**£365**	*Overall cost divided by participants (x)*

Table 2 Summary of other resource items, unit costs and source

Health Service Resource	Average Unit Cost (£)	Source
GP Surgery Visit (Per patient contact lasting 11.7 minutes	£44	PSSRU (2015) page 177
GP Telephone Consultation (Per telephone consultation lasting 7.2 minutes)	£27	PSSRU (2015) page 177
GP Home Visit (Per out of surgery visit lasting 23.4 minutes	£112	Inflated from PSSRU 2014/2015 figure of £110 at 0.9%
Nurse at GP	£56	PSSRU (2015) page 174
Mental Health Nurse	£75	PSSRU (2015) page 170
Community Pharmacy	£36	PSSRU (2015) Band 5 Page 173 - 174
Community Physiotherapist	£36	PSSRU (2015) Band 5 Page 173 - 174
Community Occupational Therapist	£36	PSSRU (2015) Band 5 Page 173 - 174
Community Speech and Language Therapist	£36	PSSRU (2015) Band 5 Page 173 - 174
Dietitian	£36	PSSRU (2015) Band 5 Page 173 - 174
Specialist Nurse (Community)	£75	PSSRU (2015) page 172
Cognitive behaviour therapy (CBT), cost of CBT session	£79 - £123	PSSRU (2015) Band 6 - Band 8 Page 90
Clinical psychologist, per hour of client contact	£136	Inflated from PSSRU 2014/2015 figure of £134 at 0.9%
Psychiatrist	£77	Inflated from PSSRU 2014/2015 figure of £76 at 0.9%
Surgery as an inpatient:		
Long stay (all elective and non-elective)	£xxxx	NHS Reference Costs (2014/2015)
Long stay (all elective and non-elective) excess bed days	£xxxx	NHS Reference Costs (2014/2015)
Short stay (all elevtive and non-elective)	£xxxx	NHS Reference Costs (2014/2015)
Non-elective inpatient long stay excess bed day	£xxxx	NHS Reference Costs (2014/2015)
Non-elective inpatient short stay	£xxxx	NHS Reference Costs (2014/2015)
Outpatient attendance (same as Non Elective Inpatient stay avg. Short Stay cost)	£xxxx	NHS Reference Costs (2014/2015)

Table 3 Parameters assessed in the uni-variate sensitivity analysis

	Control			Intervention				
Parameter	**Base-case**	**Lower Range**	**Upper Range**	**Base-case**	**Lower Range**	**Upper Range**	**Analysis**	**Justification/source**
Costs (£)								
Costs of delivering the Intervention	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx	Cost analysis	30 % + - from trial data
Health care resource usage	£xxx (£xxx, £xxx)						ICER	Based on 95% CIs from trial data
Health outcomes								
Changes in QALY estimates	xxx (xxx, xxx)						ICER	Based on 95% CIs from trial data

Figure 1: Outline of modelled intervention pathways

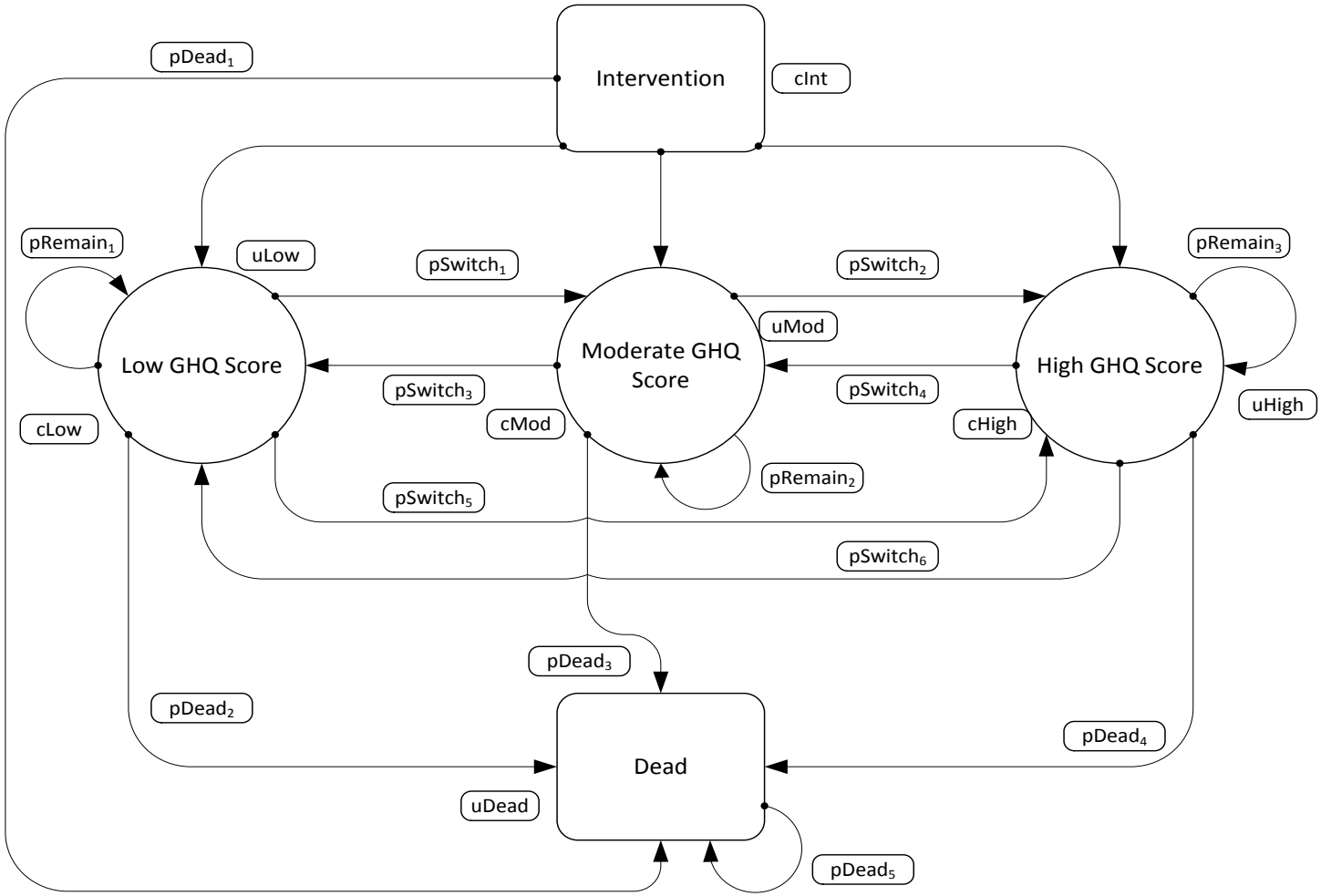


Table 4: Base case utility values used in the model based analysis

Parameter	Intervention	Control
Baseline utility of Low Mood State (GHQ Score 0-15)	0.700	0.600
Baseline utility of Moderate Mood State (GHQ Score 16-53)	0.400	0.350
Baseline utility in Severe Mood State (GHQ Score ≥54)	0.100	0.090
6-Month Follow-Up utility of Low Mood State (GHQ Score 0-15)	0.750	0.590
6-Month utility of Moderate Mood State (GHQ Score 16-53)	0.450	0.315
6-Month utility in Severe Mood State (GHQ Score ≥54)	0.150	0.090
Utility for cycles ≥ 12 months in Low Mood State	0.800	0.600
Utility for cycles ≥ 12 months in Moderate Mood State	0.500	0.400
Utility for cycles ≥ 12 months in Severe Mood State	0.250	0.100
Cost of one cycle in Low Mood State (GHQ Score 0-15)	£100	£150
Cost of one cycle in Moderate Mood State (GHQ Score 16-53)	£500	£600
Utility of one cycle in High Mood State (GHQ Score ≥54)	£1,000	£2,000

Table 5 Summary of resources utilised and because of memory problems

	Control				Intervention				Difference			95% Confidence Interval of the Difference	p-value
	Mean	**N**	**Std. Dev.**	**Sum**	**Mean**	**N**	**Std. Dev.**	**Sum**	**Mean**	**Std. Dev.**	**Sum**		
No.of GP consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Xxx (xxx, xxx)	xxx
Cost of GP consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Home Visit GP consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Xxx (xxx, xxx)	xxx
Cost of Home Visit GP consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Practice nurse consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Practice nurse consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Home Visit Practice nurse consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Xxx (xxx, xxx)	xxx
Cost of Home Visit Practice nurse consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Psychologist consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Xxx (xxx, xxx)	xxx
Cost of Psychologist consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx

No.of Home Visit Psychologist consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Home Visit Psychologist consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of SLT consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of SLT consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Home Vist SLT consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Home Visit SLT consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of OT consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of OT consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Home Visit OT consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Home Visit OT consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No.of Physiotherapist consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Physiotherapist consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx

No.of Home Visit Physiotherapist consultations per patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of Home Visit Physiotherapist consultations per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
No. of days as Hospital In-patient	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx (xxx, xxx)	xxx
Cost of days as Hosptital In-patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
Medication costs per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
Total cost to the NHS and Personal Health and Social Care Costs	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
Intervention Cost per patient	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx
Total cost to the NHS and Personal Health and Social Care Costs + Intervention Costs	£xxx	xxx	£xxx	£xxx	£xxx	xxx	£xxx	£xxx	£xxx	£xxx	£xxx	£xxx (£xxx, £xxx)	xxx

Table 6 Health utilities and quality adjusted life years by treatment arm

	Treatment Allocation	n	Mean	Std. Dev	95% Confidence Interval of the Difference	p-value
EQ-5D 5L Baseline	Control	xxx	xxx	xxx	xxx (xxx , xxx)	xxx
	Intervention	xxx	xxx	xxx		
EQ-5D 5L 6 Months	Control	xxx	xxx	xxx	xxx (xxx , xxx)	xxx
	Intervention	xxx	xxx	xxx		
EQ-5D 5L 12 Months	Control	xxx	xxx	xxx	xxx (xxx , xxx)	xxx
	Intervention	xxx	xxx	xxx		

Table 7 Health utilities and QALYs

Control			Intervention			QALY Difference
Time period	**EQ-5D 5L score**	**Change over time**	**Time period**	**EQ-5D 5L score**	**Change over time**	-
Baseline	xxx	-	**Baseline**	xxx	-	-
6 Months	xxx	xxx	**6 Months**	xxx	xxx	-
12 Months	xxx	xxx	**12 Months**	xxx	xxx	-
QALY gain at 1 Year	-	**xxx**	**QALY gain at 1 Year**	-	**xxx**	**xxx (xxx, xxx)**

Table 8 Incremental cost per quality adjusted life year (QALY)

Parameter	Incremental cost of intervention	Incremental EQ-5D 5L utility	ICER (using EQ-5D 5L utility scores)
Basecase	£xxx (£xxx , £xxx)	xxx (xxx, xxx)	£xxx -
Upper 95% bound of net cost	£xxx	xxx	£xxx
Upper 95% bound of net utility			
Upper 95% bound of net cost	£xxx	xxx	£xxx
Lower 5% bound of net utility			
Lower 5% bound of net cost	£xxx	xxx	£xxx
Lower 5% bound of net utility			
Lower 5% bound of net cost	£xxx	xxx	£xxx
Upper 5% bound of net utility			

Figure 2: Cost effectiveness acceptability curve.

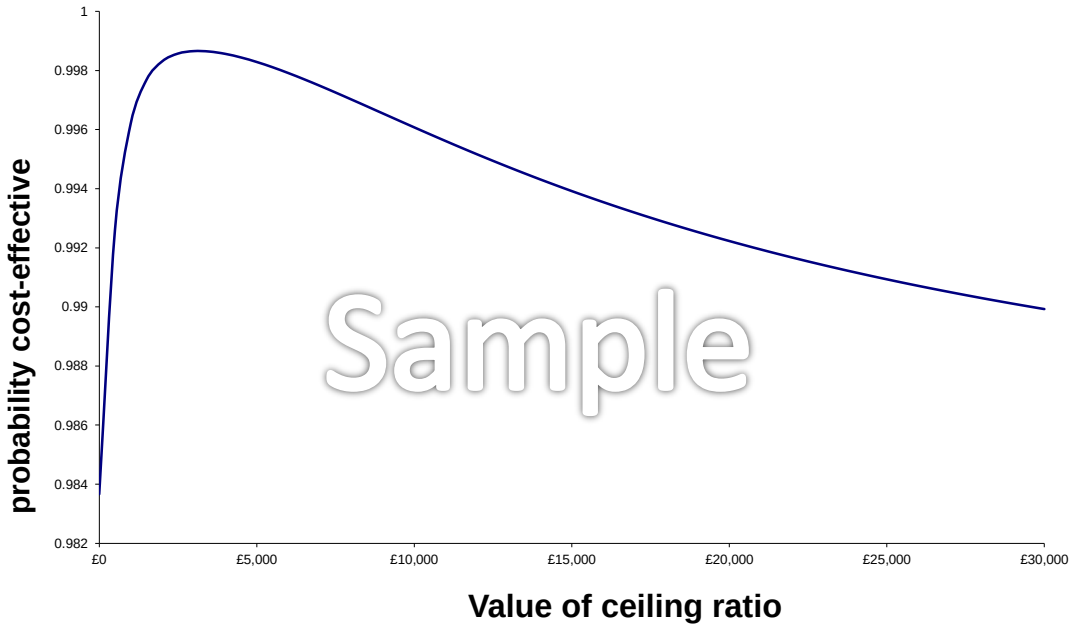


Table 9 Incremental cost analysis at 1 year based on trial population

Baseline	Control	Intervention
Total cost of appointments	£xxx	£xxx
Mean cost of appointments per patient (SD)	xxx (xxx)	xxx (xxx)
Difference (95% CI)	xxx (xxx, xxx)	
Cost of implementation	£xxx	£xxx
Number of patients	xxx	xxx
Cost of Implementation per patient	£xxx	£xxx
Overall cost differences between the interventions		£xxx
Cost saving per patient		£xxx

Table 10 Base case and sensitivity analysis

Parameter	Incremental cost of intervention	Incremental EQ-5D 5L utility	ICER (using EQ-5D 5L utility scores)
Basecase	£xxx (£xxx , £xxx)	xxx (xxx, xxx)	£xxx -
Upper 95% bound of net cost	£xxx	xxx	£xxx
Upper 95% bound of net utility			
Upper 95% bound of net cost	£xxx	xxx	£xxx
Lower 5% bound of net utility			
Lower 5% bound of net cost	£xxx	xxx	£xxx
Lower 5% bound of net utility			
Lower 5% bound of net cost	£xxx	xxx	£xxx
Upper 5% bound of net utility			

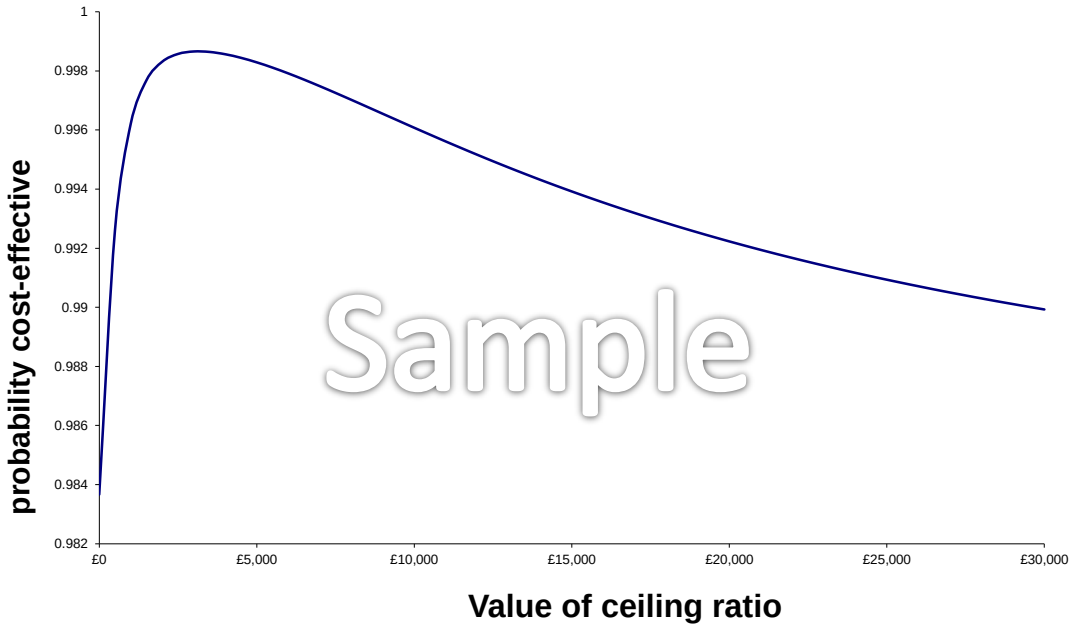
Table 11 Incremental cost per QALY at 5 year horizons

	Cost	QALYs
Control	£xxx	xxx
Intervention	£xxx	xxx
Difference	£xxx	xxx
ICERs:	per QALY	
Control vs Intervention	£xxx	

Table 12 Incremental cost per QALY at 10 year horizons

	Cost	QALYs
Control	£xxx	xxx
Intervention	£xxx	xxx
Difference	£xxx	xxx
ICERs:	per QALY	
Control vs Intervention	£xxx	

Figure 3 CEAC for a 5 year time horizon



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