Pressure **RE**lieving **S**upport **SU**rfaces: a **R**andomised **E**valuation 2

PRESSURE 2

Health Economics Analysis Plan

Version: 1.0

Date: 03/03/17

Armando Vargas-Palacios

Claire Hulme

Academic Unit of Health Economics

Leeds Institute of Health Sciences

University of Leeds

Contents

Objectives

The primary aim of the health economic analysis is to compare High Specification Foam (HSF) and Alternating Pressure Mattresses (APMs) in secondary and community in-patient facilities with evidence of acute illness, for the prevention of Category 2 (and above) pressure ulcers (PU).

Two sets of economic evaluation will be undertaken:

- A within-trial analysis comparing the outcomes and costs at 30 days post-treatment phase, using trial data.

- A long term decision analytic model to estimate the cost-effectiveness analysis outcomes and costs for the lifetime of the patients.

The proposed analyses will adhere to the methods guidance produced by the National Institute for Health and Care Excellence (NICE) (NICE 2013).

Within Trial Analysis

The within-trial analysis aims to determine the intervention(s) that would maximise health outcomes both (1) within the NHS budget, and (2) within a societal perspective.

It will adopt an intention-to-treat (ITT) perspective and consists of a cost-effectiveness (cost-utility) analysis using an ICER which is calculated as the difference between the mean costs and difference in mean QALYs in each treatment.

We will use the NICE implicit cost per QALY threshold λ of £20,000 per QALY to determine cost-effectiveness. The intervention with an ICER within or below λ= £20,000 per QALY will be considered cost-effective.

Perspective and time horizon

Direct costs and outcomes of patients randomised to HSF or APMs will be compared over the duration of the trial and follow-up (up to 90 days post randomisation). The perspective adopted for the analyses will be that of the Healthcare and Personal Social Service provider.

Discounting

As the duration of the trial is of 90 days discounting of costs and benefits will not be required.

Outcome measure

The primary economic analysis will be will be cost per incremental quality-adjusted life year (QALY) at 90 days post randomisation. QALYs is a generic measure of health that take account of both quality and length of life such that one QALY is equal to one year of life lived in a state of full health (Glick, Doshi, Sonnad, & Polsky, 2014). Health related quality of life will be estimated using responses from the EQ-5D-L (EuroQol) (NICE 2013). A secondary analysis will estimate utility values from the PUQoL-UI (condition specific utility measure derived from the PU-QoL measure) and the SF-12 instruments. Outcome measures will be obtained weekly up to day 30 or discharged, then fortnightly up to day 60 or dischargedand at weeks 1, 3 and at 30 days after the end of the treatment phase.

The standard UK tariff values will be applied to these responses at each time point to obtain utility based on the EQ-5D-5L and the using the appropriate algorithms when estimating the utility using the PUQoL-UI. QALYs will be calculated as an “area under the curve” and form the main outcome measure of the within-trial analysis (Dolan, 1997).

The utility values represent patients’ quality of life and will be multiplied by duration (t) in each health state to generate quality adjusted life years (QALYs). An area under the curve (AUC) approach will be adopted for estimating QALYS with a linear transition assumed between adjacent time points.

$$QALY = (((EQ5D_{Baseline} + EQ5D_{w1})/2) * t) + (((EQ5D_{w1} + EQ5D_{w3})/2) * t + (((EQ5D_{w3} + EQ5D_{E30})/2) * t)$$

Where, $EQ5D_{Baseline}$,$EQ5D_1$, $EQ5D_{24}$, $EQ5D_{36}$ and $EQ5D_{52}$ are the EQ-5D scores at baseline, week 1, week 3 and 30 days after end of treatment phase. Should an individual die during the trial we will assume that their utility value is 0 from the date of death to trial end and assume a linear transition to this value from their last completed outcome measure questionnaire.

Measurement of resource use and cost analysis

All healthcare resource use expected to differ between treatment groups will be considered. The main analyses will take the perspective of the UK NHS and Personal Social Services (PSS) perspective including costs incurred to the NHS in the provision of the treatment and other health care resource utilisation. This will include length of stay in hospital, use of hospital outpatient facilities, contact with community based health care services and utilization of supported living such as care and nursing homes.

NHS and PSS resource use will be collected through the trial. Healthcare utilisation will be combined with appropriate unit cost information. Wherever possible, unit costs for resources will be obtained from national sources such as the British National Formulary and the PSS Research Unit Costs of Health and Social Care (Curtis & Burns 2016). If national costs are not available we will consult with the finance departments of trusts recruiting patients to the trial to identify the mean unit cost.

These will be added to the treatment costs as identified through direct observation of the treatment provided within the study.

Adjusting for baseline imbalance

Using a randomised controlled study design means that the baseline characteristics of groups being compared should be well-balanced, except by the play of chance. However, despite randomisation there will inevitably be some differences in mean baseline values between groups. This is of particular importance because a patient's utility at baseline is likely to be correlated with their utility over the follow up period. Therefore the imbalance in baseline utilities needs to be accounted for when calculating the differential effects between treatment groups (Hunter et al., 2015; Manca, Hawkins, & Sculpher, 2005). Multiple regression analysis will be used to estimate differential mean QALYs and predict adjusted QALYs controlling for utility at baseline. Some of the variables to be considered are: gender, age, baseline EQ-5D score, centre, or any other recorded baseline characteristic that may be relevant, to examine the effect this adjustment may have on the results.

Missing data

In economic analyses conducted alongside clinical trials, incomplete or missing data are inevitable. The statistician team will make several attempts to retrieve primary endpoints missing data related to through the cleaning process. If that failed, the statistical analysis team will be assessed and if assumed to be missing at random (MAR) will be imputed based on the date of the baseline visit and the visit number of the last evaluable skin assessment using the protocol visit schedule such as to comply with the intention-to-treat analysis principle (European Medicines Agencies 2010). This same process will be used in case of missing data if utility data is missing from the primary endpoints.

If missing data exists for baseline data, we will carry out an initial descriptive analysis to determine the likely approach to deal with missingness. However, multiple imputation techniques are likely to be used (Ramsey et al. 2015).

.

Cost-effectiveness analyses

The cost effectiveness analysis will adopt and intention-to-treat (ITT) perspective for analysing and summarising the health economic trial data. The primary analysis will consist of a cost-utility analysis over the 30 days after end of treatment phase. The incremental cost per QALY gain as a result of the use of either HSF or APMs will be calculated. This is calculated by dividing the mean difference in cost of the two trial arms by the mean difference in QALYs to produce an incremental cost-effectiveness ratio (ICER), as follows:

$$ICER = (Cost_A - Cost_B)/(QALY_A - QALY_B)$$

The ICER represents the additional cost per QALY gained for each intervention compared to the next best alternative (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). The National Institute for Health and Care excellence consider a cost per QALY within the range of £20,000-£30,000 to be acceptable (NICE 2013). The lower limit of this threshold (lambda λ=£20,000) will be used to determine cost-effectiveness. Interventions with an ICER less than £20,000 per QALY gained will generally be considered cost-effective.

Sensitivity analysis

Alternate scenarios will be explored, to test the robustness of the main trial analysis results. The effect of not imputing missing data will be considered with an analysis that includes only complete cases. Additionally, in the event of an imbalance in measures taken at baseline, the effect on cost-effectiveness will be evaluated. Table 1 illustrates the main and secondary analysis to be carried out

Table 1: Within Trial Analyses

Analysis		**Time horizon**	**Outcome measure**	**Baseline adjustment**	**Missing data**	**Cost-effectiveness analysis**
Primary	ITT analysis	30 days after end of treatment	QALYs (EQ-5D)	EQ-5D-5L Costs	imputed	Cost per incremental QALY
Secondary	1. Complete case	30 days after end of treatment	QALYs (EQ-5D)	EQ-5D-5L Costs	excluded	Cost per incremental QALY
	2. Baseline adjustment	30 days after end of treatment	QALYs (EQ-5D)	None	imputed	Cost per incremental QALY
		30 days after end of treatment	QALYs (EQ-5D)	None	excluded	Cost per incremental QALY
	3. Utility measures	30 days after end of treatment	PUQOL-UI	PUQOL-UI Costs	imputed	Cost per incremental PUQOL-UI
		30 days after end of treatment	PUQOL-UI	PUQOL-UI Costs	excluded	Cost per incremental PUQOL-UI

Uncertainty analysis

The level of sampling uncertainty around the ICER will be determined using a non-parametric bootstrap to generate 10,000 estimates of incremental costs and benefits. The bootstrapped estimates will be plotted on the cost-effectiveness plane to illustrate the uncertainty surrounding the cost-effectiveness estimates (O'Brien & Briggs 2002). Net monetary benefit (NMB) will also be calculated for each of the bootstrapped estimates. NMB combines cost-effectiveness and willingness to pay to give an explicit monetary valuation of the health outcome. It is calculated by rearranging the ICER and incorporating the willingness to pay per QALY threshold value such that NMB is derived for each patient as:

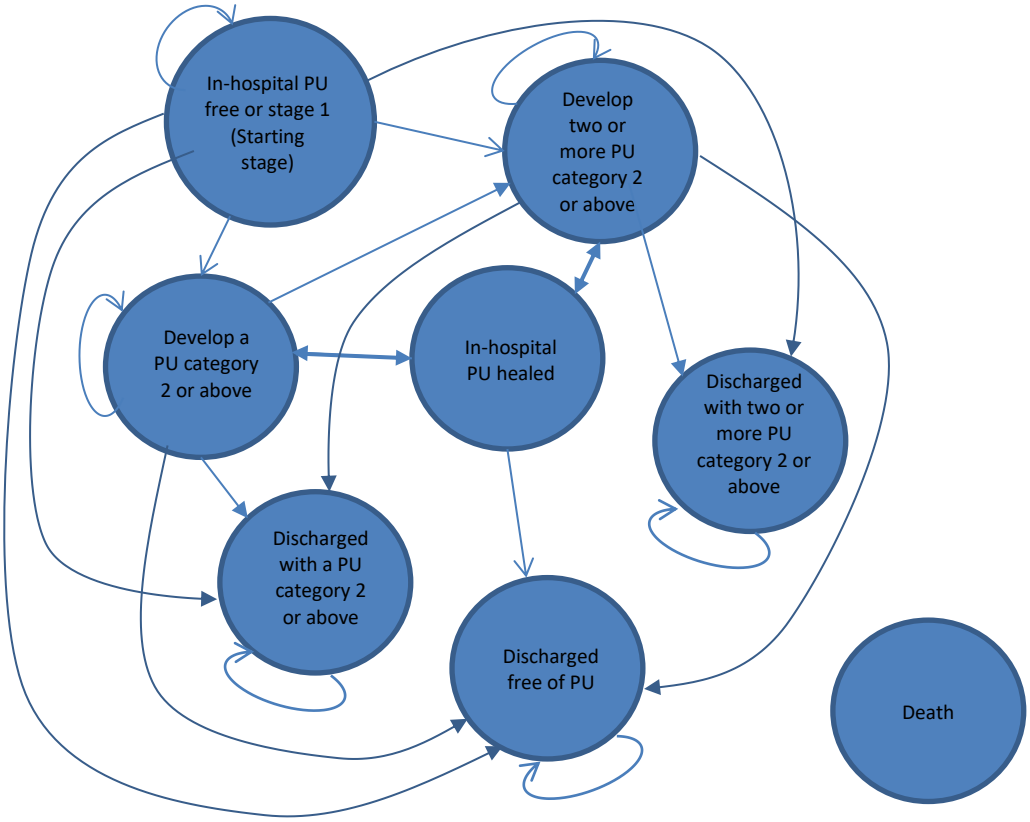
$$NMB = (\lambda \times QALYs) - costs$$

Where λ is the value a decision maker would be willing to pay per incremental QALY gained. For any given threshold value (λ) treatments with an average incremental NMB>0 should be adopted. The expected net monetary benefit will be used to estimate the probability of each intervention is cost-effective given a range of threshold values (λ=£1,000 to λ =£100,000) which will be plotted on the cost-effectiveness acceptability curve (CEAC) (Briggs, O'Brien, & Blackhouse, 2002). The CEAC will illustrate the probability the probability of HSF or APM to be cost-effective as a function of the willingness to pay threshold (λ). It will be constructed by using 10,000 bootstrapped samples from the original data and plotting the proportion of times each treatment represents the maximum average net benefit for a range of willingness to pay thresholds (λ). Mean net benefits will be reported (Bradley 1987).

Decision Analytic Model

A decision analytic modelling will be constructed to compare HSF and APM mattresses for the prevention of category 2 and above PU. A Markov decision model will be constructed. The model will start at the point of randomisation but compared to the within trial analysis, it will extend for the life time of the patients. The model will use the information of the trial the transition probabilities. Model parameters for which data could not be collected within the trial we will follow recommended best practice in identifying and synthesising the best available evidence in the literature (NICE 2013).

Although the model pathway will be re-defined with discussion with the clinicians on the study team it will likely have the following structure later in the analysis it is likely that it will have the following structure:



As in the within trial analysis the incremental cost per QALY gained will be estimated. Similarly, we use the lower threshold value (£20,000 per QALY gained) to determine which strategy is the most cost-effective.

Perspective and time horizon

Similar to the within-trial analysis, the will be conducted from the perspective of the NHS and Personal Social Services. An additional analysis will include out-of-pocket expenses and direct time costs incurred by family members/carers (societal perspective). The model will extend for the life time of the patients

Discounting

Costs and outcomes will be discounted at a 3.5% rate will, as per the NICE Methods Guide (NICE 2013).

Outcome measure

As far as possible parameters in the model will be specified using data collected within the trial. Other parameters, such as the long term 'natural history' will be parameterised using the published literature, and where necessary formally elicited expert opinion.

The outcome measure for these analyses will be the QALY. The primary analysis will estimate QALYs based using the EQ-5D data collected within the trial while a secondary analysis will estimate QALYs using the PUQoL-UI.

Missing data

Missing data will be dealt as in the within trial analysis

Base case scenario and sensitivity analyses

The base case scenario will be that with the complete cases (ignoring missing values and based on QALY estimates using the adjusted EQ-5D-5L. Alternative scenarios will impute missing data, use the PUQoL-UI. One way and multiway sensitivity analysis on the most uncertain parameters will also be carried out.

Uncertainty analysis

Parameter uncertainty will be addressed through probabilistic sensitivity analysis using Monte Carlo simulation. The outputs of the analysis will be presented as the expected ICER, a scatter plot on the cost effectiveness plane and a cost effectiveness acceptability curve comparing both types of mattresses. We will also calculate the expected net benefit of both, for a range of values of lambda.

Deterministic one-way sensitivity analysis will be performed to check the results over the most uncertain parameters. Multi-way deterministic sensitivity analyses will be undertaken to test possible different scenarios.

References

Bradley, E., 1987. Better Bootstrap Confidence Intervals. *Journal of the American Statistical Association*, 82(397), pp.171–185.

Curtis, L. & Burns, A., 2016. *Unit costs of health and social care 2016*, Kent: Personal Social Services Research Unit.

European Medicines Agencies, 2010. *Guideline on the investigation of subgroups in confirmatory clinical trials*,

NICE, 2013. *Guide to the methods of technology appraisal.*,

O'Brien, B.J. & Briggs, A.H., 2002. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. *Statistical Methods in Medical Research*, 11(6), pp.455–468.

Ramsey, S.D. et al., 2015. Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. *Value in Health*, 18(2), pp.161–172.