Health economics analysis plan for the NERVES trial

Multi-centre randomised control trial comparing the clinical and cost effectiveness of trans-foraminal epidural steroid injection to surgical microdiscectomy for the treatment of chronic radicular pain secondary to prolapsed intervertebral disc herniation: NErve Root Block VErsus Surgery (NERVES)

HEAP Version: 0.1 Dated: 9/07/2018

Trial information

EudraCT number: 2014-002751-25 **ISRCTN number:** 04820368

Funder reference: NIHR HTA – 12/201/10 **Sponsor reference:** UoL000314

Study Sponsors:	**Coordinating Centre:**	**Health Economics Centre:**
The Walton Centre NHS Foundation Trust Lower Lane Fazakerley Liverpool L9 7LJ	Clinical Trials Research Centre (CTRC) University of Liverpool Institute of Child Health Alder Hey Children's Hospital Eaton Road, Liverpool L12 2AP	Centre for Health Economics and Medicines Evaluation (CHEME) Ardudwy Building, Normal Site Bangor University Bangor Gwynedd LL57 2PZ

Date of ethics approval: 08/10/14

Date of MHRA approval: 15/08/2014

The HEAP was prepared by Eifiona Wood (HE researcher) and approved by Professor Dyfrig Hughes (lead HE). The trial health economists are responsible for conducting and reporting the economic evaluation in accordance with the HEAP. Eifiona Wood will conduct, and Professor Dyfrig Hughes will oversee the health economic analysis.

Signatures

Eifiona Wood
(HE researcher) Date: 9 July 2018

Professor Dyfrig Hughes
(lead HE) Date: 9 July 2018

Mr Martin John Wilby
(Chief Investigator) Date: 28 Sept 2018

HEAP revisions

Protocol version	Updated HEAP version	Section number changed	Description of and reason for change	Individual making the change	Date changed

The purpose of the HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated SAP and it should be read in conjunction with them.

Protocol version: 7 Dated 17/11/2017

SAP version: X.X Dated TBC

Contents

Glossary

AUC	Area Under the Curve
BNF	British National Formulary
CEAC	Cost Effectiveness Acceptability Curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
GDP	Gross Domestic Product
HE	Health Economist
HES	Hospital Episode Statistics
HRG	Health Resource Group
ICER	Incremental Cost Effectiveness Plane
ITT	Intention To Treat
ONS	Office for National Statistics
NHS	National Health Service
NICE	National Institute for health and Care Excellence
PCA	Prescription Cost Analysis
PID	Prolapsed intervertebral disc
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
QOL	Quality of life
RCT	Randomised Controlled Trial
TFESI	Transforaminal Epidural Steroid Injection

1. Economic Approach/Overview

1.1. Aims and objectives of economic evaluation

a) To compare the cost effectiveness of TFESI and microdiscectomy for the treatment of sciatica secondary to PID.
b) To compare QOL outcomes for both treatments.

1.2. Overview of economic analysis

The within-trial economic analysis will be performed using individual patient level data from the NERVES trial. The analytical approach will take the form of cost-utility analysis. Based on trial evidence, incremental cost effectiveness ratios (expressed as cost per Quality Adjusted Life Year (QALY) gained) will be calculated by taking a ratio of the difference in the mean costs and mean utility measure.

1.3. Jurisdiction and Perspective

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 primary economic analysis will be from the NHS and personal social services (PSS) perspective. A secondary analysis will include the perspective of patients and carers and will additionally consider indirect costs associated with time off work.

1.4. Time horizon

The economic analysis will compare the costs and consequences of each arm over the first 54 weeks after randomisation.

2. Economic Data Collection and Management

2.1. Monitoring collection of health economic data

Trial health economists will work closely with the trial team throughout the data collection period. Data collection forms will be assessed throughout the trial period to monitor quality of the data and amend any forms or procedures if necessary.

2.2. Database management

Economic data will be stored securely on the trial database and managed by the trial database manager.

2.3. Data entry

All data will be entered by the central research team. Baseline questionnaires will be forwarded from the recruitment site to the central research team, follow up data collected by postal questionnaires will be returned to the central research team. The database will use controls to limit data entry to plausible values

2.4. Data validation and cleaning

Face validity tests will be conducted on data (e.g. to identify numerical outliers or misspelt text) and checked against the source documents. Corrections identified will be documented.

2.5. Data archiving

A copy of HE analysis files, derived datasets, interim datasets and final analysis will be locked and archived. Archived datasets will be held in Bangor University and will conform to the department data security policy and department data compliance, Data Protection Act and GDPR policies.

2.6. Statistical software used for HE analysis

Statistical analyses will be carried out in StataIC version 13 or later (StataCorp LLc, College Station, TX).

2.7. Identification of resources

Resource use will be measured pertaining to resources used in primary, secondary and personal social care services, and medication costs relating to trial drugs and concomitant medications based on Case Report Forms (CRFs) and patient self-report. Direct non-medical costs relating to out-of-pocket expenditures and indirect costs relating to time off work will be measured based on patient self-report.

2.8. Measurement of resource use data

The measurement of resource is based on complementary approaches using data collected as part of the trial and as part of routine care.

Participants' use of hospital services will be obtained from:

- Hospital Episode Statistics (HES): Data relating to participants' use of secondary care will be requested from NHS Digital (1) by the central research team. HES data contain details of all admissions to NHS hospitals in England and provide HRGs on the type of care patients receive including hospital admissions and outpatient visits, but do not provide details on locally-reimbursed costs such as CT scans. HES data will be collected on outpatient and inpatient attendances by each patient from the beginning of the financial year immediately prior to the first patient being enrolled, to (and include) the end of the financial year immediately prior to, or following, the final follow-up of the last patient. Preliminary application approvals for HES data from NHS Digital will commence Q3 2018 with HES data being requested in March 2019, after the last patient has completed follow-up.
- CRFs completed by medical or nursing staff, relating to treatments issued and additional treatments received.
- Resource Use Questionnaires completed by the participant to collect information on use of primary care services, personal social services, non-scheduled clinic attendance, out-of-pocket expenditures and indirect costs will be collected at baseline and at 6, 18, 30, 42, 54 weeks post-randomisation by administering a specifically designed resource use questionnaire (incorporated into patient questionnaire booklets) . The resource use questionnaire will be completed during clinic appointments except for weeks 30 and 42, where no clinic visits are scheduled and postal questionnaires will be issued. Because of

potential issues relating to completeness of routine data, these will be used to compliment HES data.

- Resources triggered by adverse events will be captured in the follow-up CRF for each patients experiencing a serious adverse event requiring hospitalisation. Because of potential issues relating to completeness of routine data, these will be used to compliment HES data.
- Medications use will be extracted from Concomitant Medication CRFs and supplemented by patient completed Resource Use Questionnaires relating to concomitant medications and adverse events.

All resource use will be measured irrespective of whether they are sciatica-related or otherwise.

2.9. Valuation of resource use data

All resource use will be valued in monetary terms using appropriate UK unit costs or participant valuations estimated at the time of analysis (cost year: 2018-2019). Adjustments will be made for inflation (2).

HRGs will be used as the main currency of the economic analysis for inpatient stays with cost codes allocated based on the latest available National Tariff (3). Obsolete National Tariff and Schedule codes will be uplifted using the Hospital & Community Health Services (HCHS) Index according to the current version of the compendium of Unit Costs of Health and Social Care (2). This resource will also be the source of unit costs which will be applied to primary health care and outpatient contacts.

Bundled National Tariff costs will be based on the hospital spell and incorporated excess ward days and whether the case was elective or emergency. Tariff codes will be obtained primarily from HES data but if unavailable, they will be assigned by reference to CRFs and an appropriate HRG code will be assigned. Similarly, appropriate HRGs will be applied to unassignable National Tariff HRG codes (such as UZ01C and WA14Z) appearing in the HES data.

Unbundled costs will be assigned using information recorded in CRFs (e.g. adverse events CRF). Appropriate HRGs will be assigned and the cost calculated from the National Schedule codes (4). In the absence of any higher cost code indicators, a basic code will be applied from the National Schedule of Reference Costs.

Unit costs of medicines will be taken from the British National Formulary (BNF) (5) and the England Prescription Costs Analysis (PCA) (6).

2.10. Identification of outcome(s)

The primary economic (health) outcome measure will be Quality Adjusted Life Years (QALYs), generated from utility data measured using the EQ-5D-5L (7).

2.11. Measurement of outcomes

Participants will be asked to complete the EQ-5D-5L at baseline, 18, 30, 42 and 54 weeks after randomisation. At baseline, 18, and 54 weeks the questionnaire will be completed during a clinic visit, and at weeks 42 and 54 via a postal questionnaire.

2.12. Valuation of outcomes

Utility scores will be obtained using the EQ-5D-5L quality of life instrument using England tariffs (8). These will be used to calculate QALYs over the 54-week period, adjusting for any imbalances in baseline EQ-5D-5L utility scores.

3. Economic Data Analysis

3.1. Analysis population

The primary analyses will include all participants.

Full analysis set: All randomised participants which is in accordance with the 'intention to treat' (ITT) principle.

3.2. Timing of analyses

The within-trial analysis will be conducted once all patients have been followed for 54 weeks after the first intervention (microdiscectomy surgery or TFESI injection). Recruitment commenced in January 2015 and completed in December 2017. The follow-up period will run for 54-60 weeks (to allow for a 6 week window for the final visit), until February 2019.

3.3. Discount rates for costs and benefits

The time horizon for the analysis is 54 weeks; discounting will not be applied since the analysis period is restricted to 1 year.

3.4. Cost-effectiveness thresholds

The estimated mean QALYs and costs associated with each treatment option will be combined with a feasible range of values for decision makers' willingness to pay (ʎ), to obtain distribution of net benefits at different levels of ʎ. The primary economic analysis will use a cost-effectiveness threshold of £20,000 per QALY (9).

3.5. Statistical decision rules

All statistical tests will be two-sided and the statistical significance level will be set at 5%

3.6. Analysis of resource use

Differences in the use of services between randomised groups will be described and tabulated, reporting mean resource use items for each intervention and the difference between the interventions, with bootstrapped 95% confidence intervals.

3.7. Analysis of costs

For the primary analysis, within-trial total costs for each patient will be calculated from the sum of all costs (associated with primary, secondary and community care services, and medication use). Indirect costs (including time off work) will be calculated and included in a secondary analysis.

Costs at baseline, relating to the 3-months preceding randomisation, will be calculated from HES data, CRFs and patient questionnaires. This will relate to all primary and secondary care usage, and

concomitant medication. This will be used in case an adjustment is necessary for any baseline differences (10).

If a hospitalisation is observed for the period subsequent to randomisation, an adjustment may be necessary to apportion costs given that ward costs relate to episodes of care which could start prior to randomisation.

Participants' use of healthcare resources, and total costs will be calculated for the intention to treat population, with summary statistics generated by intervention group. We will apply regression techniques to analyse the data as appropriate (11). We propose the use of Seemingly Unrelated Regression (SUR) (12) which allows for the correlation between the costs and the QALYs, but will consider other regression techniques as the data allows.

3.8. Analysis of outcomes

The primary outcome for the economic evaluation will be quality-adjusted life years (QALYs) of the patient at 54 weeks. Utility values will be obtained from the individuals' health related quality of life responses to the EQ-5D-5L questionnaire at baseline, 18, 30, 42 and 54 weeks. Responses will be converted into a utility using English tariff values. These utilities will represent patients' overall quality of life and be multiplied by the time spent in each state according to the trapezium rule, and corrected for baseline utility score, to generate QALYs for each intervention.

An appropriate regression model will be used to adjust for any imbalance in baseline utility (however small) and the minimisation variables of the randomisation process (11,13). We propose the use of Seemingly Unrelated Regression (SUR) (12) which allows for the correlation between the costs and the QALYs, but will consider other regression techniques as the data allows.

A sensitivity analysis will be conducted to consider the impact on the incremental cost-effectiveness ratio, of the EQ-5D Visual Analogue Scale (VAS), an alternative utility score measured alongside the EQ-5D-5L.

3.9. Missing data

Trial data will be examined for any missing data. The appropriate method for dealing with missing data will depend on the share of missing data and likely mechanism of missingness. For example multiple imputation methods may be used if the data is missing at random (MAR) or missing not at random (MNAR) (14,15). Datasets generated with imputed data will subsequently be utilised within costs and outcomes regressions to generate point estimates for the base case analysis.

3.10. Analysis of cost effectiveness

Cost and QALY data will be combined to calculate incremental cost-effectiveness ratios (ICERs).

The ICERs will be calculated as:

$$ICER = \Delta Costs / \Delta QALY$$

where, ΔCosts is the difference in mean total costs between interventions (cost TFESI subtract cost surgery); and ΔQALY is the difference in mean QALYs between interventions (QALY TFESI subtract QALY surgery).

Dominance and will be reported, following standard definitions.

3.11. Subgroup analyses/Analysis of heterogeneity

Subgroup analysis will be conducted on the final data sets in accordance with the NERVES SAP to investigate how cost-effectiveness varies by subgroup. However, due to the small patient numbers recruited into the trial (N=150), any conclusions drawn from subgroup analyses may be subject to uncertainty and of limited value.

All analyses will be adjusted for site in accordance with the NERVES SAP. Heterogeneity will be analysed using appropriate regression based methods.

3.12. Sensitivity analyses

Sensitivity analyses will be conducted to assess the impact of parameter uncertainty on the ICER through a range of one-way sensitivity analyses. Multivariate sensitivity analyses will be applied where interaction effects are suspected.

Joint uncertainty in incremental costs and QALYs will be considered through nonparametric bootstrapping using 10,000 replicates and represented as a cost-effectiveness plane, and as a cost-effectiveness acceptability curve (CEAC), illustrating the probability of each intervention being cost effective for £20,000 per QALY and higher cost-effectiveness thresholds (16).

Uncertainty relating to missing data will be assessed through considering complete cases and through bootstrapping the entire imputation and estimation process (17).

3.13. Post hoc analyses

We will identify and clearly record any post hoc analyses.

4. Reporting/Publishing

4.1. Responsibility for health economic results and reporting

The following HEs [Professor Dyfrig Hughes, Eifiona Wood] have overall responsibility for the production and reporting of the results of the economic evaluation. The HEs are responsible for checking that the results for any outcomes reported in the economic evaluation are consistent and accurate. Any differences in results are to be raised with the Trial Statistician before being reported.

4.2. Reporting standards

CHEERS guidelines will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers (18).

4.3. Reporting deviations from the HEAP

Any deviation from HEAP will be described and justified in the final report (HTA monograph)

5. Document location

The economic evaluation master file is held at CHEME, Bangor University. The statistical master file holding details of the randomisation process and relevant protocol deviations is held at CTRC, University of Liverpool.

6. References

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Health Economic Evaluation Reporting Standards (CHEERS) statement. Eur J Heal Econ. 2013;14(3):367–72.

7. Appendices

7.1. Appendix 1: CHEERS checklist

Section/item	Item No	Recommendation
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.

Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.

Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.