UCL Comprehensive Clinical Trials Unit

TARVA
RANDOMISED CLINICAL TRIAL

TARVA (Total Ankle Replacement Versus Arthrodesis Trial)

HEALTH ECONOMIC ANALYSIS PLAN (HEAP)

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1. ABBREVIATIONS

BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CI	Confidence interval
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
HRG	Healthcare Resource Groups
ICER	Incremental cost-effectiveness ratio
MOXFQ	The Manchester-Oxford Foot Questionnaire
QALY	Quality adjusted life-year
PSSRU	Personal Social Services Research Unit
RRP	Recommended Retail Price
SAP	Statistical analysis plan
TAR	Total Ankle Replacement
VAS	Visual Analogue Scale
UK	United Kingdom

PURPOSE OF HEALTH ECONOMIC ANALYSIS PLAN

The purpose of this health economic analysis plan is to set out in detail the analysis and reporting procedure intended for the economic analyses to be undertaken in the TARVA trial.

While the intentions outlined in this plan will be followed as closely as possible, any deviations from this plan will be justified in the final report.

2. ECONOMIC ANALYSIS BACKGROUND

Aim

The aim of the economic evaluation is to assess the cost-effectiveness of Total Ankle Replacement (TAR) versus ankle arthrodesis in patients with end stage ankle osteoarthritis.

All analyses will follow the assumptions made in the statistical analysis plan (SAP) regarding missing data and loss to follow-up. In line with the SAP, the primary economic evaluation will be an intention-to-treat analysis.

Perspective

The primary health economic (within-trial) analysis will be cost-utility analysis and will be conducted from the health care and personal social services perspective, and the societal perspective.

Time horizon

The primary analysis will compare the costs and benefits of each arm of the trial over the time horizon of 52 weeks. A further economic analysis will use patients' lifetime as the time horizon.

3. OUTCOMES

A full description of all outcomes and analysis are provided in the statistical analysis plan (SAP).

The following outcomes will be used for the economic evaluation:

- Quality of life: EQ-5D-5L. This is a five item, five level questionnaire, scored 1 (no problem) to 5 (extreme problems). The questionnaire is completed at baseline, 12, 26 and 52 weeks post-operation. EQ-5D-5L Crosswalk Index Value Calculator was used to estimate the index values. It maps EQ-5D-5L to EQ-5D-3L value set and is recommended by National Institute for Health and Care Excellence (NICE) (van Hout et al., 2012). They are used to calculate utility scores used in the quality-adjusted life year (QALY) calculation. The EQ-5D-5L also includes a 100-point visual analogue scale (VAS), anchored at 0 with the worst health you can imagine and 100 with the best health you can imagine. Participants mark how they feel on the day they complete the measure.
- Healthcare resource use: adapted client service receipt inventory (CSRI) (Beecham & Knapp, 1992). It is a patient completed questionnaire asking about health and social care resource use, impact on employment, out of pocket costs and help from unpaid carers at baseline and 12, 26, and 52 weeks post-operation. Surgery Case Report Form (CRF) provides information on the surgery procedure that will allow us to estimate the cost of the TAR intervention and the cost of ankle arthrodesis. It is completed by Designated Individual with input from operating surgeon. It consists of two parts: Part I for both TAR and ankle arthrodesis and Part II for arthrodesis operation only. Additional data was collected from patient records to assist with the costing of the intervention.

4. COST DATA

Cost data are comprised of cost of the intervention (TAR or ankle arthrodesis) and other health service resource use.

Cost of the TAR intervention

The cost of TAR will be calculated based on the information in the "Surgery" CRF and patient records. It collects information on the duration of the operation, whether Tourniquet is applied and its duration, whether drain is used, skin closure approach, dressing type, immobilisation type and its duration. The following data is also collected from patient records:

- operating surgeon and his/her grade,
- surgical approach,
- if the surgery was computer guided,
- whether bone graft was used,
- list of components (talar component, tibial tray component, meniscal component, cement (if used) and accessories).

Unit costs will be based on Recommended Retail Price (RRP) for various TAR devices sites used.

We will report mean cost per patient of TAR. We will stratify in line with the SAP by the following variables:

- surgeon;
- presence of OA in two adjacent joints (subtalar and talonavicular) as determined by a pre-operative MRI scan.

Cost of ankle arthrodesis

The cost of the arthrodesis will be calculated based on the information in the "Surgery" CRF. It includes details on the duration of the operation, whether Tourniquet is applied and its duration, whether drain is used, skin closure approach, dressing type, immobilisation type and its duration. Part II of the CRF also includes information on the surgical approach, anaesthesia, associated procedures, thromboprophylaxis regime, intra-operative event(s) and implant details (type, manufacturer, number of implants used). Operating surgeon's grade is obtained from patient records. Unit costs for the implants will be based on RRP.

We will report mean cost per patient of the arthrodesis procedure. We will stratify by the variables listed above.

Cost of health service resource use

The data on health service resource use is collected in the CSRI. It is completed at baseline, 12, 26 and 52 weeks post-operation. Cost components include overall hospital length of stay, outpatient attendances and prescribed medications. Descriptive statistics for the percentage of patients and mean number of contacts for each type of health, social

care and employment outcome collected by the CSRI will be reported for patients that have completed the CSRI at 12, 16 and 52 weeks post-operation. Information on data completeness will also be reported.

The cost components will be costed for each patient using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) and reference costs (Curtis & Burns, 2018; NHS Improvement, 2018). Mean cost per patient for the intervention arm versus control arm will be reported by type of service use at 12 and 52 weeks post-operation. To calculate the difference in costs at 12 months between intervention and control arm costs will be adjusted by baseline values. 95% CIs will be calculated based on bootstrapped results.

Total costs

The overall mean cost per patient will be reported and will be the sum of the different costs per patient described above. For patients who die during the follow-up, their recorded costs will be included up to their date of death. We will stratify by the variables listed above.

Societal costs

The CSRI questionnaire is used to collect information on costs borne by the patient, including time and travel costs incurred in the receipt of care, out-of-pocket expenditures and time off work/usual activities.

The cost of lost employment for the TAR arm versus arthrodesis arm will be calculated from patients completed CSRI at baseline, 12, 26 and 52 weeks post-operation using the human capital approach. The approach is to multiply the number of lost hours by the median hourly wage in the United Kingdom (UK).

5. THE OVERALL ECONOMIC EVALUATION

Cost-utility analysis: mean incremental cost per QALY gained of TAR versus ankle arthrodesis. The primary measure used to calculate QALYs will be the EQ-5D-5L. QALYs will be calculated as the area under the curve using the EQ-5D-5L utility values at baseline and 12, 26 and 52 weeks post-operation adjusting for baseline values using regression analysis (Hunter et al., 2015). Stratification covariates will also be tested in the regression analysis.

We will report the incremental mean difference in costs and QALYs between the two arms of the trial and 95% confidence intervals adjusting for surgeon clustering and other variables described in the SAP.

Analyses will be performed using STATA programs (*.do).

6. PRIMARY WITHIN-TRIAL ANALYSES

Incremental cost-effectiveness ratio (ICER)

Cost and QALY data will be combined to calculate an incremental cost-effectiveness ratio (ICER). Uncertainty in the point estimate of cost per QALY will be quantified using bootstrapping methods to calculate confidence intervals around the ICER. Costs will be bootstrap adjusted costs calculated as reported in section 4 and will include the cost of TAR and ankle arthrodesis and costs of health service resource use (Briggs, Wonderling, & Mooney, 1997). QALYs will be bootstrap adjusted calculated using the EQ-5D-5L and the methodology described in section 5.

Cost-effectiveness acceptability curve (CEAC) and cost-effectiveness plane (CEP)

The bootstrap results will be used to calculate the CEAC (Hunter et al., 2015): the probability that TAR is cost-effective compared to ankle arthrodesis at 52 weeks for a range of willingness-to-pay for an additional QALY. A CEP of the bootstrap results will also be reported.

The results will also be subjected to extensive deterministic (one-, two and multi-way) sensitivity analyses.

7. MISSING DATA AND SENSITIVITY ANALYSES

In line with the SAP, the primary analysis will be conducted following the intention-to-treat principle in accordance with the randomised intervention. The primary analysis will be a complete case analysis unless >15% of patients are missing an ICER. If >15% of patients are missing an ICER, we will examine the data for predictors of missingness assuming that data are missing at random. If predictors of missingness can be identified these will be used to impute data using multiple imputation by chained equations. The primary ICER and CEAC will be reported based on imputed results.

8. FURTHER ECONOMIC ANALYSIS

A decision analytic model will be developed to combine all relevant input data and to estimate costs and benefits over a lifetime horizon. This section presents a brief description of the model.

We are planning to use Markov model with the following health states: revision operation, reoperation other than revision, infection, non-union, adjacent arthritis, below knee amputation and death. The model structure will be confirmed after the systematic search of literature is completed. Following the final decision about model structure, a list of parameters required for the model will be developed. Both costs and outcomes will be obtained from the trial, where relevant, and from published sources and administrative databases, such as the National Joint Registry.

Costs will be estimated using unit costs from the most recent Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) (Curtis & Burns, 2018) and reference costs (NHS Improvement, 2018).

Outcomes will be measured in terms of QALYs. Outcomes beyond the trial follow-up period will be obtained from the literature. Complication rates will also be estimated from the best available literature relevant to the NHS population.

Cost-effectiveness will be reported as the incremental cost per QALY gained. Uncertainty in the model parameters will be captured by probabilistic sensitivity analysis using Monte Carlo simulations. In this approach model parameters are defined by probability distributions and model results are calculated repeatedly over a specified number of simulations. For each simulation a random draw from each distribution is made and used to estimate parameter values for that simulation. All simulations are then taken together to provide mean estimates of costs and outcomes along with Bayesian credible intervals. Mean costs and outcomes for each treatment are compared and expressed as incremental cost per QALY gained. Overall decision uncertainty will be calculated and presented using CEACs. Additional one-way, two-way and scenario sensitivity analysis will be undertaken to test assumptions made in the initial model structure (these assumptions are not subject to parameter uncertainty but may influence results).

Long term costs and outcomes will be discounted using discount rates recommended by NICE (NICE, 2013).

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