TOPSY

HEALTH ECONOMICS ANALYSIS PLAN (HEAP)

FINAL VERSION 1.0

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Contents

Section 1: Economic Approach 3
1.1 Aims of economic evaluation 3
1.2 Objectives of economic evaluation 3
1.3 Overview of economic analysis 3
1.4 Perspectives 3
1.5 Time horizon 3
Section 2: Economic Data Collection and Management 3
2.1 Statistical software use for health economic analysis 3
2.2 Identification of resources 3
2.3 Measurement of resource use data 3
2.4 Valuation of resource use data 4
2.5 Outcomes 4
Section 3: Economic Data Analysis 4
3.1 Analysis population 4
3.2 Timing of analyses 4
3.3 Discount rate for costs and benefits 4
3.4 Cost-effectiveness thresholds 4
3.5 Statistical decision rule 5
3.6 Missing data 5
3.7 Analysis of cost-effectiveness 5
3.8 Uncertainty 5
3.9 Impact of COVID-19 pandemic on resource use 5
Section 4: Modelling 5
4.1 Extrapolation using decision analytic modelling 5
4.2 Model type 5
4.3 Model structure 6
4.4 Treatment effect beyond the end of the trial 6
4.5 Methods for identifying and estimating parameters 6
4.6 Model uncertainty 6
Section 5: References 7

Section 1: Economic Approach

1.1 Aims of economic evaluation

The aim of this economic evaluation is to investigate the cost-effectiveness of self-management of vaginal pessaries to treat pelvic organ prolapse, compared to standard care to improve women's quality of life.

1.2 Objectives of economic evaluation

The primary objective of the economic evaluation is to calculate the cost-effectiveness of self-management to treat pelvic organ prolapse versus standard NHS treatment in a within-trial-economic evaluation. A secondary objective is to estimate the long-term cost-effectiveness by using decision analytic modelling to examine costs and outcomes of pessary self-management compared to standard pessary care beyond the trial period and over a period of 5 years.

1.3 Overview of economic analysis

The within-trial economic analysis will be performed using individual patient level data from the TOPSY RCT. The analytical approach will take the form of cost-utility analysis (CUA) which will include calculation of incremental cost-effectiveness ratios (ICERs) and probability of cost-effectiveness for a given level of a willingness to pay. Sub-group analysis will be performed according to the main trial statistical analysis and similarly to how this is described in the trial Statistical Analysis Plan.

1.4 Perspectives

This economic evaluation will take an NHS perspective. We will separately report all collected variables and some of these may have wider societal implications such as care arrangements of patients.

1.5 Time horizon

The primary economic analysis will compare the costs and consequences of each arm over the first 18 months after randomisation. A secondary analysis will extend this using modelling beyond the data trial collection period having a 5-year time-horizon. A 5-year horizon was chosen because it can be safely assumed that conditions and characteristics of patients will be broadly the same across the period. This may also be relevant to NHS funding cycles.

Section 2: Economic Data Collection and Management

2.1 Statistical software use for health economic analysis

Stata version 13 (1) will be used for the main statistical analysis involving multiple imputation in case of missing data and cost-effectiveness analysis reporting probability of cost-effectiveness.

2.2 Identification of resources

The following items will be recorded: health service resource use, personal expenditure on health care and costs related to the continued implementation of the intervention such as training of staff and patients excluding one off trial set up costs.

2.3 Measurement of resource use data

Patients' NHS Resource use will be recorded with a combination of routinely collected data and questionnaires designed for this trial. Randomised women will complete questionnaires at 6, 12 and 18 months about health service resource use and quality of life. In particular, standard care women

will be seen up to 4 times (the actual number of times for each woman will be centre driven) at baseline, 6, 12 and 18 months. Due to the nature of self-management women in the intervention group will be seen at baseline and 18 months but attendance will be recorded via a clinic visit log CRF. We will also make use of telephone log CRF's to capture how many times women call for support in both trial arms. All the above information will be incorporated in the cost-effectiveness analysis. We will report on how COVID-19 may have impacted on data collection and if this is relevant to the economic analysis e.g. if data collection employed shorter questionnaires which were adapted for conditions related to the COVID-19 pandemic.

2.4 Valuation of resource use data

All resource use will be valued in monetary terms using appropriate unit costs from published sources (2). NHS reference costs will be employed to value hospital and primary care resource use (3). Medications will be valued using the BNF (4).

2.5 Outcomes

The primary economic outcome measure will be quality-adjusted life years (QALYs) derived from utility scores using the EQ-5D-5L (5) quality of life instrument. Measurements will be recorded at baseline and 6, 12 and 18 months post randomisation. Utility scores will be derived from responses to the EQ-5D-5L. UK utility values will be derived using an approach recommended by NICE. These will be used to calculate QALYs over the 18-month period, adjusting for baseline patient characteristics and any imbalances in baseline EQ-5D-5L scores.

Section 3: Economic Data Analysis

3.1 Analysis population

The full analysis set will include all randomised participants based on the definition of "on treatment" for the TOPSY trial (see definition in the TOPSY statistical analysis plan). We will report incremental cost-effectiveness results based on an "intention to treat" sample. The intervention and control groups for the purposes of the economic analysis will follow the same sampling approach as in the main statistical analysis of the TOPSY trial in both "on treatment" and "intention to treat" analyses. The data for the economic analysis will be prepared by the trial statistician according to the same principles of the main statistical analysis (6).

3.2 Timing of analyses

The primary analysis will be conducted once all patients have been followed for 18 months after randomisation.

3.3 Discount rate for costs and benefits

A discount rate of 3.5% will be applied to costs and outcomes as recommended by NICE (7).

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, to obtain the distribution of net benefits at different levels of willingness-to-pay. The primary economic analysis will report the probability of cost-effectiveness for the range of willingness-to-pay between £20,000 to £30,000 per QALY gained.

3.5 Statistical decision rule

Mean differences in costs QALYs and net benefits between the treatment groups will be estimated with associated 95% confidence intervals.

3.6 Missing data

Multiple imputation will be employed to maximise the usable data in the economic evaluation. Both costs and outcomes will be analysed using methods to account for missing data. We will investigate if the missing data are being generated randomly for example due to a missing completely at random or a missing at random mechanism or not randomly and appropriate multiple imputation methods will be used (8). We will only impute resource use data that are missing at 12- or 18-months using data from the 6-month follow-up. In the case of unbalanced missing data in the two trial arms multiple imputation will be performed using predictive mean matching (9).

3.7 Analysis of cost-effectiveness

Cost-effectiveness analyses will follow standardised protocols (6). The main economic outcome will be the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per incremental change in per QALY gained. Results will be reported according to published guidelines (10).

3.8 Uncertainty

The CEA will be conducted using methods that account for uncertainty in the cost and outcomes of the trial participants. This will be combined with the multiple imputation methods used to deal with missing data. The chosen methods will minimise bias in the CEA estimates of cost-effectiveness.

3.9 Impact of COVID-19 pandemic on resource use

The COVID-19 pandemic started in March 2020 which may have affected resource use of trial participants in both arms. We will investigate this by examining patterns of resource use pre- and post-March 2020. We expect to see a rise in telephone or virtual appointments taking place after the lockdowns have started since patients may have been unable to attend in-person. We will conduct sensitivity analysis on the costings of these replacement appointments which will be costed either as a normal face-to-face appointment or as a telephone appointment according to published sources (2).

Section 4: Modelling

4.1 Extrapolation using decision analytic modelling

Decision analytic modelling will be undertaken to extrapolate costs and outcomes beyond the follow up period of the trial, irrespective of statistical significance in trial results, to investigate if there is potential for the cost effectiveness to improve under a longer analysis time horizon than the 18 months follow up. With the development of this model the main analysis will be extended to a 5-year horizon. Any information or knowledge about future use of services collected during the trial will inform the development of the model to make it as accurate as possible in terms of its predictive power. The model will be developed using recommended methods (11).

4.2 Model type

A Markov microsimulation decision model with monthly cycle will be used to evaluate effects of the intervention on costs, health related quality of life (HRQoL) gains and cost-effectiveness over a 5-year horizon.

4.3 Model structure

The decision model will comprise two arms, with one arm for each intervention evaluated (intervention vs standard practice). Each arm will be structured as a Markov model built around health states to which health care cost and HRQoL data collected as part of the trial will be linked. The model structure will be designed with clinical input from the trial management team.

4.4 Treatment effect beyond the end of the trial

The mean difference in HRQoL observed during the trial between the intervention and standard practice will be assumed to persist after then end of trial follow up. This will be sensitivity tested with scenarios where the impact of the intervention on HRQoL diminishes over time.

4.5 Methods for identifying and estimating parameters

We will make use of any information collected in the trial about future resource use and apply this in the decision analytic model. The model parameters will be derived from the trial data. 1) Transition probabilities between states 2) Treatment effects of the intervention 3) Quality of life 4) Health care costs. Other parameters will be parameterised using published data. Expert opinion will be used for any parameters that were not available in trial or published sources.

4.6 Model uncertainty

Key parameters will be manually varied to examine the impact on cost-effectiveness. Probabilistic sensitivity analysis will be employed to account for uncertainty across all model parameters (12).

Section 5: References

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