STANDARD OPERATING PROCEDURE 33
Health Economic Evaluation Considerations

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Version 3.0	16 July 2024	Biennial review. Addition of some definitions. Added to the responsibilities of the junior health economist (4.1). Expanded the economic database section (4.3.2.2). Expanded the monitoring of health economics data section (4.3.2.3). Added to the list of terms and updated some references.
Version 2.0	8 April 2022	Biennial review. Change to new format.
Version 1.2	30 January 2020	Biennial review. Change to new format.
Version 1.1	3 November 2017	Change to new format. Addition of use of eQMS (Q-Pulse) to approve Economic Evaluation Analysis Plans.
Version 1.0	23 February 2015	

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Health Economic Evaluation Considerations

1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to outline the requirements for an economic evaluation conducted alongside a clinical study. This SOP is applicable to all research staff who work on studies which include a health economic evaluation and for the Health Economists who work on University of Warwick sponsored research studies.

2. Definitions

Health economic evaluation	Health economics is a branch of economics concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of health and healthcare. A health economic evaluation compares the costs and outcomes of a healthcare intervention against a suitable comparator to assist decision makers in maximising benefits from limited healthcare resources.
Cost-benefit analysis (CBA)	An economic evaluation that expresses all gains and losses in common units (usually money), allowing a judgement to be made of whether, or to what extent, an intervention should be pursued.
Cost-consequences analysis (CCA)	A form of economic evaluation where the whole array of outcomes is presented alongside the costs, without any attempt to aggregate these.
Cost-effectiveness analysis (CEA)	An economic evaluation where costs are measured in monetary terms and outcomes are measured in units directly related to the intervention
Cost-effectiveness acceptability curve (CEAC)	A graph summarising the impact of uncertainty on the result of an economic evaluation, expressed as the probability of cost-effectiveness at a range of threshold values of willingness to pay.
Cost-minimisation analysis (CMA)	An economic evaluation where the outcomes of competing healthcare interventions are equivalent, so comparison is made on the basis of resource costs alone. The aim is to determine the lowest-cost way of achieving the same outcome.
Case Report Form (CRF)	A printed or electronic document designed to record all of the protocol required information to record for each study participant.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis where a health-preference measure is repeatedly recorded in patients over time, to calculate a quality-adjusted life year (QALY).
Incremental cost-effectiveness ratio (ICER)	Obtained by dividing the difference between the costs of the two interventions by the difference in the outcomes (i.e., the extra cost per extra unit of effect).
Willingness-to-Pay (WTP) threshold	The maximum amount that society is willing to pay for an additional quality-adjusted life-year (QALY)
Net monetary benefit (NMB)	A way to express measured costs and QALYs as a single monetary value at a given willingness to pay threshold (where NMB = QALY*WTP-Cost)
Health Economics Analysis Plan (HEAP)	Prospectively agreed analysis plan describing the presentation of results, base case, and secondary analysis.

Within trial analysis	Analysis of the costs and effects of treatment alternatives limited to changes occurring within the duration of the follow-up of a trial.
Cost-effectiveness model	A mathematical extension of a within trial analysis to facilitate (variously) extrapolating beyond the trial follow-up, adjusting the study population, and facilitating further analyses.
Expected value of perfect information (EVPI)	The monetary value to a decision maker of eliminating all decision uncertainty

3. Background

Health economic evaluation has increasingly been used to inform the regulatory and reimbursement decisions of government agencies throughout the industrialised world. A common vehicle for the conduct of economic evaluation is the randomised controlled trial (RCT). A key goal of a trial-based economic evaluation is to estimate the additional cost of a new intervention compared to the existing alternative, and what additional health benefits it produces, and to combine this information within a cost-effectiveness ratio. In order to undertake a rigorous trial-based economic evaluation, access to health economics expertise is essential at each stage of the study. This includes input from health economists during the design, conduct, analysis and reporting of the study.

4. Procedure

4.1 Responsibilities

Lead Health Economist	• Contribute to the design of the study • Supervise the junior health economist • Review the appropriateness of planned health economic analyses • Audit analysis coding • Review and contribute to reports of results and publications
Junior Health Economist	• Provide day-to-day input on health economics for the trial/study • Draft the HEAP (supervised by the senior health economist) • Access trial data to provide data completeness/quality updates to trial meetings, as agreed with the trial team. • Conduct (under supervision) the health economic analysis for the trial. • Draft reports of results and publications

Since mentoring is a key part of career development, variations in the above roles are sometimes appropriate. For example, for both lead and junior roles, a trial may include a more experienced economist supporting a colleague-in-training.

4.2 When?

Health economics input should be provided at each stage of the study, including during its design, conduct, analysis, and reporting.

4.3 How?

4.3.1 Planning and preparation of a clinical study

After agreement on the objectives and the economic question of interest in a study, the lead economist should identify a health economics researcher who will be responsible for the day-to-day running of the economic evaluation alongside the study.

A number of important choices regarding the economic evaluation will have to be made by the lead economist (with input from the junior health economist) and included in the protocol including:

i. Form(s) of economic evaluation to be adopted: these include Cost Utility Analysis (CUA), Cost-effectiveness Analysis (CEA), Cost consequences analysis (CCA), Cost-minimisation analysis (CMA) or Cost-benefit analysis (CBA). This choice will be guided by the scope and perspective of the study, the requirements of the decision maker/funder and the type of costs and outcomes data which are collected. See the following references for more information: Drummond and McGuire, 2001; Donaldson *et al*., 2002; Eggar *et al*., 2003; Drummond *et al*., 2015; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2022.

ii. Measure of outcome (effect/consequence/utility). This decision will be made in consultation with colleagues in the wider study team. More information can be found in the following references for guidance: Drummond and McGuire, 2001; Donaldson *et al*., 2002; Eggar *et al*., 2003; Drummond *et al*., 2015; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2022.

iii. The perspective of analysis. The current preferred approach is to adopt a National Health Service and Personal and Social Services (NHS/PSS) perspective or multi agency public sector where possible. Where this is not relevant, an NHS or societal perspective should be adopted (NICE, 2022).

iv. Type and range of resource use items to be measured. This choice will be informed by the perspective of the analysis and consultation with the wider study team. Further information can be found in the following references to help identify relevant resource and cost categories: Drummond and McGuire, 2001; Donaldson *et al*., 2002; Eggar *et al*., 2003; Drummond *et al*., 2015; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2022.

v. Method of measurement of resource utilisation. This could be by extraction of data from patient records, by patient recall using a variant of the Client Service Receipt Inventory (CSRI) (Knapp et al, 2006) or similar prospective data capture form, or by the use of data from a secondary data source, (e.g., Hospital Episode Statistics records). This decision should be made in consultation with the wider study team.

vi. Source of unit costs. Resource inputs should be valued (£ Sterling for the UK, for the most recent available financial year) using national tariffs where available or routine data sources if agreed by the study team. An early assessment should be made regarding how much primary research will be required for the estimation of unit costs. Where unit costs derive from different years these will be adjusted to a common base year using published health service reflators (Jones *et al.,* 2023)

vii. Method of collecting data relating to prescribed medicines. Data may be collected directly (from hospital notes and/or primary care) or through patient recall using a variant of the CSRI (i.e., a type of Case Report Form (CRF) that measures resource utilisation) or a similar approach. This decision will be made in consultation with the wider study team.

4.3.2 During the data collection period

4.3.2.1 Health Economic Analysis Plan

The study economist(s) will prepare a health economic analysis plan (HEAP) for the study following guidance on economic evaluations from the following references: Drummond and McGuire, 2001; Donaldson *et al*., 2002; Eggar *et al*., 2003; Drummond *et al*., 2015; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2022, Thorn et al 2021. This plan will be written and then, following consultation, approved by the Chief Investigator, at an early stage of the study (preferably before the end of recruitment, and certainly before data are shared with the HE team).

The HEAP would usually be expected to reflect the following general principles for economic analysis:

i. An intention to treat approach should be used for the base case analysis.
ii. The study health economist(s) should consistently address missing or censored data by making use of relevant statistical techniques to handle missing or censored cost and health-related quality of life data (Glick *et al*. 2007).
iii. Uncertainty analysis should be conducted by applying the standard methods (e.g., bootstrapping for calculating cost-Effectiveness acceptability curves (CEACs) and confidence intervals) (Glick *et al*. 2007; Groot Koerkamp *et al*., 2007; NICE, 2022).
iv. A time horizon that is appropriate to the analysis should be adopted (NICE, 2022).
v. Recommended discount rates for long-term costs and benefits should be applied (NICE, 2022).
vi. An appropriate cost-effectiveness threshold should be adopted according to established guidelines (NICE, 2022).

4.3.2.2 Economic database

The study economist should request access to the database via the trial manager and obtain the project's functional requirement specification (FRS) from the programming team. The study health economist(s) will manage the economic data in an appropriate software package (STATA, R, WinBUGS) in accordance with University SOPs and in compliance with the UK GDPR. For Warwick Clinical Trials Unit (WCTU) studies, the study health economist(s) will work in collaboration with WCTU's programming team to manage the data as specified above and resolve any coding issues or devise appropriate changes in response to issues arising early in each trial. All the documentation, programs for analysis, and data should be stored in a location on the M drive accessible only to the study economist and an appointed colleague that can access their encrypted files if the study economist is unavailable.

4.3.2.3 Monitor collection of health economics data

The study health economist(s) will work closely with the study team throughout the data collection period to ensure suitable data are collected and provide updates on data completeness for trial meetings as and when agreed with the Chief Investigator and statistician. Data collection forms (e.g. CRFs) will be assessed throughout the study period to monitor the quality of data and amend any forms or procedures if necessary.

The health economist(s) should carry out validation checks on the data quality and integrity (e.g., range checks, outliers, missing observations), recording checks performed within analysis records. These checks should begin early in the life of a trial, after an agreed initial recruitment, to identify and resolve coding/programming problems. The study economist(s) should refer any data queries arising during the analysis to the Study Manager/Coordinator for investigation or resolution.

4.3.2.4 Preparation for analysis

Where possible the health economics team will access an intermediate trial data set, e.g. follow-up is 50% complete. This permits detailed quality checks, may help identify data issues and allows analysis code to be developed that can be used for the final analysis. The adequacy of within trial analysis (or the need for further modelling) should be explored. Once developed, the analysis code and output should be audited by the lead health economist or other experienced colleague. The lead health economist is responsible for ensuring the veracity of the analysis coding.

4.3.3 After the data collection period

4.3.3.1 Economic analysis of data

i. Final validation checks should be completed, with any data queries referred to the Study Manager/Coordinator for investigation or resolution.
ii. Costs and outcomes for each study participant will be calculated. Costs and utilities should (normally) be analysed using a net monetary benefit framework (at a patient or group level) to produce incremental cost-effectiveness ratios (ICERs), cost-effectiveness planes and CEAC and EVPI.
iii. The base case (prospectively planned primary analysis) should be reported.
iv. The handling of any missing data within clinical studies is an important consideration, as failure to identify properly the influences of the missing data may cause bias and reduce the validity of findings.
v. Supportive sensitivity analyses should be carried out to assess the impact of uncertainties on the base case findings (e.g. relevant sub-groups, regression model specification, observed vs. imputed data). Prospectively planned and post hoc analysis should be clearly delineated.
vi. Decision-analytic modelling should be considered where within trial analysis may be inadequate. Reasons modelling may not be required include convergence of treatment group costs or utilities during the within trial follow-up; clear dominance of one of the treatments; or uninformative (poor quality) trial data.
vii. After completion of the trial, the key economic analysis documents (e.g., HEAP, analysis programs/scripts and final analysis report) should be added to the Trial/Study Master File (T/SMF) for archiving.

4.3.4 Report and publish

The results will be published in accordance with standard guidelines (e.g., Drummond, 1996; Ramsey *et al*., 2005; NICE, 2022; Husereau *et al*., 2022). In general:

i. The results of the analyses will be presented in a format that is appropriate for the stake holders and incorporated into the final study report.
ii. Wherever possible, the economic evaluation results will be published alongside clinical results.
iii. Effort will also be made to publish secondary analyses, particularly of a methodological nature, based on economic data collected as part of the study.

List of Terms/Abbreviations

CBA	Cost-benefit analysis
CCA	Cost-consequences analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CMA	Cost-minimisation analysis
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CUA	Cost-utility analysis
EVPI	Expected value of perfect information
FRS	Functional requirement specification
HEAP	Health Economics Analysis Plan
ICER	Incremental cost-effectiveness ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
PSS	Personal and Social Services
RCT	Randomised Controlled Trial
R&IS	Research & Impact Services
SOP	Standard Operating Procedure
WCTU	Warwick Clinical Trials Unit
WTP	Willingness-to-Pay