STANDARD OPERATING PROCEDURE 33
Health Economic Evaluation Considerations

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Version 2.0	8 April 2022	Biennial review. Change to new format.
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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	

STANDARD OPERATING PROCEDURE 33
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 sacrifices 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 are 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, frequently expressed as an ICER (incremental cost-effectiveness ratio) in relation to possible values of the cost-effectiveness threshold.
Cost minimisation analysis (CMA)	An economic evaluation where the outcomes of competing healthcare interventions are identical, 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 report on each study participant.
Cost utility analysis (CUA)	A form of cost-effectiveness analysis where outcomes are measured in terms of a utility measure such as the 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).

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 and confirm appropriateness of health economic analyses • Review and contribute to reports of results and publications
Junior Health Economist	• Provide day-to-day input on health economics for the trial • Conduct (under supervision of the senior health economist) health economic analysis for the trial. • Write first draft reports of results and publications

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 senior study economist should select 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 senior study 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*., 2005; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2013.

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*., 2005; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2013.

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, 2013).

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*., 2005; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2013.

v. Method of measurement of resource utilisation. This could be via, extraction of data from patient records, by patient recall via 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.

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*., 2005; Ramsey, *et al*., 2005; Glick *et al*., 2007; NICE, 2013, 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). via the Q-Pulse electronic quality management system.

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 calculation of cost-Effectiveness acceptability curves (CEACs) and confidence intervals) (Glick *et al*. 2007; Groot Koerkamp *et al*., 2007; NICE, 2013).
iv. A time horizon that is appropriate to the analysis should be adopted (NICE, 2013).
v. Recommended discount rates for long-term costs and benefits should be applied (NICE, 2013).
vi. An appropriate cost-effectiveness threshold should be adopted according to established guidelines (NICE, 2013).

4.3.2.2 Economic database

The study health economist(s) will manage the economic data in an appropriate software package 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.

4.3.2.3 Monitor collection of health economics data

Training will be provided to individuals responsible for administering the health economics questionnaires. The study health economist(s) will work closely with the study team throughout the data collection period to ensure suitable data are collected. 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.

4.3.3 After the data collection period

4.3.3.1 Economic analysis of data

i. Prior to analysing the data, 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 be performed early in the life of a trial, after an agreed initial recruitment, to identify and resolve coding/programming problems not identified earlier in the recording and monitoring process. The study economist(s) should refer any data queries arising during the analysis to the Study Manager/Coordinator for investigation or resolution.
ii. Costs and outcomes for each study participant will be calculated.
iii. The costs and benefits should be analysed to produce: incremental cost-effectiveness ratios (ICERs), cost-effectiveness planes and CEACs.
iv. Sensitivity analyses should be carried out to assess the impact of uncertainty on the final results.
v. Decision-analytic modelling should be considered where this would be of assistance to decision-making e.g. when costs and outcomes need to be extrapolated beyond the follow-up period of the study.
vi. 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 possibly nullify the value of the obtained results, as their validity could be questionable.

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, 2013; 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
ICER	Incremental cost-effectiveness ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PSS	Personal and Social Services
RCT	Randomised Controlled Trial
R&IS	Research & Impact Services
SOP	Standard Operating Procedure
WCTU	Warwick Clinical Trials Unit