

# Synthesizing Economic Evidence

Catalin Tufanaru

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# **Synthesizing Economic Evidence**

**Catalin Tufanaru**

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This series of concise texts is designed to provide a “toolkit” on synthesising evidence for healthcare decision making and for translating evidence into action in both policy and practice. The series seeks to expand understanding of the basis of evidence-based healthcare and brings together an international group of scholars to describe, discuss and debate critical issues in the field.

Incredible developments in the synthesis and use of evidence in healthcare over the last several years have occurred, but the accompanying science and emerging practices that underpin evidence based healthcare are often poorly understood by policy makers and health professionals. This is unfortunate because several emerging and exciting developments have much to offer this group. Firstly, new, deeper understandings of the nature of evidence and of ways to appraise and synthesise it have led to the development of more sophisticated methodologies for synthesis science. Secondly, the realisation that the rapid increase in the availability of high quality evidence has not been matched by increases in the translation of this evidence into policy and/or clinical action has spurred on developments in the science of knowledge implementation and practice improvement.

The burgeoning publications in this area – particularly books on evidence based healthcare: can go only so far in informing responsible and conscientious policy makers and healthcare practitioners. This new series, Lippincott/Joanna Briggs Institute, “Synthesis Science in Healthcare”, is devoted to communicating these exciting new interventions to both researchers and clinicians who are on the front line of practice or influence policy.

The books in this series contain step-by-step detailed discussions and practical processes for assessing, pooling, disseminating and using the best available international evidence. In all healthcare systems, there is growing consensus that evidence-based practice offers the most responsible course of action for improving health outcomes. All clinicians and health scientists want to provide the best possible care for patients, families and communities. In this series, our aim is to close the evidence to action gap and make that possible.

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# Introduction

Systematic reviews of economic evidence select, critique and synthesize data from multiple economic evaluation primary research studies on the economic aspects of healthcare. They can provide relevant evidence on efficiency, resulting in less biased, decision-maker oriented information, which may be more likely to convince decision makers compared with evidence from single studies.

In resource-constrained environments, it is essential that decision makers not only examine the effectiveness of interventions but also consider the economic aspects of an intervention, such as whether its adoption will lead to a more efficient use of resources. Promoting effective care without taking into account the costs of care can lead to the inefficient use of funds allocated within health care, which may result in harm for individuals and society.

The increased availability and acceptance of economic evaluation is evidenced by its growth as a tool in health technology appraisals to guide pharmaceutical listings and reimbursement decisions. Similar to effectiveness reviews, it is equally important to systematically appraise and synthesize economic evidence to produce robust evidence on cost-effectiveness. Healthcare providers and policy makers are often provided with large amounts of information. It is unlikely that all will have the time, skills and resources to find, appraise and interpret this evidence and to incorporate it into healthcare decisions.

The primary aim of systematic reviews is to use explicit, pre-specified scientific methods to identify, select, assess, and synthesize the results of similar separate studies, and help users to understand the evidence. Reviews of economic evaluations are complementary to systematic reviews of effectiveness in supporting more efficient health policies and reduce the cost of decisions made based on methodologically weak studies. Other reasons for undertaking this type of review include to inform the development of a decision model; to identify the most relevant economic evaluation to inform a particular question; and to identify the key economic trade-offs implicit in a particular treatment choice.

When healthcare decisions are evidence-based, patients will receive care that is safe, effective, cost-effective, promotes comfort and facilitates best outcomes. It is important to ensure that this evidence is easily accessible to those who are involved in planning and implementing care to support the decisions they make in collaboration with patients, their families and members of the multidisciplinary team. The increasing volume of healthcare articles and vast amount of information creates a more pressing need for a summary/synthesis of all available evidence. Systematic reviews provide a means of having comprehensive and unbiased summaries of research.

Systematic reviews are an advance compared to traditional literature review. Systematic reviews are the best available source of evidence.

This book presents step by step methodological guidance for systematic reviews of economic evidence that are designed to inform healthcare decision making.



## The Synthesis of Economic Evidence

# Chapter 1:

## *The nature of economic evidence*

**E**conomics is a field of study that examines and analyses the allocation of scarce resources amongst alternative uses. The foundation of economics relates to addressing the problem that resources are limited relative to human wants and that resources have alternative uses. The cost of medical care has been rising steadily for many years in all countries but it has only been relatively recent that the level of expenditure has become so large so as to cause concern amongst policy makers and payers. Healthcare costs present significant fiscal challenges in many developed countries and new policies have been introduced to contain the rising cost of medical care. Decision-makers must now consider cost when designing programs to prevent, diagnose, and treat disease.

The reasons for undertaking systematic reviews of economic evidence include: to inform the development of a decision model; to identify existing economic evaluation evidence to inform a particular question; and to identify the key economic trade-offs implicit in a particular treatment choice.

Healthcare decision makers have to consider evidence from different types of research, including effectiveness research and economic evaluation research. Evidence-based practice without evidence from economic evaluation is not realistic and may contribute to inefficient health policy and inequalities in health. The main issue in economics involves the choices made between different options based on the scarcity of resources. Resources available in a specific society have alternative beneficial uses and different people may place different values on the various health outcomes. In order to make the best decisions about alternative courses of action, evidence is needed on the value of benefits and also on the cost of resources used for these courses of action.

The current healthcare environment is one in which institutions and healthcare plans face limited budgets that need to be utilized in the most efficient manner. Thus, choices must be made regarding different treatments, taking into consideration both efficacy and cost. While practitioners often view cost as a non-important issue in the care of a patient, the impact of economics on day-to-day practice is increasing. Financial issues affect the availability of new technologies.

Where resources are limited, decision-makers need to consider not only whether an intervention is effective but whether it is also cost-effective. If a new intervention requires more resource

than current practice, then this will have to be found from elsewhere within the health system and adoption may displace other treatments or services. Considering economic aspects can make systematic reviews useful to health care decision-makers.

Archie Cochrane argued in his 1972 book, *Effectiveness and efficiency: random reflections on health services*, that “*allocations of funds and facilities are nearly always based on the opinions of senior consultants, but, more and more, requests for additional facilities will have to be based on detailed arguments with ‘hard evidence’ as to the gain to be expected from the patients’ angle and the cost.*”

## Economics and Economic Evaluation

Economics is the study of the optimal allocation of limited resources for the production of benefit to society. Resources include human time and skills, equipment, premises, energy and any other inputs required to implement and sustain a given course of action.

Health economics applies economic principles and theories to health and the health sector (Annemans, 2008). Health economic evaluation is only one part of the discipline of health economics.

A health economic evaluation is defined as a comparative analysis of both the costs and the health effects of two or more alternative health interventions (Annemans, 2008). The aim is to identify, measure, value and compare the cost and consequences of the alternative interventions being considered.

Cochrane (1972) asserts that: “*... if we are ever going to get the ‘optimum’ results from our national expenditure on the NHS we must finally be able to express the results in the form of the benefit and the cost to the population of a particular type of activity, and the increased benefit that would be obtained if more money were made available*”.

Some potential uses of health economic evaluation are: to justify the existence of a service; to justify the development of a new service; to justify the extension of an existing service; to inform the development of clinical guidelines; to inform the decisions on reimbursement of medicines; and to inform guidance on health technologies (Elliott and Payne, 2005).

An economic evaluation is essentially a tool to allow comparative health interventions to be evaluated in order to address the issue of efficient resource allocation. It is widely accepted that on their own, economic evaluations are not sufficient to inform decision making, but that they are a necessary component of the decision-making process.

A full economic evaluation provides a framework for structuring specific decision problems and considers both the effectiveness and cost data for two or more interventions being compared within the analysis. These can be conducted alongside, and incorporating, a systematic review of effects, including use of a decision-analysis approach for pooling or modeling the available evidence on intervention costs and effects (Briggs et al. 2006). A partial economic evaluation makes no comparison and simply describes a single intervention or service through consideration of costs or consequences alone.

A wide range of methods are used in economic evaluation, and therefore the methodological rigour of studies can vary; methods can be used inappropriately and decisions about the appropriateness of methods can impact on the quality and validity of a review. It is therefore

important that reviewers understand the methodological concepts associated with economic evaluation prior to undertaking a review of them.

The purpose of economic analyses is to try to address a particular question. This is most useful when there is a discrepancy between economic aspects and effectiveness. Effectiveness is a critical issue in economic evaluations because of the fixed nature of resources. If there were unlimited resources then one would always choose the most effective treatment or approach to a problem. The issue in economic analysis is that there is a trade-off in adopting a more effective but more costly alternative.

The elements of an economic evaluation study include:

- Type of economic evaluation
- Perspective of the analysis
- Types of costs
- Types of benefits
- Discounting
- Uncertainty/Sensitivity analysis
- Generalizability/transferability.

## Types of economic evaluation

A partial economic evaluation simply describes interventions or services through consideration of costs or consequences alone (but not both). Examples of types of partial economic evaluation are cost description; cost analysis; and cost of illness studies.

In a cost consequences analysis (CCA), the consequences of two or more alternatives are measured as well as the costs, but costs and consequences are listed separately (Rascati, 2009). The analyst provides a matrix of the outcomes by each strategy evaluated. This comparison enables decision makers to form their own opinions about the relative importance of the findings. In addition, the consequences of the two alternative interventions are measured using an appropriate scale for each consequence.

There are four basic types of economic evaluation studies:

- Cost-minimization analysis (CMA);
- Cost-effectiveness analysis (CEA);
- Cost-utility analysis (CUA); and
- Cost-benefit analysis (CBA).

Full economic evaluation provides a framework for structuring specific decision problems and considers both the effectiveness and cost data for two or more interventions being compared within the analysis. Generic types of full economic evaluation are: Cost-effectiveness analysis (CEA); Cost-utility analysis (CUA); and Cost-benefit analysis (CBA).

### ***Cost-minimization analysis (CMA)***

Cost-minimization analysis (CMA) is an analytic tool used to compare the net costs of programs that achieve the same outcome (Gold et al., 1996). In cost-minimization analysis, the effects of two alternatives offer equivalent outcomes. As such, only the costs of the interventions are compared. It is essentially a search for the minimal cost strategy and can only be

justified when outcomes are proved to be equivalent. The choice of cost-minimization analysis implies that the researchers are certain that there are no differences between the intervention and comparator in any of the patient outcomes (Hoch and Dewa, 2005). However, CMA is rarely an appropriate method of analysis because outcomes are not often considered equivalent. If there is concern that the outcomes may be different qualitatively then one should consider performing a cost-effectiveness analysis, assuming a difference in effect.

A common example of a cost-minimization analysis is comparing two generic medications that are rated as equivalent. If the drugs are equivalent in efficacy, the differences in the cost are used to choose the one that provides the best value. Another common example of a CMA is comparing the costs of receiving the same intervention in different settings (for example hospital versus home; inpatient versus outpatient). Further details for cost-minimization analysis are provided by Basskin (1998), Briggs and O'Brien (2001), Newby and Hill (2003), and Robinson (1993).

### **Cost-Effectiveness analysis (CEA)**

Cost-effectiveness analysis (CEA) is an economic evaluation in which costs and effects of a program and at least one alternative are calculated and presented in terms of their relative costs to achieve a given unit of effects (Drummond, 1990). Effects are health outcomes rather than monetary measures as in cost-benefit analysis (Gold et al., 1996). Cost-effectiveness analysis (CEA) uses one outcome common to both alternatives but achieved to different degrees as a measure of effects measured in natural units such as mmHg, cholesterol levels, symptom-free days, years of life saved (Hoch and Dewa, 2005).

The incremental cost-effectiveness ratio (ICER) is the incremental cost of obtaining a unit of health effect (such as dollars per year, or life expectancy) from a given health intervention, when compared with an alternative (Gold et al., 1996). Lists of ICERs in league tables are available for comparing the economic attractiveness of alternatives. However, the uncertainty inherent in measuring cost and effectiveness of medical interventions, and the methodological variations among studies, may influence the ranking of the studies and therefore decisions made using the league table.

One advantage of using a common unit for analysis is that comparisons can be made across groups or settings. Results of separate analyses from various health care settings can then be, at least in theory, compared across patient populations. However, one disadvantage of \$/life year (LY) gained is that 1 year of life in an altered health state is considered equal to any other year of life. Dollars per life year gained includes only length of survival, not quality-of-life issues such as patient inconvenience or suboptimal health states. Additionally, another drawback of CEA is that programs with different types of outcomes cannot be compared.

Further details for Cost-Effectiveness analysis are provided by Gray et al., (2011), Rascati (2009), Annemans (2008), Haddix et al., (2003), Petitti (2000), Bala and Zarkin (2002), Black (1990), Drummond et al., (2005), Gold et al., (1996), Lopert et al., (2003), Luce and Simpson (1995), Robinson (1993), and Willan and Briggs (2006).

### **Cost-utility analysis (CUA)**

Cost-utility analysis (CUA) is a special type of cost-effectiveness analysis that measures health consequences in terms of both quantity and quality of life. Consequences are typically

measured or valued as healthy years or quality-adjusted life-years (QALYs). Further comprehensive details about measuring and valuing health benefits, including a critical discussion of QALYs is provided by Brazier et al. (2007).

Composite outcome analyses, such as \$/QALY, have been used because they include both the quantity and quality of life and they require standardized measurement. Thus, comparison of people within and across disease states may be possible.

For the qualitative measure, individual preferences or utilities for different health outcomes are sought and included. Preferences generally indicate health states on a scale from 0 to 1. Perfect health is equal to 1 and death is a 0. Methods for eliciting utilities vary. The preference weights are then multiplied by the amount of time experienced in that health state. The outcome measure is quality-adjusted life years (QALYs).

Expecting that a person would sustain the same quality of life consistently over time is not realistic. People experience changes in health status. To calculate a QALY over time, individual QALYs are calculated for the time spent in each health state weighted by the quality of life in that health state. These scores are then summed to arrive at an overall QALY for each person. Because of the complexity of these equations, decision-analytic modeling techniques are often used.

Further details for Cost-utility analysis are provided by Drummond et al. (2005), Petitti (2000), Haddix et al. (2003), Gray et al. (2011), Rascati (2009), and Brazier et al. (2007), and Glick et al. (2007).

### ***Cost-benefit analysis (CBA)***

Cost-benefit analysis (CBA) is the broadest form of economic evaluation. Unlike cost-effectiveness analyses and cost-utility analyses, all costs and consequences of the program are expressed in the same units, usually dollars (Hoch and Dewa, 2005). Consequences can be identified as single or multiple effects; the effects are not necessarily common to both alternatives. This analytical method allows for comparisons across programmes within the healthcare system, or with programmes outside health care, such as education, energy, transportation or defence.

A single-dollar figure, representing the net social benefit of a program or intervention is expressed as the incremental benefit of the program less the incremental costs (Gold et al., 1996). If the net present value of benefits is positive, then decision makers may consider it desirable to use the proposed intervention.

The challenge with this approach is that it is difficult to measure the value of all health outcomes in dollars (Hoch and Dewa, 2005). Some benefits require a value judgment. Furthermore, ethical concerns complicate assigning a dollar amount to the value of human life. Because of these issues, the use of CEA is reported more often in the literature than is CBA.

Further details for Cost-benefit analysis are provided by McIntosh et al. (2010), Haddix et al., (2003) and Drummond et al. (2005).

### ***Prospective, Retrospective and Modeling Studies***

In a different classification model there are two categories of methods for economic evaluation: comparative studies (prospective or retrospective) and economic modeling studies (Annemans, 2008).

In a prospective health economic evaluation a number of patients are receiving the intervention or the comparator and all clinical and economic data are collected and recorded for the patients in both groups (Annemans, 2008). An important field is represented by economic evaluations conducted as part of randomized trials. A gold standard economic evaluation conducted in a trial is conducted in naturalistic settings, uses as comparator a commonly used therapy used in usual care, has adequate power to assess the economic results and has an adequate follow-up to assess the full impact of the therapy. A comprehensive presentation of economic evaluation in clinical trials is provided by Glick et al. (2007). Details on prospective health economic evaluation are provided by Baker et al. (1995) and Mauskopf et al. (1996). Specific guidelines have been developed for prospective studies (Ramsey et al., 2005).

In retrospective health economic evaluations one looks back and studies the clinical and economic consequences for patients who once started intervention treatment and others who once started the comparator intervention (Annemans, 2008). Motheral et al. (2003) offer specific guidelines for retrospective designs for health economic evaluations.

Even when trial-based economic evaluation exist, modeling is likely to be undertaken to extend the analysis beyond the observed time periods to allow for the assessment of longer-term impacts. Decision analytical modeling compares the expected costs and consequences of decision options by synthesising information from multiple sources and applying mathematical techniques, usually with computer software (Briggs et al., 2006). Different analytical methodologies such as decision tree models, state-transition models, microsimulation models, types of dynamic models (such as difference equations models) can be found in literature (Gold et al., 1996). Markov models are special types of state-transition models. One important consideration is whether there is a need to explicitly model the individual patient or to consider the average experience of a cohort of patients (Briggs et al., 2006).

Models can be either deterministic models or stochastic (probabilistic) to reflect the uncertainty in the input parameters of the decision model (Gold et al., 1996; Briggs et al. 2006).

Details on economic modeling studies are provided by Drummond and McGuire (2001), Drummond et al. (2005), Gold et al. (1996), Haddix et al. (2003), Petitti (2000), Briggs et al. (2006).

## Perspective of the analysis

The perspective describes whose costs and benefits are relevant for the purpose of the economic evaluation study. The choice of analytical perspective will influence the types of costs, and outcome measures considered relevant for inclusion in the evaluation.

Common perspectives for economic evaluation are: societal, national health care system, government as a whole, government as health care payer, hospital, consumers (Weinstein, 1990). Another way to express the analytical perspectives (or viewpoints) adopted in economic evaluations are: provider (hospital, physician, nonphysician practitioner, outpatient centre, laboratory centre, diagnostic centre, health maintenance organization), insurer (public insurer, private insurer), individual (patient), society, taxpayers, government (state government, local government), employer (Davidoff and Powe, 1996).

In literature, the societal perspective is often recommended for economic evaluation because it looks at the costs and benefits most comprehensively, including indirect and intangible costs

borne outside of the healthcare sector, such as productivity losses, travel cost and outcomes for patients' family. However, this perspective has not been widely adopted for policy making because it does not explicitly demonstrate the effect on each individual stakeholder. Given the wide spectrum of end-users of systematic reviews of economic evidence, a pragmatic approach is to consider cost and benefits from the full range of perspectives.

There are different inclusion and exclusion of costs, dependent on perspective for the economic evaluation (Meltzer, 2000; Meltzer, 2001).

From the patient perspective, the following costs are considered: physician time costs, drugs costs, patient's travel costs, temporary hired care-giver costs, costs of time off from work to visit physician, costs of time off work while ill and recuperating, costs of hire temporary household help while ill (Meltzer, 2000; Meltzer, 2001).

From the physician perspective, the following costs are considered: physician time costs, other medical personnel time (e.g., nurse) costs, utilities costs (Meltzer, 2000; Meltzer, 2001).

From the hospital perspective, the following costs are considered: physician time costs, other medical personnel time (e.g., nurse) costs, drugs costs, medical devices costs, laboratory tests costs, administration costs, physical facility costs (Meltzer, 2000; Meltzer, 2001).

From society perspective, all of the above costs and benefits irrespective of who pays and who benefits, will be aggregated (Meltzer, 2000; Meltzer, 2001).

## Types of Costs

All costs relevant to the chosen perspective must be determined and included in the analysis. Resources used should be quantified as opportunity costs (i.e. cost of the best alternative forgone) (Abdelhamid and Shelmit, 2010). In a competitive market, market prices can be used. In reality, due to market imperfection, charges, costs or reimbursement rates are often used.

Evaluating the literature regarding health economics can be confusing because of the interchangeable use of the terms cost and charge. The charge of a service, procedure or medication incorporates the cost of an item, indirect costs and profit margins. Discerning between analyses that use cost data as opposed to charge data is critical because there are significant differences in how these values are derived and their accuracy in reflecting the value of resources utilised.

The correct identification, measurement and valuation of costs are essential in health economics. Economic studies use a range of costs. It is important to be able to distinguish between the different types of costs that are used. There are two basic approaches for cost categorization: cost can be categorized in one approach into direct medical costs, direct nonmedical costs, indirect costs, and intangible costs; or in another approach cost can be categorized into health care sector costs, other sector costs, patient and family costs, and productivity costs.

Direct costs are those costs associated directly with a healthcare intervention. Direct costs represent the value of all goods, services, and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future

consequences linked to it (Gold et al., 1996). Direct medical costs represent the value of health care resources (e.g., tests, drugs, supplies, health care personnel, and medical facilities) consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it (Gold et al., 1996). Direct medical costs are the costs incurred by the health service. These costs include costs associated with staff time, physician visits, medical intravenous supplies, pharmaceuticals, diagnostic tests, hotel costs, capital costs and overhead costs. Examples of direct medical costs are: institutional inpatient care costs, institutional outpatient care costs, home health care costs, physician services costs, ancillary services costs, overhead allocated to technology costs, variable costs of utilities, medications costs, devices and appliances costs, research and development costs, diagnostic tests costs, treatment services costs, prevention services costs, rehabilitation costs, training and education costs (Luce and Elixhauser, 1990).

Direct nonmedical costs represent the value of nonmedical goods, services, and other resources, such as child care and transportation, consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it (Gold et al., 1996). Direct nonmedical costs are direct costs not incurred by the health service. These costs include patients' travelling costs, child care costs, and domestic help costs. Examples of direct nonmedical costs are: costs of care provided by family and friends, costs of transportation to and from medical services, childcare, house-keeping, modification of home to accommodate patient, costs of social services, and costs of repair of property destruction (Luce and Elixhauser, 1990).

Indirect costs refer in economics to the productivity gains or losses related to illness or death. In accounting, indirect costs is a term used to describe overhead or fixed costs of production (Gold et al., 1996). Indirect costs are incurred by the reduced productivity of a patient and their family resulting from illness, death or treatment. Indirect costs may include time off work or housekeeping, time spent going to healthcare providers, time spent caring for the patient by relatives or paid carers, time forgone from leisure, early retirement.

Examples of indirect costs are: change in productivity, lost productivity while on the job, income lost by family members, foregone leisure time, time spent by patient seeking medical services, time spent by family and friends attending patient, psychosocial costs, valuations others put on patient's health and wellbeing, pain, changes in social functioning and activities of daily living (Luce and Elixhauser, 1990). Intangible costs include anxiety, fatigue, pain or suffering from an illness or treatment.

Health care sector costs include medical resources consumed by health care entities. These types of costs are similar to the definition of direct medical costs but do not include direct medical costs paid for by the patient or other non-health care entities.

Other sector costs are the costs associated with the impact of the disease and the treatment on other sectors such as housing, homemaker services, educational services, public assistance, prison system.

Patient and family costs include the patient's or family's share of direct medical as well as direct nonmedical costs.

Productivity costs are the costs associated with lost or impaired ability to work or to engage in leisure activities due to morbidity and lost economic productivity due to death.

Capital costs include the cost of equipment, vehicles, buildings and one-time training programmes. Recurrent costs are the value of recurrent resources. Recurrent resources are those with useful lives of less than one year and have to be purchased at least once a year – yearly, monthly, weekly, daily or irregularly but frequently. A fixed cost is a cost of production that does not vary with the level of output. Fixed costs are those incurred whether patients are treated or not. The two major components of fixed costs are overhead costs and capital costs. Overhead costs are costs that are not incurred directly from providing patient care but are necessary to support the organization overall. Overhead costs are those incurred by the running of the service, such as lighting, heating and cleaning costs. Capital costs are incurred when major capital assets such as buildings or equipment are purchased. A variable cost is a cost of production that varies directly with the level of output. Variable costs are incurred from the patient's treatment. Variable costs include for example, drugs, blood products, medical investigations. Some items have both a fixed and a variable cost component. These are termed semi-variable costs or semi-fixed costs. Semi fixed costs tend to increase only when there is a large increase in activity.

## Types of benefits

There are different types of outcomes/benefits reported in economic evaluation studies expressed in terms of mortality measurements (survival, survival at 1 year, survival at 5 years), morbidity measurements (cure of the disease, eradication of the infection, stroke avoided, fractures avoided, complications avoided) and health-related quality of life measurements (QALYs).

Primary outcomes or final outcomes such as cure of the disease, the eradication of the infection or life years saved or QALYs are the preferred reported outcomes. Intermediate or surrogate outcomes such as laboratory measures or disease markers are used only as proxies or surrogates.

In cost-minimization analysis the outcomes are assumed to be equivalent. In CMA only the costs of the interventions are compared. Cost-effectiveness analysis (CEA) measures outcomes in natural units: mmHg, cholesterol levels, symptom-free days, years of life saved. In Cost-utility analysis (CUA) there are two effects measured (quality and length of life) whose product is taken as quality-adjusted life years (QALYs). In cost-benefit analysis (CBA) not only are costs valued in monetary terms so are the benefits.

Further details on identifying, measuring and valuing outcomes for economic evaluation studies are presented by McIntosh et al. (2010), Gray et al. (2011), Glick et al. (2007), Drummond and McGuire (2001), Drummond et al. (2005), Gold et al. (1996), Brazier et al. (2007), and Haddix et al. (2003).

## Discounting

In many analyses, the time profiles of cost and consequences may differ. To ensure comparability, we require a common time reference. Therefore, future streams of costs and health benefits must be discounted to the present.

Discounting is the process of determining the present value of the costs and benefits as experienced in future. It is based on a time preference that is shared; most people prefer to experience the benefits now and pay later (even if there were no interest rates or inflation).

For example, \$1 today is worth more to an individual than the same \$1 next year. Therefore, discounting places a higher weight on current costs and benefits than on those experienced in the uncertain future.

In an economic evaluation, the discount rates used for costs and for benefits and effects should be stated. Discount rates used in literature commonly range between 3% and 5% per annum. Discounting is very important for economic analyses evaluating screening or preventive interventions where the initial costs are high but benefits may take a long time to materialize. For instance, this is highly relevant for many cancer-related analyses in which the main outcome such as survival occurs at a different time points.

Further details for discounting in economic evaluation studies are provided by Gold et al. (1996), Drummond and McGuire (2001), Drummond et al. (2005), Haddix et al. (2003) and Pettiti (2000).

### **Methodological uncertainty (include issues such as the methods used to identify, measure, and value costs and health consequences)**

There are different types of uncertainty in economic evaluation studies: methodological uncertainty (relates to the methods used within an economic evaluation and includes issues such as the methods used to identify, measure and value costs and health consequences); sampling variation; parameter uncertainty; modeling uncertainty; generalizability/transferability (refers to the extent to which the results can be applied to different settings, such as different patient groups and contexts). Further details on uncertainty in economic evaluation studies are provided by Drummond and McGuire (2001), and Drummond et al. (2005).

Sensitivity analyses refer to mathematical calculations that isolate factors involved in a decision analysis or economic analysis to indicate the degree of influence each factor has on the outcome of the entire analysis (Gold et al., 1996). Sensitivity analysis evaluates the stability of the conclusions of an analysis to assumptions made in the analysis (Pettiti, 2000).

When a conclusion is shown to be invariate to the assumptions, confidence in the validity of the conclusions of the analysis is enhanced (Pettiti, 2000). Sensitivity analysis also helps identify the most critical assumptions of the analysis (Pettiti, 2000).

There are different types of sensitivity analysis: one-way sensitivity analysis, threshold analysis, two-way sensitivity analysis, three-way sensitivity analysis, *n*-way sensitivity analysis, worst case scenarios and best-case scenarios, probabilistic sensitivity analysis (PSA).

In one-way sensitivity analysis, the assumed values of each variable in the analysis are varied, one at a time, while the values of the other variables in the analysis remain fixed (Pettiti, 2000).

In threshold analysis, the value of one variable is varied until the alternative decision strategies are found to have equal outcomes, and there is no benefit of one alternative over the other in terms of estimated outcome (Pettiti, 2000). In two-way sensitivity analysis, the expected outcome is determined for every combination of estimates of two variables, while the values of all other variables in the analysis are held constant at baseline (Pettiti, 2000).

In three-way sensitivity analysis, the expected outcome is determined for combinations of estimates of three variables, while the values of all other variables in the analysis are held constant

at baseline (Pettiti, 2000). In *n*-Way sensitivity analysis, the expected outcome is determined for every possible combination of every reasonable value of every variable (Pettiti, 2000).

It is also possible to test worst case scenarios and best-case scenarios (Annemans, 2008). In worst case scenarios the different variables assume an extreme but still feasible value which is to the disadvantage of the intervention (Annemans, 2008).

Another type of sensitivity analysis is probabilistic sensitivity analysis (PSA), also sometimes known as a Monte Carlo analysis (Annemans, 2008). Probabilistic sensitivity analysis assumes that every variable in the analysis is subject to uncertainty characterized by a probability distribution (Annemans, 2008).

Further details for sensitivity analysis in economic evaluation studies are provided by Gold et al. (1996), Haddix et al. (2003), Briggs et al. (2006), Drummond and McGuire (2001) and Drummond et al. (2005).

## **Generalizability/Transferability of economic evaluation data**

Issues relating to the lack of generalizability of economic data have been widely discussed by health economists.

There are different issues in relation to the generalizability of economic data: problems of generalizing from data collected alongside clinical trials to regular practice; problems of the generalizability of economic data over time; transferability of economic evaluation results from place to place.

Factors limiting the transferability of economic data are: demographic factors; epidemiology of the disease; availability of health care resources; variations in clinical practice; incentives to health care professionals; incentives to institutions; relative prices; relative costs; population values.

Further details for generalizability of the results in economic evaluation studies are provided by Drummond and McGuire (2001) and Drummond et al. (2005). For comprehensive discussions of transferability of economic evaluations see Welte et al. (2004), Boulenger et al. (2005), Goeree et al. (2007), Nixon et al. (2009).

## **Conclusion**

Understanding methods of economic evaluation is important. The ability to assess and contribute to rigorous economic evidence is an essential competency for responsible practice.

As health care technology continues to expand and available funds decrease, the costs of using all effective clinical interventions will likely exceed available resources. Decisions about health care delivery will increasingly require assessing the cost-effectiveness of health care services. Economic evaluations especially cost-effectiveness studies and cost-utility studies can be valuable tools for health policymakers to incorporate into their evidence-based decisions.

Economic analysis is designed to assist decisions about the allocation of scarce resources. Economic efficiency is but one of many policy goals and issues of fairness are also central to medical care and must be considered as well.

Economic considerations play a major role in healthcare decisions both directly and indirectly. As new technologies and medications are introduced there will be an increased scrutiny into the likely benefit of these. At the same time, any decision to incorporate these new interventions/approaches into practice will also include an attempt to evaluate the likely economic impact. Economic evaluation analyses will help in this type of decision-making.

# Chapter 2:

## *Developing a protocol for a review of economic evidence*

The approach proposed in this chapter is based on comprehensive guidance provided by the Cochrane Collaboration (Higgins and Green, 2008), the Centre for Review and Dissemination CRD (CRD, 2009), the US Institute of Medicine IOM (IOM, 2011), and the Joanna Briggs Institute (JBI, 2008; 2011).

Researchers undertaking reviews first should search for existing or ongoing reviews and evaluate the quality of any reviews on similar topics.

The systematic review protocol is a detailed description of the objectives and methods of the review. The protocol should include information regarding the context and rationale for the review, primary outcomes of interest, search strategy, inclusion/exclusion criteria, data synthesis strategy, and other aspects of the review.

The review protocol is about future planned work. The review protocol should be written in the future tense. The challenge to writing a systematic review protocol is accurately specifying the review objectives and questions and methods before the review begins. (As the review report is about completed work it should be written in the past tense.)

At least two independent reviewers are needed in a systematic review with a third independent reviewer called in if there is differing of views.

Developing the protocol is an iterative process. Preparing a review protocol is complex and involves many judgements. In order to minimize the potential for bias in the review process, these judgements should be made in ways that do not depend on the results of the studies included in the review. Publication of a protocol for a review prior to knowledge of the available studies reduces the impact of authors' biases, promotes transparency of methods and processes, reduces the potential for duplication, and allows peer review of the planned methods.

While the intention should be that a review will adhere to the published protocol, changes in a review protocol are sometimes necessary. While every effort should be made to adhere to a predetermined protocol, this is not always possible or appropriate. It is important, however, that changes in the protocol should not be made on the basis of how they affect the results/conclusions.

Protocols for reviews should be published before the systematic review is completed or better before the start of the review process. The review protocol should be sent to peer review.

The first step in the review process is to agree on a review topic. The review title should be registered.

A protocol should be made publicly available at the start of a systematic review in order to prevent the effects of author bias, and tell readers of the review about protocol changes that

occur as the systematic review develops. A publicly available protocol has the benefit that other researchers can identify ongoing reviews, and thus avoids unnecessary duplication and encourages collaboration.

The review protocol sets out the methods to be used in the review. Decisions about the review question, inclusion criteria, search strategy, study selection, data extraction, quality assessment, data synthesis should be addressed. Specifying the methods in advance reduces the risk of introducing bias into the review. If modifications to the protocol are required, these should be clearly documented and justified. Modifications may arise from a clearer understanding of the review question, and should not be made because of an awareness of the results of individual studies.

Sticking rigidly to a protocol when it becomes apparent that a change of direction is required, can result in a review that is not useful to end users. It is possible that consideration of the primary research may raise questions which were not anticipated at the protocol stage. Where this results from a clearer understanding of the review question, it can be appropriate to carry out documented and justified amendments to the protocol. In the report of the review it is helpful to distinguish between the initial review question and any subsequent amendments.

Many reviews undergo protocol modification. Protocol amendments should be documented in a revised protocol and in the final report of the review.

The first and most important decision in preparing a systematic review is to determine its focus. This is best done by clearly framing the questions the review seeks to answer. Well-formulated questions will guide many aspects of the review process, including determining eligibility criteria, searching for studies, collecting data from included studies, and presenting findings. It is generally not possible to formulate an answerable question for a review without knowing some of the studies relevant to the question, and it may become clear that the questions a review addresses need to be modified in light of evidence accumulated in the process of conducting the review.

The review question should be precise so that the reviewers can structure the other components of the systematic review. To inform decision making, review questions should focus on the uncertainties that underlie disagreement and the outcomes and interventions that are of interest to patients and clinicians. Also important is ensuring that the review questions are addressing new issues, and not duplicating existing reviews or other ongoing reviews. Any changes to the protocol that result from revising the review question should be documented in the review protocol and the review report.

The questions addressed by a review may be broad or narrow in scope. Determining the scope of a review question is a decision dependent upon multiple factors. There are advantages and disadvantages to both broad and narrow questions.

Well-formulated systematic review questions use a structured format to improve the scientific rigor such as the PICO or PICOS or PICOST mnemonic: Population, Intervention, Comparator, Outcome, Setting, Timeframe. These elements of the review question, together with study design, will then be refined in order to determine the specific inclusion criteria that will be used when selecting studies for the review.

## The title of the systematic review protocol

The title of the systematic review protocol should be as descriptive as is reasonable and should reflect the systematic review type to be conducted. If the review is examining for example cost-effectiveness (or cost-benefit or cost-utility) this should be stated in the title of the protocol. If the specific interventions and patient outcomes are to be examined, these should also be included in the title. Where possible the setting and target population should be stated.

Example of a title for systematic reviews of economic evidence:

- *A systematic review of cost-minimization of intracervical prostaglandin gel for cervical ripening in an outpatient versus inpatient setting*

In this example, it is clear that it is the title for a systematic review of a specific type of economic evaluation method (cost-minimization). Also, from the title it is clear what intervention is examined (intracervical prostaglandin gel), and what settings (outpatient and inpatient). The title is for the systematic review of cost-minimization studies comparing only the costs of the utilization of the same intervention in two different settings.

The target population is implicit as female patients requiring the intracervical gel. In this example there is no need to specify the outcomes in the title. In cost-minimization studies, the outcomes are assumed to be identical and only the costs are compared.

Example of a title for systematic reviews of economic evidence:

- *Cost-effectiveness and cost-utility of best supportive care versus oncoplatin and oncotaxel in the treatment of recurrent metastatic breast cancer in women: A systematic review*

In this example, it is clear that it is the title for a systematic review of two different specific types of economic evaluation methods (cost-effectiveness and cost-utility). Also, from the title it is clear what interventions are examined (best supportive care versus oncoplatin and oncotaxel). The settings are not specified. The target population is explicitly stated (women with recurrent metastatic breast cancer). In this example, we assume that appropriate outcomes for cost-effectiveness and cost-utility studies are examined.

Example of a title for systematic reviews of economic evidence:

- *Survival in recurrent metastatic breast cancer: A systematic review of cost-effectiveness studies*

In this example, it is clear that it is the title for a systematic review of a specific type of economic evaluation method (cost-effectiveness studies). From the title it is not clear what interventions are examined. From the title it is not clear what settings are considered. The measured outcome (survival) is explicitly stated in the title. The target population is only partially stated recurrent metastatic breast cancer. We do not know if it is a study regarding male or female patients. There are very rare cases of breast cancer in male patients.

Review of economic evidence may be incorporated into a comprehensive review of clinical effectiveness and economic evidence. Both elements can be readily incorporated in the title of the protocol, for example:

- *A systematic review of the effectiveness and cost-effectiveness of oncoplatin and oncotaxel compared to best supportive care on five years survival in treating recurrent*

*metastatic breast cancer in women 40 to 45 years old in outpatient and inpatient settings”.*

This provides readers with a clear indication of the specific interventions of interest, and the dual focus on clinical effectiveness and cost-effectiveness. This does describe a specific population and comparator.

The clearer and more specific a title of a systematic review is, the more readily users of electronic databases will be able to make decisions about the systematic review’s applicability to their information needs.

## Background

The background section should communicate the key contextual factors and conceptual issues relevant to the review question. It should explain why the review is required and provide the rationale underpinning the inclusion criteria and the focus of the review question, for example justifying the choice of interventions to be considered in the review.

The background should describe the issue under review including the target population, interventions and outcomes that are documented in the literature.

The background should provide sufficient detail on each of the elements to justify the conduct of the review and the choice of various elements such as interventions and outcomes. Where complex or multifaceted interventions are being described, it may be important to detail the whole of the intervention for an international readership.

Well-formulated review questions occur in the context of an already-formed body of knowledge. The background should address this context, help set the rationale for the review, and explain why the questions being asked are important. It should be understandable to the users of the intervention under investigation.

A statement that a systematic review has not previously been conducted, or if conducted, a rationale for performing another review should also be provided.

## Review Objectives/Questions

Systematic reviews should set clear objectives, which will provide meaningful information that can be used to guide decision-making. These should be stated clearly and precisely in the protocol. Objectives may be extremely specific or very broad, although if broad, it may be more appropriate to break this down into a series of related more specific objectives. Where there are several objectives it may be necessary to prioritise by importance and likelihood of being able to fulfil. It may even be necessary to restrict the scope of the objectives to a level that is manageable within set resources.

The objectives guide and direct the development of the specific review criteria. Clarity in the objectives and specificity in the review questions assists in developing a protocol, facilitate more effective searching, and provide a structure for the development of the full review report.

The review objectives must be stated in full. Conventionally a statement of the overall objective is made and elements of the review are then listed as review questions.

Example of the objective for systematic reviews of economic evidence:

- *The objective of this systematic review is to synthesize the evidence on cost-effectiveness and cost-utility of best supportive care versus oncoplatin and oncotaxel on five years survival in the treatment of recurrent metastatic breast cancer in women 40 to 45 years old in outpatient and inpatient settings.*

Once a topic has been identified, a specific, answerable question is developed. The level of detail in the question should be adequate to inform the development of review criteria that address the specific components of the review question.

Systematic reviews should set clear questions, the answers to which will provide information that can be used to guide decision-making. Review questions should be stated clearly and precisely in the protocol. Questions may be extremely specific or very broad. Broad questions should be broken down into a series of specific questions.

The review question can be framed in terms of the population, intervention(s), comparator(s) and outcomes of the studies that will be included in the review. These elements of the review question together with study design will be used in order to determine the specific inclusion criteria for the review.

Example of a review question for systematic reviews of economic evidence:

- *What is the cost-effectiveness of best supportive care versus oncoplatin and oncotaxel on five years survival in the treatment of recurrent metastatic breast cancer in women 40 to 45 years old in outpatient and inpatient settings?*

## Criteria for inclusion/exclusion

The inclusion criteria should be set out in the protocol to ensure that the boundaries of the review question are clearly defined. Reviewers need to be clear about definitions used. Conceptual and operational definitions will usually be helpful.

The inclusion criteria should capture all studies of interest. If the criteria are too narrowly defined there is a risk of missing potentially relevant studies. If the criteria are too broad the review may contain information which is hard to compare and synthesise. Inclusion criteria need to be practical to apply.

The ideal for most systematic reviews is to include all available relevant evidence. In principle, this includes studies written in any language to avoid the introduction of language bias into the review. If reviews include only studies reported in English, their results and inferences may be biased. Whenever feasible, all relevant studies should be included regardless of language. However, realistically this is not always possible due to a lack of time, resources and facilities for translation. Researchers need to give careful thought as to whether imposing language restrictions may potentially bias the results of their individual review.

Studies are not always published as full papers in peer-reviewed journals; they may be published as reports, conference abstracts, theses or they may be informally reported or remain unpublished. Ideally a review should aim to include all relevant studies, regardless of publication status, in order to avoid publication bias. There are practical issues that limit the inclusion of all studies regardless of publication type/status. Unpublished studies are likely to be harder to source, and more difficult to obtain, than published studies. The inclusion of conference

abstracts and interim results should be considered, bearing in mind that contact with the study authors may be required to obtain full study details. The effects of including any data from abstracts alone should be carefully considered, since differences often occur between data reported in conference abstracts and their corresponding full reports, although differences in results are seldom large. The identification of ongoing studies is important for a number of reasons. They may provide a useful starting point for subsequent reviews and updates; they may also improve the quality of conclusions about future research by indicating where new research has already commenced.

Including data from unpublished studies is important in minimizing bias. However, this can be time-consuming. The practical difficulties of locating and obtaining information from unpublished studies may, for example, make the ideal of including relevant unpublished studies unachievable in the timescales available for many reviews.

### ***Types of participants/Population***

When expanding the title and objectives/questions through the criteria for inclusion, reviewers will need to consider whether the whole population of people with a specific condition should be included, or if the population will be limited to specific subsets. Specific reference to population characteristics (participants' gender, age, disease severity, co-morbidities, socio-economic status, ethnicity, geographical area) either for inclusion or exclusion should be based on a clear, scientific justification rather than based on unsubstantiated or personal reasoning.

The included population should be relevant to the population to which the review findings will be applied. If the inclusion criteria are broad it may be useful to investigate subgroups of participants. Where analysis of participant subgroups is planned this should be specified in the protocol.

Important details for types of participants are: specific disease/conditions, stage of the disease, severity of the disease, co-morbidities, age, gender, ethnicity, previous treatments received, previous condition, explicit standardized criteria for diagnosis, setting (for example, hospital, community, outpatient), who should make the diagnosis of the specific disease, other important characteristics of participants (such as for example different response to the treatment).

*Examples of types of participants:* patients with hyperthyroidism and solitary thyroid nodule, patients with morbid obesity with serious comorbidity, patients age 80 or over with abdominal aortic aneurysm, patients with severe claudication, patients on liver transplant waiting list, symptomatic lung cancer men aged 65-74, patients with severe ileocolonic Crohn's disease, heavy smokers eligible for lung resection.

*Examples for more specific details for types of participants:*

- Pathologically verified epithelial ovarian cancer, Stage III suboptimal residual disease (>1 cm residual mass), all patients with Stage IV disease, no prior radiotherapy or chemotherapy. Borderline cancers excluded.
- Histologically or cytologically proven adenocarcinoma of the breast, metastatic disease with measurable lesions, prior hormone therapy, radio- or immunotherapy permitted

but this had to be stopped on study entry, prior adjuvant therapy permitted if at least 3 month previously, no exposure to anthracyclines or taxanes, no chemotherapy for advanced disease.

The criteria for considering types of people included in studies in a review should be sufficiently broad to encompass the likely diversity of studies, but sufficiently narrow to ensure that a meaningful answer can be obtained when studies are considered in aggregate.

### ***Types of Interventions***

Where possible, the intervention should be described in detail, particularly if it is multifaceted. The nature of the intervention(s) explored in the review may be framed in very broad terms or may be more specific.

Elements usually specified include the nature/type of the intervention, the person(s) delivering the intervention(s) and the setting in which the intervention is delivered. Important details for types of interventions are: explicit and clear description of interventions, dosage, intensity, mode of delivery, types of personnel who deliver it, frequency of delivery, duration of delivery, timing of delivery, critical doses/intensity, co-interventions.

*Examples of types of interventions:* thyroid lobectomy, gastric banding, endovascular repair, duplex ultrasound and angioplasty, liver transplantation, screening for abdominal aortic aneurysms, annual CT screening.

Stating a particular comparator limits the scope of a review, assisting with ensuring a clear focus for determining inclusion and exclusion once searching and appraisal is complete. However, when a broader question is being considered, particularly one where multiple interventions exist, limiting the types of comparators may not be appropriate or desirable. Where an intervention has not been subject to previous economic evaluation, the comparator can reasonably be identified based on either a known gold standard, or an approach which is considered to be “current practice”.

Important details for comparators are: explicit and clear description of interventions, dosage, intensity, mode of delivery, types of personnel who deliver it, frequency of delivery, duration of delivery, timing of delivery, critical doses/intensity, co-interventions.

*Examples of types of comparators:* Radioactive iodine (comparator for thyroid lobectomy), no surgery (comparator for gastric banding), open operative repair (comparator for endovascular repair), supervised exercise program (comparator for duplex ultrasound and angioplasty), medical treatment (comparator for liver transplantation), no screening (comparator for screening for abdominal aortic aneurysms).

### ***Types of outcomes***

The types of outcomes and the timing of outcomes measurements are key decisions in development of a systematic review protocol. There should be a list of all the outcome measures to be considered. Note that outcome measures might be primary or secondary. The background should provide enough information to justify the outcomes included and potentially those that were not included. The outcomes need to be measurable and appropriate to the review objective. It is useful to list outcomes and identify them as primary or secondary,

short-term or long-term, relative or absolute. The outcome may be described in relation to the type of review. Therefore the appropriate specific outcomes should be described in relation to cost-minimisation analysis, cost-effectiveness analysis, cost-benefit analysis or cost-utility analysis.

There may be one or a range of outcomes of interest depending on the nature of the topic and planned scope of the review. In identifying which outcomes will be specified, it is useful to consider the interests of the target audience.

### ***Types of costs***

In economic evaluations, the costs accruing from an intervention depend on whose perspective it is from. Whenever possible all relevant costs should be included and presented by perspective and categorised by type.

### ***Types of summary measures***

There are different incremental summary economic measures reported in economic evaluation studies: incremental net present value of benefits (in CBA), the incremental cost-effectiveness ratio (in CEA), and the incremental cost-utility ratio (in CUA), and also different average summary measures. Average summary measures should not be used to compare interventions. In a CBA, all costs and benefits are measured in monetary terms and then combined into a summary measure. Examples of such summary measures for CBA are the Net Present Value (NPV) and the Benefit-Cost Ratio (BCR).

### ***Types of benefits***

The success or failure of an intervention will usually be assessed in terms of differences in mortality or morbidity or quality-adjusted life years in the populations treated. Primary outcomes are likely to include measures of mortality and morbidity but other outcomes may also be of importance, for example measures of quality of life and participants' subjective experiences of pain or physical functioning. A review should explore a clearly defined set of relevant outcomes and it is important to justify each outcome included.

The use of surrogate outcomes may be misleading, giving an over or underestimate of the true clinical outcome. In economic evaluations conducted alongside trials, due to the short study timeframe, typically, surrogate outcomes are collected. Additionally, in many economic modeling studies, intermediate outcome parameters are used to extrapolate final outcomes. Decisions about whether to consider surrogate outcomes should therefore be informed by available evidence about associations between the surrogate and the outcome of interest. Often, surrogate outcomes are included only where a study also reports a relevant clinical outcome.

When defining the timing of outcome measurement, authors may consider whether all time frames or only selected time-points will be included in the review. Economic evaluations carried out alongside trials measure short to medium term cost-effectiveness effects whereas models extrapolate costs and effects often over a lifetime time horizon. It is important to give the timing of outcome measure considerable thought. It may be helpful for review authors to consider those measures used in related reviews when defining the type and timing of measurement within their own review. In addition, several clinical areas are developing agreed

core sets of outcome measures for use and consideration of these in defining the detail of measurement of outcomes selected for the review is likely to be helpful.

### ***Types of studies***

This section should flow naturally from the criteria that have been established to this point, and particularly from the objective and questions the review seeks to address.

The reviewers should specify if they will include in the systematic review only one specific study design (for example, only cost-minimization studies) or two (cost-effectiveness and cost-utility) or more than two study design types.

The reviewers should also clarify the types of studies they will include in the systematic review: comparative prospective economic evaluation studies, comparative retrospective economic evaluation studies, health economic evaluation modeling studies. For economic evaluation modeling studies the reviewers should specify the types of modeling studies they will include in the systematic review.

Eligible study designs should be stated. Exclusion of particular types of studies should be justified.

Certain study designs are more appropriate than others for answering particular questions. Authors should consider a priori what study designs are likely to provide reliable data with which to address the objectives of their review.

The types of study included in the review will play a major role in determining the reliability of the results and the validity of estimates of effect is linked to the study design. While some study designs are clearly more robust than others, this should not be the only factor in determining which types of study are eligible for inclusion. Scoping searches may reveal that there are likely to be only a limited number of relevant studies. In this case researchers have the option of justifying a decision to limit study design, bearing in mind that the identification of gaps in the current evidence base may in itself be a significant finding of the review. In some cases a range of study designs may be needed to address different questions within the same review. There will always be a trade-off between restrictive study design criteria and more liberal design criteria. Excessively broad criteria might result in the inclusion of misleading evidence.

### **Search strategy**

The methods used to identify studies should be summarized. Systematic reviews are international sources of evidence; particular nuances of local context should be informed by and balanced against the best available international evidence.

The protocol should provide a detailed search strategy that will be used to identify all relevant international research within an agreed time frame. This should include databases that will be searched, and the search terms that will be used. In addition to this, it should also specify what types of study design for economic evaluation studies (for example, Cost-Effectiveness CEA etc) will be considered for inclusion in the review.

A preliminary search strategy for identifying relevant research should be included in the protocol. This should specify the databases and additional sources that will be searched, and

also the likely search terms to be used. The search strategy should be constructed to take into account population, interventions, comparators, outcomes and study design.

Also list grey literature sources, such as internal reports and conference proceedings. If journals are specifically hand searched for the review, this should be noted.

Reviewers are required to state the databases to be searched, the initial key words that will be used to develop full search strategies and if including unpublished studies what sources will be accessed. The search strategy should also describe any limitations to the scope of searching in terms of dates, resources accessed or languages; each of these may vary depending on the nature of the topic being reviewed, or the resources available to each reviewer.

Limiting by date may be used where the focus of the review is on a more recent intervention or innovation. However, date limiting may exclude seminal early studies in the field and should thus be used with caution, the decision preferably be endorsed by topic experts, and justified in the protocol.

Obtaining the input of an experienced librarian to develop the search strategy is recommended.

It is usual to include in the protocol details of the software that will be used to manage references.

## **Critical appraisal/quality assessment criteria**

The systematic review protocol should provide details of the method of study appraisal to be used. Details of how the study appraisal is to be used in the review process should be specified. The protocol should specify the process of appraisal of study quality, the number of reviewers involved and how disagreements will be resolved. The protocol should specify any exclusion criteria based on quality considerations.

The protocol should provide details of the method of study appraisal to be used, including examples of the specific quality criteria.

The main object of critical appraisal is to assess a study's quality and determine the extent to which a study has excluded the possibility of bias in its design, conduct and analysis. If a study has not excluded the possibility of bias, then its results are questionable and could well be invalid. Therefore, part of the systematic review process is to evaluate how well the potential for bias has been excluded from a study, with the aim of only including high quality studies in the resulting systematic review.

## **Data extraction**

The systematic review protocol should outline the information that will be extracted from studies identified for inclusion in the review. The protocol should state the procedure for data extraction including the number of reviewers who will extract the data and how discrepancies will be resolved. The protocol should specify whether authors of primary studies will be contacted to provide missing or additional data.

Whether data are extracted independently by more than one reviewer should be stated, along with how any disagreements are resolved.

The protocol should outline the information that will be extracted from studies identified for inclusion in the review and provide details of any software to be used for recording the data.

## Data synthesis

The protocol should describe the methods of data synthesis.

The review protocol should state whether a meta-analysis is planned. The reviewers should provide details on proposed meta-analysis of economic evaluation evidence including relevant references to methodological literature on meta-analysis of economic evidence. Whether a planned meta-analysis will ultimately prove possible will depend on the studies and data that are available. Although meta-analyses are widely used to synthesize clinical measurements, there are currently no agreed-upon methods for pooling combined estimates of cost-effectiveness (ICER, cost-utility, cost-benefit ratios) from different studies.

As analyses will depend on what data are available, and because it is difficult to anticipate all of the statistical issues that may arise, it can be difficult to pre-specify full details of the planned synthesis. Where appropriate, the approach to narrative synthesis should be outlined.

Economic results can be described in this section of the review protocol as being subject to: narrative summary, reported in tables or tabulated in a matrix. Reviewers are encouraged to describe them in their protocol as a cascade of options, which will in part depend on the quantity, quality and nature of the economic papers they identify.

## Conflict of Interest

A statement should be included in every review protocol that either declares the absence of any conflict of interest, or describes a specified or potential conflict of interest.

## Acknowledgements

The source of financial grants and other funding must be acknowledged, including the reviewers' commercial links and affiliations. The contribution of colleagues or Institutions should also be acknowledged.

## References

Reviewers should adopt and use for the entire review protocol the same style of references. For example, a proposed style of references for review protocols could be a modified Vancouver style. References should be numbered in the order in which they appear with superscript Arabic numerals in the order in which they appear in text. Full reference details should be listed in numerical order in the reference section. More information about the Vancouver style is detailed in the International Committee of Medical Journal Editors' revised 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication', and can be found at <http://www.ICMJE.org/>

## Appendices

Appendices should be placed at the end of the review protocol and for example could be numbered with Roman numerals in the order in which they appear in text. At a minimum this will include critical appraisal and data extraction tools.

### *Amendments to protocols*

Any modification or edit of a published protocol gives the protocol the status of amended. Amended protocols are re-published. A protocol may receive an amendment at anytime.

## Conclusion

The systematic review protocol is a detailed description of the objectives and methods of the review including information regarding the context and rationale for the review, primary outcomes of interest, search strategy, inclusion/exclusion criteria, data synthesis strategy, and other aspects of the review. The review protocol is about future planned work and should be written in the future tense. The review title should be registered and published only after peer review. A protocol should be made publicly available at the start of a systematic review in order to prevent the effects of author bias, and to advise readers of the review about protocol changes that occur as the systematic review develops.

## Conducting a Systematic Review of Economic Evidence

# Chapter 3:

## *Searching for Economic Evidence*

The approach proposed in this section is based on comprehensive guidance provided by the Cochrane Collaboration (Higgins and Green, 2008), the Centre for Review and Dissemination CRD (CRD, 2009), the US Institute of Medicine IOM (IOM, 2011), and the Joanna Briggs Institute (JBI, 2008; 2011).

The search strategy should be an integral component of the review protocol that specifies procedures for finding the evidence directly relevant to the systematic review. Items described in the protocol include, but are not limited to, the study question; the criteria for a study's inclusion in the review and the databases, journals, and other sources to be searched for evidence; and the search strategy.

Finding all relevant studies that have addressed a single question is not easy. A systematic search is essential in order to identify all of the best evidence available that addresses the question. As a first step, it is helpful to find out if a systematic review has already been done or is under way. If not, published original articles need to be found.

A search of at least the Cochrane Library, MEDLINE and NHS EED databases will assist to establish whether or not a recent systematic review report exists on the economic evaluation topic of interest.

Systematic reviews are international sources of evidence. Particular nuances of local context should be informed by and balanced against the best available international evidence.

The reviewers should use the search strategy declared in the approved systematic review protocol. If there are deviations from the review protocol reviewers should provide details (different databases, different time frame, language restrictions, specific search terms) and also justifications for all deviations. It is useful to use the Population, Interventions, Comparators, Outcomes, and Studies structure to guide the search.

It is useful to use search terms related to the following aspects of types of participants (population): specific disease/conditions, stage of the disease, severity of the disease, co-morbidities, age, gender, ethnicity, previous treatments received, setting (for example, hospital, community, outpatient).

It is also useful to use search terms related to the following aspects of types of interventions: specific interventions, mode of delivery, types of personnel who deliver it, co-interventions. It is also useful to do the same for search terms related to types of comparators.

It is recommended to use search terms related to different types of outcomes: mortality outcomes, morbidity outcomes, health related quality of life outcomes, economic outcomes.

It is recommended to use also different search terms related to types of studies such as: cost-minimization analysis, CMA, cost-effectiveness analysis, CEA, cost-utility analysis, CUA, cost-benefit analysis, CBA, decision tree, state-transition model, dynamic model, Markov model, cohort longitudinal model, population cross-sectional model, deterministic model, stochastic model, probabilistic model, prospective study, trial-based study, retrospective study.

Search terms need to be adapted to the different resources in which the strategy will be run to reflect the differences in database indexing, search commands and search syntax (Glanville and Paisley, 2010).

If the search is undertaken in a general database (for example, Medline) the subject search terms (for participants, interventions, comparator, outcomes) should be combined with search terms related to the economic evaluation studies.

If the search is undertaken in a specialist economic database additional economic search terms may not be required (Glanville and Paisley, 2010).

It is recommended to search economic databases (for example, NHS EED, HEED, or HTA) and also general databases (Medline).

In order to help the reviewers to get a preliminary understanding of search strategies used in systematic reviews of economic evidence we'll present examples with some details of real published search strategies.

In a review on addiction (Andlin-Sobocki, 2004) with the aims at reviewing the economic data available on substance abuse in Europe, the reviewers searched PubMed (MEDLINE) and OHE HEED. Limited search was also performed in governmental databases in European countries. The reference lists of relevant articles were searched for other possibly relevant articles. Known experts were contacted to ask for other possibly relevant articles, published or unpublished. A restriction on language was set to English, Spanish, German and French. The reviewers used search terms such as: economics, economic evaluation, cost/costs, cost of illness, burden of illness, burden of disease, cost-effectiveness, cost-utility, cost benefit and cost-minimization/cost-minimisation.

In a systematic review (Plosker and Lyseng-Williamson, 2006) on Clopidogrel use in patients with Non-ST Elevation Acute Coronary Syndromes authors searched MEDLINE. The search terms were for example 'clopidogrel' or 'acute coronary syndromes' and 'economics' or 'health-policy' or 'quality-of life' or 'models-statistical' or 'health-planning' or 'epidemiology'. They also search EMBASE using for example the following search terms 'clopidogrel' or 'acute coronary syndromes' and 'economics' or 'health economics' or 'economic evaluation' or 'health status' or 'pharmacoeconomics' or 'drug cost' or 'drug utilization' or 'utilization review' or 'health survey' or 'practice guideline' or 'quality of life' or 'treatment outcome' or 'cost' or 'cost benefit analysis' or 'cost control' or 'cost effectiveness analysis' or 'cost minimisation analysis' or 'cost of illness' or 'cost utility analysis'.

In a systematic review (Sprague et al., 2003) of economic analyses of low-molecular-weight heparin for the treatment of venous thromboembolism, the reviewer searched MEDLINE and EMBASE database and Cochrane Library. They used medical subject headings (MeSH) and text words: “low-molecular-weight heparin”, “unfractionated heparin”, “deep-vein thrombosis”, “pulmonary embolism”, and “economic analysis”.

In a systematic review (Langer and Rogowski, 2009) of economic evaluations of human cell-derived wound care products for the treatment of venous leg and diabetic foot ulcers, the authors searched BIOSIS Previews, Cochrane Library, Database of Abstracts of Reviews of Effects (DARE), EconLit, Embase, HTA Database, Medline, NHS Economic Evaluation Database (NHS EED), and Web of Science. Additionally, the internet was searched by Google and Google Scholar, and references of recent economic evaluations and reviews were tracked. For example for the Medline search the search strategy terms used included “Biological Dressings”, “Collagen”, “Skin, Artificial”, “Bandages”, “Platelet-Derived Growth Factor”, “Cost-Benefit Analysis”, and “economics”.

In a systematic review (Dixon et al., 2004) on economic evaluations of treatments for systemic fungal infections, the authors searched Medline, EMBASE, Science Citation Index, HealthSTAR, CINAHL, Cochrane Database of Systematic Reviews, NHS CRD DARE, CENTRAL/CCTR (Cochrane Central Controlled Trials Database), NHS CRD HTA, NHS CRD NHS EED (UK NHS Centre for Reviews and Dissemination NHS Economic Evaluation Database), OHE HEED (Office of Health Economics Health Economic Evaluation Database), INAHTA Clearing House (International Network of Agencies for Health Technology Assessment), CCOHTA (Canadian Coordinating Office for Health Technology Assessment), SBU (Swedish Council for Health Technology Assessment), Harvard Cost Utility Analysis database, AHRQ (US Agency for Healthcare Research and Quality).

In a systematic review (Vale et al., 2008) of economic evaluations of laparoscopic surgery for colorectal cancer, the authors searched Medline, Embase, Medline Extra, Science Citation Index, National Health Service Economic Evaluations Database (NHS EED), HTA Database, Health Management Information Consortium and Journals @ Ovid Full Text for selected surgical journals. In addition, recent conference proceedings and reference lists of all included studies were scanned to identify additional potentially relevant studies. Other sources of information consulted included for example the references in relevant articles; and selected experts in the field.

In a systematic review (Orme and Boler, 2006) on economic evidence of prostaglandin analogues for the treatment of Glaucoma and Ocular Hypertension, the authors searched MEDLINE, EMBASE and the UK NHS economic evaluation (NHS EED) databases.

In a systematic review (Getsios et al., 2005) of economic evaluations of pharmacological management of overactive bladder, the authors searched MEDLINE using for example search terms such as: ‘overactive bladder’; ‘incontinence’; ‘cost’; ‘cost-effectiveness’; ‘pharmacoeconomics’; and ‘economics’.

In a systematic review (Stone et al., 2005) of economic analyses of health care-associated infections, the authors searched MEDLINE, EconoLit, and HealthSTAR using for example search terms such as “nosocomial infections”, “infection control”, “hospital acquired infections”, “costs”, “cost analysis”, “economics”, or “cost-effectiveness analysis”.

In a systematic review (Halton and Graves, 2007) of economic evaluation of catheter-related bloodstream infections, the authors searched Medline, the Cumulative Index to Nursing and Allied Health Literature, Biologic Abstracts, Academic Search Elite, and Econlit by using search terms such as catheterization, central venous, costs and cost analysis, infection; bacteremia, sepsis, cost-effective, cost-benefit, or cost-utility.

Recommended selected databases for economic evaluations are (Glanville and Paisley, 2010):

- NHS Economic Evaluation Database (NHS EED)
- Health Economic Evaluation Database (HEED)
- Cost-effectiveness Analysis (CEA) Registry
- Health Technology Assessment (HTA) database
- Paediatric Economic Database Evaluation (PEDE)
- European Network of Health Economic Evaluation Databases (EURONHEED)
- COnnaissance et Decision en Economie de la Sante (CODECS)

***NHS Economic Evaluation Database (NHS EED)***

<http://www.crd.york.ac.uk/CMS2Web/AboutNHSEED.asp>

Produced by the Centre for Reviews and Dissemination, this database is available free on the WWW. Contains quality assessed structured abstracts of economic evaluations. Bibliographic details of costing studies, methodological papers and reviews of economic evaluations are also included in the database. NHS EED aims to assist decision-makers by systematically identifying and describing full economic evaluations, appraising their quality and highlighting their relative strengths and weaknesses. The abstracts provided give a detailed breakdown of the key components of the economic evaluation. A critical commentary summarises the overall reliability and generalisability of the study.

***Health Economic Evaluations Database (HEED)***

<http://onlinelibrary.wiley.com/book/10.1002/9780470510933>

Produced by Office of Health Economics and the International Federation of Pharmaceutical Manufacturers & Associations IFPMA, it contains information on studies of cost effectiveness and other forms of economic evaluation of medicines and other forms of health care intervention. In addition, it includes cost analyses and cost of illness studies. It is available online on an institutional subscription basis.

***Cost-Effectiveness Analysis Registry (CEA)***

<https://research.tufts-nemc.org/cear4/default.aspx>

The objective of the CEA Registry project is to create a single electronic source comprised of all the information contained in a detailed database of cost-utility analyses. The web site can be used to compare the cost-effectiveness of a broad range of interventions using standardizing cost-utility ratios, and to investigate variations in the methods used in their estimation.

***Health Technology Assessment (HTA) database***

<http://www.crd.york.ac.uk/CMS2Web/AboutHTA.asp>

HTA contains details of completed and ongoing health technology assessments from around the world. The abstracts in the database are descriptive rather than critical. The HTA database provides free access to information about technology assessments carried out around the world. Many different types of research are included in the HTA database. As well as systematic reviews and economic evaluations, the database contains ongoing and completed research based on trials, questionnaires and other types of study.

### ***Paediatric Economic Database Evaluation (PEDE) Database***

<http://pede.ccb.sickkids.ca/pede/index.jsp>

Free database arising out of the PEDE project. It contains citations from 1980 onwards, all of which are full economic evaluations of interventions targeted at neonates, infants, children, and adolescents up to age 19.

### ***European Network of Health Economic Evaluation Databases (EURONHEED)***

<http://infodoc.inserm.fr/euronheed/Publication.nsf>

This is a Database of European health care economic evaluations

### ***Connaissance et Decision en Economie de la Sante (CODECS)***

[http://infodoc.inserm.fr/codecs/codecs.nsf/\(Web+Startup+Page\)?OpenForm](http://infodoc.inserm.fr/codecs/codecs.nsf/(Web+Startup+Page)?OpenForm)

This is a French database of French health care economic evaluations.

### ***EconLit***

<http://www.aeaweb.org/econlit/index.php>

Provides bibliographic citations to the international literature on economics since 1969. EconLit covers a broad range of document types published world wide, including journal articles, books, and dissertations, as well as articles in collective works, such as conference proceedings and collected essay volumes.

### ***PubMed***

<http://www.pubmed.gov>

PubMed is a general database available free over the Internet.

### ***EMBASE***

<http://www.embase.com/>

Embase is a database with over 24 million indexed records. In 1997 Elsevier extended and restructured the pharmacoeconomics terminology, and introduced new links to capture the concepts of pharmacoeconomics and disease management.

### ***Sources for grey literature and economics grey literature***

REPEC (Research Papers in Economics) is a recommended source for economics grey literature (<http://repec.org/>) (Glanville and Paisley, 2010).

OALster is recommended for grey literature in all fields (<http://www.oclc.org/oaister>) (Glanville and Paisley, 2010).

Specific guidance on resources to search and approaches to searching are provided by Glanville and Paisley, (2010) but general guidance provided by the same authors is useful as a starting point:

- Medline is the key general database for identification of published economic evaluations in health care.
- A recommended search strategy is to search Medline, Embase and NHS EED.
- An effective strategy is to search NHS EED supplemented by a search of a general database such as Medline.

Focusing the search strategy can be achieved by using search filters. Search filters are collections of search terms developed to capture specific themes such as study design. Although many economic search filters are available few have been validated (Glanville and Paisley, 2010).

McKinlay et al. (2006) proposed an optimal search strategy for Embase. Wilczynski et al. (2004) proposed an optimal search strategy for Medline. There are CRD (York University, UK) proposed search strategies for Medline, CINAHL, Embase, and PsycInfo.

It is relevant to specify the hand search strategies and the electronic databases search strategies used by CRD (York University, UK) for identification of economic evaluation studies for inclusion in NHS EED database. The following journals are hand searched for identification of economic evaluation studies for inclusion in NHS EED: Annals of Internal Medicine; Archives of Internal Medicine; BMJ; Canadian Medical Association Journal; Expert Review of Pharmacoeconomics; International Journal of Technology Assessment in Health Care; JAMA; Joint Commission Journal on Quality Improvement and Patient Safety; Lancet; Medical Care; New England Journal of Medicine. The following electronic databases are searched for identification of economic evaluation studies for inclusion in for NHS EED: MEDLINE; CINAHL; EMBASE; PsycINFO.

The search approaches recommended in the literature tend to emphasise sensitivity, seeking to identify as many relevant published and unpublished studies as possible specific to the question and within available resources (Glanville and Paisley, 2010).

A central tactic is to take a systematic approach to breaking down the study question into components using a Venn diagram. Once the study question has been broken into its components, they can be combined using 'AND' and 'OR'. When the general structure of the question is developed, it is worth looking for synonyms for each component. Similar terms may be generated by thinking both up and down the hierarchy of abstraction, that is, by being less and more specific. In looking for synonyms you should consider both text words and key words in the database.

The MEDLINE keyword system, known as MeSH, has a tree structure that covers a broad set of synonyms very quickly. The 'explode' (exp) feature of the tree structure allows you to capture an entire subtree of MeSH terms within a single word.

The process of identifying papers is an iterative one. It is best to devise a strategy on paper initially. However, this will inevitably miss useful terms, and the process will need to be repeated and refined. The results of the initial search are used to retrieve relevant papers, which can then be used in two ways to identify missed papers: the bibliographies of the relevant papers can be checked for articles missed by the initial search; and a citation search, using the

Science Citation Index can be conducted to identify papers that have cited the identified relevant studies, some of which may be subsequent primary research. These missed papers are invaluable, they provide clues on how the search may be broadened to capture further papers by studying the MeSH keywords that have been used. The whole procedure may then be repeated using the new keywords identified.

If the relevant articles appear in a limited range of journals or conference proceedings, it may be feasible and desirable to search these by hand. This is obviously more important for unindexed or very recent journals, but may also pick up relevant studies not easily identified from title or abstracts.

Studies are conducted in all parts of the world and published in different languages. The systematic reviewer has two options. Firstly, to try to identify all relevant studies irrespective of the country in which they were conducted or the language in which they have been published. This option, however, is generally difficult. An alternative is to consider restricting the inclusion criteria.

The converse of an unpublished study is a study that is published several times. Unfortunately, there is no simple routine means of detecting such duplicates. If duplicate publications represent several updates of the data, then the most recent should be used.

The expectation is that the systematic review will provide a complete picture of all that is known about an intervention. A librarian or other qualified information specialist with training or experience in conducting systematic reviews should work with the reviewers to design the search strategy. Search errors include spelling errors, the omission of spelling variants and truncations, the use of incorrect Boolean operators and inadequate translation of the search strategy for different databases, misuse of MeSH and free-text terms, unwarranted explosion of MeSH terms, and redundancy in search terms. Experts recommend peer review of the electronic search strategy to identify and prevent these errors from occurring. The peer review process should take place prior to the search process.

At present, no one database or information source is sufficient to ensure an unbiased, balanced picture of what is known about the effectiveness, harms, and benefits of health interventions.

Scopus, Web of Science, and other citation indexes are valuable for finding cited reports from journals, trade publications, book series, and conference papers from the scientific, technical, medical, social sciences, and arts and humanities fields. Searching the citations of previous systematic reviews on the same topic could be particularly fruitful.

Grey literature includes trial registries, conference abstracts, books, dissertations, monographs, and reports held by government agencies, academics, business, and industry. Grey-literature databases, are important sources for technical or research reports, doctoral dissertations, conference papers, and other research.

Hand searching is the manual examination page by page, each article, abstract, editorial, letter to the editor, or other items in journals to identify reports or other relevant evidence. A combination of hand searching and electronic searching is necessary for full identification of relevant reports published in journals, even for those that are indexed in MEDLINE. Authors can prioritize hand searching based on where they expect to identify the most reports.

It is important to try to identify possibly relevant studies reported in conference abstracts through specialist database sources and by hand searching or electronically searching those abstracts.

Colleagues can be an important source of information about unpublished studies, and informal channels of communication can sometimes be the only means of identifying unpublished data. It is also important to identify ongoing studies, so that when a review is later updated these can be assessed for possible inclusion. Information about possibly relevant ongoing studies should be included in the review.

Searches for systematic reviews aim to be as extensive as possible in order to ensure that as many as possible of the necessary and relevant studies are included in the review. It is, however, necessary to strike a balance between striving for comprehensiveness and maintaining relevance when developing a search strategy. Increasing the sensitivity of a search will reduce its precision and will retrieve more non-relevant articles.

Developing a search strategy is an iterative process in which the terms that are used are modified, based on what has already been retrieved.

MEDLINE and EMBASE (and many other databases) can be searched using standardized subject terms assigned by indexers. Standardized subject terms (as part of a controlled vocabulary or thesaurus) are useful because they provide a way of retrieving articles that may use different words to describe the same concept and because they can provide information beyond that which is simply contained in the words of the title and abstract.

When designing a search strategy, in order to be as comprehensive as possible, it is necessary to include a wide range of free-text terms for each of the concepts selected.

Search filters should be used with caution. They should be assessed not only for the reliability of their development and reported performance but also for their current accuracy, relevance and effectiveness given the frequent interface and indexing changes affecting databases.

Specially designed bibliographic or reference management software such as EndNote, ProCite, Reference Manager and RefWorks is useful and relatively easy to use to keep track of references to and reports of studies.

The review search process needs to be documented in enough detail throughout the process to ensure that it can be reported correctly in the review, to the extent that all the searches of all the databases are reproducible. It should be borne in mind that the full search strategies for each database will need to be included in an Appendix of the systematic review.

## Conclusion

Finding all relevant studies for a systematic review that have addressed a specific question is not easy. A systematic search is essential in order to identify all of the best evidence available that addresses the question. At present, no one database or information source is sufficient to ensure an unbiased, balanced picture of what is known about the effectiveness, harms, and benefits of health interventions. The search process needs to be documented in the systematic review report.

# Chapter 4:

## *Selecting and critically appraising economic studies*

The approach proposed in this section is based on comprehensive guidance provided by the Cochrane Collaboration (Higgins and Green, 2008), the Centre for Reviews and Dissemination CRD (CRD, 2009), the US Institute of Medicine IOM (IOM, 2011), and the Joanna Briggs Institute (JBI, 2008; 2011).

### **Selecting economic studies**

When the search for evidence is complete reviewers decide which papers found should be retrieved and then subjected to critical appraisal. This initial process is referred to as the selection of papers for appraisal. All selected papers are then subjected to critical appraisal to determine methodological quality.

Once full-text papers of potentially relevant health economics studies have been obtained the next step is to assess the relevance of each of these studies to the specific review topic. Decisions to either include or exclude health economics studies on grounds of relevance should be based on whether or not they meet eligibility criteria relating to the target populations, interventions, comparisons and outcomes, and study design, that were specified in the protocol for the review. Reasons for excluding health economics studies at this stage should be reported in the review report.

Study selection is usually conducted in two stages: an initial screening of titles and abstracts against the inclusion criteria to identify potentially relevant papers followed by screening of the full papers identified as possibly relevant in the initial screening.

The process for selecting studies should be explicit and conducted in such a way as to minimize the risk of errors and bias. The process by which decisions on the selection of studies will be made should be specified in the systematic review protocol, including who will carry it out and how it will be performed. The aim of selection is to ensure that all relevant studies are included in the systematic review.

It is important that the selection process should minimize biases, which can occur when the decision to include or exclude certain studies may be affected by pre-formed opinions. The process for study selection therefore needs to be explicit, objective and minimize the potential for errors of judgement. It should be documented clearly in the review report to ensure it is reproducible.

A first decision is made based on titles and, where available, abstracts. These should be assessed against the predetermined inclusion criteria. If it can be determined that an article does not meet the inclusion criteria then it can be rejected straightaway. It is important to err on the side of over-inclusion during this first stage. For studies that appear to meet the inclusion criteria, or in cases when a definite decision cannot be made based on the title and/or abstract alone, the full paper should be obtained for detailed assessment against the inclusion criteria.

The reliability of the decision process is increased if all papers are independently assessed by more than one reviewer. Agreement between reviewers may be formally assessed using for example a Kappa statistic. The process for resolving disagreements between reviewers should be specified in the protocol. These disagreements should be discussed and, where possible, resolved by consensus after referring to the protocol. If necessary a third person may be consulted.

The selection process should be piloted by applying the inclusion criteria to a sample of papers in order to check that they can be reliably interpreted and that they classify the studies appropriately.

The pilot phase can be used to refine and clarify the inclusion criteria and ensure that the criteria can be applied consistently by more than one person. Piloting may also give an indication of the likely time needed for the full selection process.

Judgements about inclusion may be affected by knowledge of the authorship, institutions, journal titles and year of publication, or the results and conclusions of articles. Blind assessment may be possible by removing such identifying information, but the gain should be considered against the time and effort required to disguise the source of each article. The general opinion is that unmasked assessment by two independent reviewers is acceptable.

Sometimes the amount of information reported about a study is insufficient to make a decision about inclusion, and it can be helpful to contact study authors to ask for more details. However, this requires time and resources, and the authors may not reply, particularly if the study is old. If authors are to be contacted it may be advisable to decide in advance how much time will be given to allow them to reply.

Although sometimes there is a single report for each study, it should never be assumed that this is the case. It is important to look for duplicate publications to ensure they are not treated as separate studies in the review. Duplicate publication can introduce substantial biases if studies are inadvertently included more than once. Duplicate publication can take various forms, ranging from identical manuscripts to reports describing different numbers of participants and different outcomes. It can be difficult to detect duplicate publication. It may be worthwhile comparing multiple publications for any discrepancies, which could be highlighted and the study authors contacted for clarification.

Reviewers must decide if more than one of them will assess the titles and abstracts of records retrieved from the search. Using at least two reviewers may reduce the possibility that relevant reports will be discarded. It is most important that the final selection of studies into the review is undertaken by more than one reviewer.

The screening and selection process requires careful, sometimes subjective judgments and meticulous documentation. Decisions on which studies are relevant to the review question are among the most significant judgments made during the course of a systematic review. If the study inclusion criteria are too narrow, critical data may be missed. If the inclusion criteria are too broad, irrelevant studies may overburden the systematic review process.

Using pre-specified inclusion and exclusion criteria to choose studies is the best way to minimize the risk of researcher biases influencing the ultimate results of the systematic review.

The review protocol should make explicit which studies to include or exclude based on the patient population and patient outcomes of interest, the healthcare intervention and comparators, clinical settings and study designs that are appropriate for the research question. Only studies that meet all of the criteria and none of the exclusion criteria should be included in the systematic review.

Even when the selection criteria are pre-specified and explicit, decisions on including particular studies can be subjective.

A systematic review report should include a list of all excluded studies. By listing such studies as excluded and giving the reasons for exclusion, the review authors can show that consideration has been given to these studies. The reasons for any disagreement should be explored. It is important to have a record of decisions made for each article. This may be in paper form, or the selection process may be computerised. If the search results are provided in electronic format, they can be imported into a reference management program such as EndNote.

A flow chart is a simple and useful way of documenting the study selection process.

## **Assessment of methodological quality/critical appraisal**

A preliminary stage to be undertaken is to classify the included health economics studies by study design. The critical appraisal method will vary according to the study design of the economic evaluation studies. Therefore, it will be useful to categorise the study into partial or full economic evaluations, with further breakdown into study design categories such as cost analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis. Authors may also find it useful to group studies by analytical technique i.e. economic evaluation alongside randomized controlled trials, observational studies, or economic modeling studies.

The main object of critical appraisal is to assess a study's quality and determine the extent to which a study has excluded the possibility of bias in its design, conduct and analysis. If a study has not excluded the possibility of bias, then its results are questionable and could well be invalid. Therefore, part of the systematic review process is to evaluate how well the potential for bias has been excluded from a study, with the aim of only including high quality studies in the resulting systematic review. A secondary although no less strategic benefit of critical appraisal is to take the opportunity to ensure each retrieved study has included the population, intervention and outcomes of interest specified in the review.

Providing an explicit and standardized appraisal of the studies that have been identified is important for two reasons. Firstly, a systematic review should try to base its conclusions on the highest-quality evidence available. To do this requires a valid and standardized procedure to select from the large pool of studies identified so that only the relevant and acceptable quality studies are included in the review. Secondly, it is important to convey to the reader the quality of the studies included as this indicates the strength of evidence for any recommendation made.

Because of the importance of appropriately selecting studies, at least two reviewers should be used. Each reviewer should independently read and examine each of the studies that can potentially be included in the review. They should then meet to resolve any discrepancies

between the appraisal of the paper by open discussion about their justification for each of the decision.

Some have suggested that all appraisals should be done blind to the results of the individual study. This requires removing identification of the authors, journal and all reference to any results from the paper. Generally, the methods and the results section of the paper are sufficient to provide the information necessary for the appraisal. However, this approach is very time-consuming. At present there is not a consensus about whether the gain is worth the effort. However, for particularly controversial and important issues, such a blinded appraisal should be considered.

A systematic review should be based on the best quality evidence available. Whatever the study included, it should not be assumed that all studies are equally well-conducted. The quality of the included studies should be formally assessed as this will impact on the reliability of the results and therefore on the conclusions drawn. Quality assessment can sometimes be used to exclude studies that do not meet certain criteria.

Simply reporting which quality criteria were met by studies included in a systematic review is not sufficient. The implications of the quality assessment for interpreting results need to be explicitly considered.

Quality assessment is likely to focus on the following elements of the economic evaluation, each of which can have an important impact on the validity of the overall results of that study:

- Methods of deriving the effectiveness data
- Measurement of resource data
- Valuation of resource data
- Measurement and valuation of health benefits
- Method of synthesising the costs and effects
- Analysis of uncertainty
- Generalizability of the results

A number of tools/instruments/checklists have been developed to guide critical appraisal of health economics studies. Probably the most widely used is the BMJ guidance on critical appraisal of economic studies (Drummond and Jefferson, 1996). The BMJ 35-item checklist is available from the BMJ journal website:

<http://resources.bmj.com/bmj/authors/checklists-forms/health-economics>

Use of the 'Drummond checklist' (Drummond et al., 2005) and the 'Evers checklist' (Evers et al., 2005) is also recommended. The 'Philips checklist' (Philips et al., 2004) is recommended to inform critical appraisal of the methodological quality of economic modeling studies.

Guidelines for specific economic evaluation studies and methods can also be used for benchmarking the analytical components that should have been included if the authors had adhered to good practices. There are guidelines focusing specifically on decision-making models and Markov analyses for health economic evaluations (Weinstein et al., 2003). Motheral et al. (2003) offer specific guidelines for retrospective designs for health economic evaluations. Specific guidelines have been developed for prospective studies for health economic evaluations (Ramsey et al., 2005).

Quality assessment of the clinical effectiveness data incorporated in an economic evaluation will depend on the type of clinical data used; whether the data were obtained from a single study or from the literature or from expert opinion; and whether modeling techniques were used. When the effectiveness data has been synthesised from a variety of sources assessment should focus on the quality of the review and the methods used to synthesise the data.

Quality assessment of cost analysis should consider which costs were evaluated in the study, the measurement of the associated resource quantities, and the valuation of those resources. All costs consistent with, and relevant to the study question and the perspective adopted should have been included. Reviewers should assess whether resources were valued credibly and whether the units of resource use measured in physical units was accurate. For trial-based economic evaluations, the most valid resource estimates are considered to be those collected prospectively alongside effectiveness data. For modeling studies, clinical pathways describing the resource consumption expected during the management of the patients, can help reviewers assess whether all relevant costs including resource implications arising from new interventions, have been included.

#### *Common Critical Appraisal Questions for Economic Evaluation studies*

Reviewers should be aware that there are multiple dimensions examined in critical appraisal of economic evaluation studies.

- Was a well-defined research question posed in answerable form? Was there a well defined question? Was the problem or question being analyzed well defined?
- Did the analysis provide a full economic comparison of health care interventions/strategies?
- Did the study examine both costs and effects of the services or programs or interventions?
- Was the economic study design appropriate to the stated objective? (The problem or question being analyzed in the study influences the types of effects and costs included in the analysis and introduces the alternative interventions to be compared.)
- Was Modeling and statistical extrapolation reported in an explicit manner?
- Was the study population clearly described? (The study population should be described by time, place, and person. Information about participants should include age and the relevant characteristics that are key to the study.)
- Was a viewpoint for the analysis stated or was the study placed in a particular decision-making context? Was study perspective mentioned? (The perspective of the study determines the type of costs and benefits included in the analysis. Perspectives could be societal, public health department, program, healthcare provider, or other.)
- Did the study use a societal perspective? (Most community intervention studies should use the societal perspective, which means that all benefits of a program and all costs, no matter who receives the benefits or who receives the program, should be analyzed.)
- Was a broad enough view-point adopted?
- Was the actual perspective chosen appropriate?

- Did the study define the time or analytic horizon? (Analytic horizon refers to the period of time over which health effects benefits and costs are measured. The analytic horizon should be long enough to capture all costs and benefits originated by the intervention.)
- Was the chosen time horizon appropriate in order to include relevant costs and consequences?
- Did the study involve a comparison of alternatives?
- Were alternative interventions, including comparator, well described? Are competing alternatives clearly described? (Descriptions of alternative/comparator interventions are important because they influence the type of costs and effects included in the analysis and give the reader a sense of the degree of applicability of results for the reader's own setting.)
- Were all relevant clinical strategies compared?
- Were any important alternatives omitted?
- Was (should) a do-nothing alternative (have been) considered?
- Comparative treatments relevant/appropriate?
- Was clinical effectiveness established? Was there evidence that the effectiveness has been established?
- Was the effectiveness data used appropriate?
- Was the expert opinion used in the study analysis appropriate?
- Source of clinical outcomes data stated?
- Method of eliciting utility values stated?
- Were the sources of all values clearly identified?
- Were market values used for changes involving resources gained or used?
- When market values were absent or did not reflect actual values were adjustments made to approximate market values?
- Were all important and relevant outcomes for each alternative identified?
- Was the primary outcome measure clearly specified? (Outcomes need to be explicitly defined. Although a study might consider more than one outcome measure, the outcome measure used to calculate the final ratio or summary measure must be appropriate for the intervention under consideration.)
- Were outcome measures consistent with the study perspective?
- Were all outcomes measured appropriately?
- Were outcomes that would occur in the future discounted? (Outcomes that would occur in the future should be discounted before comparing costs and health outcomes for a single time period.)
- Were all important and relevant costs for each alternative identified?
- Relevant costs included?
- Were costs measured accurately?
- Unit costs provided?
- Year of costing provided?

- Sources of costs and healthcare resource use stated?
- Were data sources for all costs reported? (The study might have used cost data as calculated in the study or might have taken the data from the literature, reimbursement records, or expert opinion.)
- Was an incremental analysis of costs and outcomes of alternatives performed?
- Were all future costs and outcomes discounted appropriately? (Because costs and health outcomes occur during different time periods, discounting is used to reduce the stream of costs and benefits to a single time period. Therefore, discounting costs as well as benefits is important.)
- Was any justification given for the discount rate used?
- Discounting applied appropriately?
- Were all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
- Were estimates of cost and outcomes related to the baseline risk in the treatment population?
- Incremental analysis conducted? Were the additional (incremental) costs generated by the use of one alternative over another compared with the additional effects, benefits or utilities generated?
- Was appropriate allowance made for uncertainties in the analysis?
- Was justification provided for the ranges of values (for key parameters) used in the sensitivity analysis?
- Was a sensitivity analysis performed on the discount rate? (The reporting of sensitivity analysis on the discount rate facilitates the adjustment process and contributes to reducing uncertainty in standardizing results.)
- Was a sensitivity analysis performed on the effect size? (A good analysis should contain alternative results for changes in important variables and assumptions. For example, effectiveness effect sizes are important variables and studies should include a sensitivity analysis on effect sizes.)
- Was a sensitivity analysis performed on any other important parameter of the model? (Important parameters are incidence, prevalence of diseases, test cost, treatment costs, and so forth. If large variations in assumptions or variables do not produce changes in the results, the reader can have confidence in the strength of the results. If the opposite occurs, applicability of the results to other settings, under different assumptions or circumstances, is greatly reduced.)
- Were the study results sensitive to changes in the values (within the assumed range)?
- How much does allowance for uncertainty change the results?
- Were the results compared with those of other studies that had investigated the same questions?
- Did the study actually report the summary measure indicated in the title?
- Do the conclusions follow from the data reported?

- Did the study discuss the generalizability of the results to other settings and patient/client groups? (Factors limiting the transferability of economic data are: demographic factors; epidemiology of the disease; availability of health care resources; variations in clinical practice; incentives to health care professionals; incentives to institutions; relative prices; relative costs; population values.)
- Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?
- Are ethical and distributional issues discussed appropriately?

*10 Critical Appraisal Questions Approach*

Another approach is to use 10 specific common questions for critical appraisal of economic evaluation studies (Drummond, 1990; JBI, 2008). The complete JBI critical appraisal checklist has 11 appraisal questions, including a separate question on generalizability of the results. This is a general critical appraisal tool.

*Question 1: Is there a well defined question?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Did the study examine both costs and effects of the services or programs?
- Did the study involve a comparison of alternatives?
- Was a viewpoint for the analysis stated or was the study placed in a particular decision-making context?

*Question 2: Is there a comprehensive description of alternatives?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were any important alternatives omitted?
- Was (should) a do-nothing alternative (have been) considered?

*Question 3: Are all important and relevant costs and outcomes for each alternative identified?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Was the range wide enough for the research question at hand?
- Did it cover all relevant viewpoints (e.g., those of the community or society, patients and third-party payers)?
- Were capital costs as well as operating costs included?

*Question 4: Has clinical effectiveness been established?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Was there evidence that the program's effectiveness has been established?
- Was this done through a randomized, controlled clinical trial? If not, how strong was the evidence of effectiveness?
- Were observational data used to establish effectiveness?

*Question 5: Are costs and outcomes measured accurately?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were costs and consequences measured accurately in appropriate units prior to valuation?
- Were any identified items omitted from measurement?
- Were there any special circumstances that made measurement difficult? Were these circumstances handled appropriately?

*Question 6: Are costs and outcomes valued credibly?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were the sources of all values (e.g., market values, patient or client preferences and views, policy makers' views and health care professionals' judgments) clearly identified?
- Were market values used for changes involving resources gained or used?
- When market values were absent were adjustments made to approximate market values?

*Question 7: Are costs and outcomes adjusted for differential timing?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were costs and consequences that occurred in the future discounted to their present values?
- Was any justification given for the discount rate used?

*Question 8: Is there an incremental analysis of costs and consequences?*

Question that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were the incremental costs generated by the use of one alternative over another compared with the additional effects, benefits or utilities generated?

*Question 9: Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?*

Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Was justification provided for the ranges of values (for key parameters) used in the sensitivity analysis?
- Were the study results sensitive to changes in the values (within the assumed range)?

*Question 10: Do study results include all issues of concern to users?*

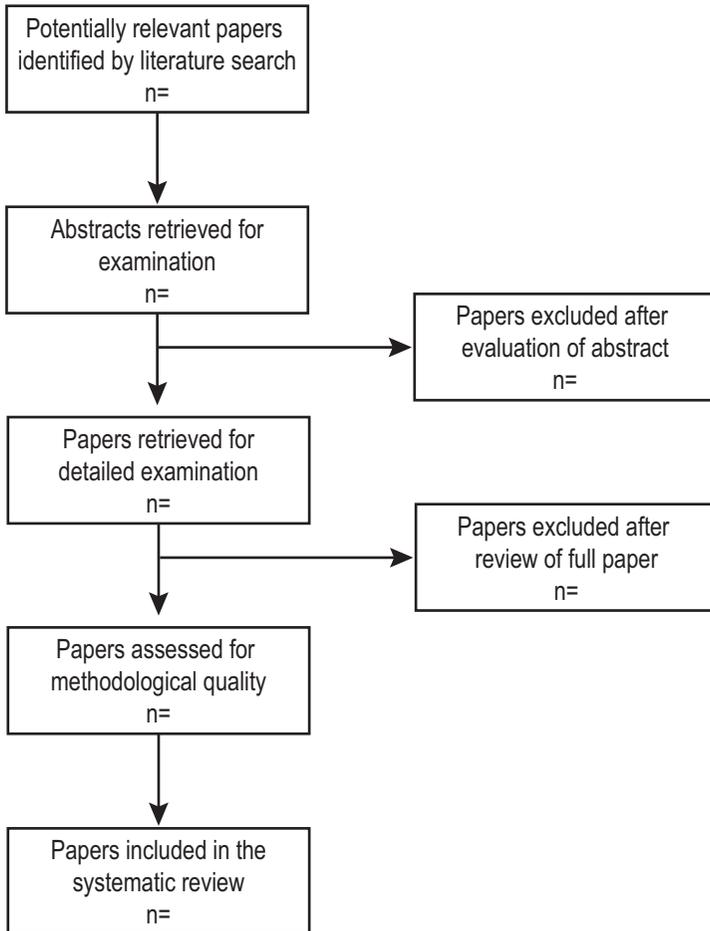
Questions that will assist you in addressing this criterion (Drummond, 1990; Drummond et al., 2005):

- Were the conclusions of the analysis based on some overall index or ratio of costs to consequences?

- Were the results compared with those of other studies that had investigated the same questions?
- Did the study discuss the generalizability of the results to other settings and patient/client groups?
- Did the study take account of, other important factors in the choice or decision under consideration (e.g., relevant ethical issues)?
- Did the study discuss issues of implementation, such as the feasibility of adopting the preferred program?

A flow chart is a simple and useful way of documenting the results of initial study selection based on title, abstract and full text compared with the inclusion criteria and study selection based on selection of best quality studies after critical appraisal of full text papers (Figure 1).

**Figure 1: Flowchart documenting paper selection**



## Conclusion

The aim of selection in the systematic review process is to ensure that all relevant appropriate studies are included in the systematic review. Study selection should be transparent, and should minimize biases and human error.

The main object of critical appraisal is to assess a study's quality. An important part of the systematic review process is to evaluate how well the potential for bias has been excluded from a study, with the aim of only including high quality studies in the resulting systematic review.



# Chapter 5:

## *Data Extraction*

The approach proposed in this section is based on comprehensive guidance provided by the Cochrane Collaboration (Higgins and Green, 2008), the Centre for Reviews and Dissemination CRD (CRD, 2009; CRD, 2007), the US Institute of Medicine IOM (IOM, 2011), the US Preventive Task Force (2010), and the Joanna Briggs Institute (JBI, 2008; 2011).

Data extraction is the process by which reviewers obtain the necessary information about study characteristics and findings from the included studies. Data extraction requirements will vary from review to review, and the extraction forms should be tailored to the review question. The results to be extracted from each individual study may be reported in a variety of ways, and it is often necessary for a researcher to manipulate the available data into a common format.

A sample data extraction form and details of the data extraction process should be included in the review protocol. A common problem at the protocol stage is that there may be limited familiarity with the topic area.

Precise data collection forms/instruments and procedures will need to be specified for each individual systematic review, depending on the specific economics review question/objective and on the economic and effectiveness measures included as outcomes.

Two types of data will need to be collected: details of the characteristics of included health economics studies and details of their results. The potential to extract data from published reports may be constrained by the quality of reporting of the health economics studies. Where information is missing, a further option is to contact study authors to request additional details.

Data extraction requirements are specific to each review question but will need to include: study question, analytical perspective, included population, intervention, comparator and setting; modeling techniques; sources and quality of clinical effectiveness data; sources and quality of cost data; study outcomes in terms of health benefits and costs, and the methods used to synthesise them; methods for dealing with uncertainty; study results, including results of analyses of uncertainty. Additional useful data to be collected regarding the characteristics of each economic study include: year of study; geographical and organizational setting; analytic viewpoint; and time horizon for both costs and effects.

When designing/adapting a data collection form, review authors should first consider how much information should be collected. Collecting too much information can lead to forms that are very long and can be very wasteful of time. Collection of too little information, or omission of key data, can lead to the need to return to study reports later in the review process.

Data extraction forms should be piloted on a sample of included studies to ensure that all the relevant information is captured and that resources are not wasted on extracting data not required. The consistency of the data extracted should be assessed to make sure that those extracting the data are interpreting the forms, and the instructions and decision rules in the same way. This will help to reduce data extraction errors.

Data extraction needs to be as unbiased and reliable as possible, however it is prone to human error and often subjective decisions are required. The number of reviewers that will perform data extraction is likely to be influenced by constraints on time and resources. Ideally two reviewers should independently perform the data extraction. As an accepted minimum, one reviewer can extract the data with a second reviewer independently checking the data extraction forms for accuracy and completeness. This method may result in significantly more errors than two reviewers independently performing data extraction but may also take significantly less time. Any disagreements should be noted and resolved by consensus or by arbitration by an additional independent reviewer.

A record of corrections or amendments to data extraction forms should be kept for future reference, particularly where there is ambiguity which cannot be resolved after discussion between the two reviewers. Any disagreements that cannot be resolved should be addressed by contacting the study authors. If this is unsuccessful, the disagreement should be reported in the review.

Blinding reviewers to the journal and author details has been recommended. However, this is a time-consuming operation, and is likely to be of limited value.

Participant characteristics that should always be extracted include socio-economic details (race, gender, age) and the presence of co-morbid conditions.

If the settings of studies may influence intervention effects or applicability, then information on these should be collected. Typical settings of healthcare intervention studies include acute care hospitals, emergency facilities, general practice, nursing homes, and communities. Sometimes studies are conducted in different geographical regions with important differences in cultural characteristics that could affect delivery of an intervention and its outcomes.

Timing of the study may be associated with important technology differences or trends over time. If such information is important for the interpretation of the review, it should be collected.

Diagnostic criteria that were used to define the condition of interest can be a particularly important source of diversity across studies and should be collected. The degree to which specified procedures or components of the intervention are implemented as planned can have important consequences for the findings from a study.

For results, estimates of specific items of resource use associated with interventions and comparators and estimates of their unit costs should be extracted separately as well as estimates of costs of the resource use. The type and quantity of each resource used should be extracted in natural units. It is also important to collect information on the price year and currency used to calculate estimates of costs and incremental costs.

Results should be collected only for the outcomes specified to be of interest in the protocol. Results for other outcomes should not be extracted unless the protocol is modified to add them, and this modification should be reported in the review. However, review authors should be alert to the possibility of important, unexpected findings, particularly serious adverse effects.

Both a point estimate and a measure of uncertainty should be extracted for measures of incremental resource use, costs and cost-effectiveness, if reported. Additionally, it is useful

to collect details of any sensitivity analyses undertaken, and any information regarding the impact of varying assumptions on the magnitude and direction of results.

Other information will be required from each report of a study, including the citation, contact details for the authors of the study and any other details of sources of additional information about it. Of particular importance in many areas is the funding source of the study, or potential conflicts of interest of the study authors.

The review authors should collect the key conclusions of the included study as reported by its authors. Further comments by the study authors, for example any explanations they provide for unexpected findings, might be noted.

## Proposed Data extraction details/fields

- Reviewer's Name
- Data Extraction Completion Date
- Bibliographic details (Journal, Year published, Volume)
- Authors details/Authors contact details for further information
- ID (Tracking) Number
- Author(s) Affiliation(s) and Funding Sources
- Conflict of interest
- External peer review of the primary study
- Policy question that is addressed or Study Objectives/Goals/Aims/Questions
- Publication Type (Peer-Reviewed Published Article; Non-Peer Reviewed Published Article Abstract/Presentation; Unpublished Dissertation/Thesis; Other)
- Language /Translation
- Economic Evaluation Study Design/Analytic Method (Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), Cost-Benefit Analysis (CBA), Cost-Minimisation Analysis (CMA))
- Study design (RCT; observational study; Other)
- Study population
- Other Potentially Important Characteristics of Study Population
- Study sample and sample size
- Location of the Study (Country, City)
- Setting of the Study (Hospital, Nursing Home, Community, Home, Other)
- Type of intervention (Primary prevention, Secondary prevention, Screening, Diagnosis, Treatment, Rehabilitation, Palliative care, Other)
- Interventions Descriptions
- Comparators Descriptions
- Follow-up Period
- Analysis of effectiveness
- Source of effectiveness data (Systematic review of RCTs; primary research effectiveness studies; expert opinion)

- Outcomes assessed in the study
- Effectiveness results
- Effectiveness Effect Size Measures Used in the Study
- Clinical/Practical effectiveness conclusions
- Measure of benefits used in the economic analysis
- Perspective of the Study (Societal, Patient and Patient Family, Healthcare Provider, Insurer, Other)
- Analytic Horizon of the Study
- Costs Included (Medical costs, Non-Medical costs, Productivity Losses)
- Direct costs
- Indirect Costs
- Productivity costs
- Cost Data Sources (Estimated Directly in Study, Published Related Study, Unpublished Related Study, Expert Opinion, Diagnostic-related Group, Insurance Company, Other)
- Statistical analysis of costs
- Cost results
- Values of Summary Measures (CUA or CEA Ratio, Net Benefits or Net Present Value, OR Costs)
- Currency Used in the Study and Base Year
- Discount Rate Used in Study
- Link between effectiveness and cost data
- Modeling and statistical extrapolation
- Methods used to allow for uncertainty/ Sensitivity analysis
- Synthesis of costs and benefits
- Funding body
- Author's conclusions
- Reviewer's Comments (Selection of comparators; Validity of estimates of measures of effectiveness; Validity of estimates of measures of benefits; Validity of estimates of costs, Other issues)
- Conclusions of the study
- Implications of the study

### **Outcomes Matrix for an economic evaluation**

The outcome matrix (Figure 2) is a method proposed by Nixon et al. (2001) and used by Joanna Briggs Institute in the ACTUARI software for systematic reviews of economic evidence (JBI, 2008). The outcome matrix is a three by three matrix of possible outcomes of an economic evaluation. The final decision about the incremental clinical effectiveness and incremental costs of the intervention under examination is entered here, using data extracted on both the clinical effectiveness and costs of the intervention.

**Figure 2: Outcome Matrix (Nixon et al., 2001)**

Key	Effectiveness	Cost
+	Better	Higher
0	Equal	Equal
-	Poorer	Lower

	+	0	-
+	A	B	C
0	D	E	F
-	G	H	I

In comparing the clinical effectiveness of two alternatives there are three possibilities: the intervention of interest is more effective than the comparator ('+'), the intervention is equally effective ('0') or the intervention is less effective ('-').

Similarly, in terms of costs, there are three possibilities: the intervention is more expensive ('+'), the intervention and comparator's costs are the same ('0'), or the intervention is less expensive ('-').

Each of the comparisons between intervention and comparator can only be classed as one of nine options (A – I). For example, an intervention that was shown to be more effective and less expensive would be scored as 'G', whereas an intervention that was less effective and of equal cost would be scored as 'F'.

## Conclusion

Data extraction is the process by which reviewers obtain the necessary information about study characteristics and findings from the included studies. Precise data collection forms and procedures will need to be specified for each individual review, depending on the specific economics question or objective and on the measures of outcomes. Data extraction needs to be as unbiased and reliable as possible, however it is prone to human error and often subjective decisions are required.



# Chapter 6:

## *Data synthesis*

The objective of a systematic review is to answer a specific review question by using an explicit, pre-planned protocol to identify, select, assess, and summarize the findings of similar but separate studies.

Systematic reviews of effectiveness data often include a quantitative synthesis, a meta-analysis. Meta-analysis is not always possible or sensible. However, when used appropriately, meta-analysis has the advantage of being explicit in the way that data from individual studies are combined, and is a powerful tool for combining study findings, helping avoid misinterpretation and allowing meaningful conclusions to be drawn across studies. Theoretically, a meta-analysis of economic evaluations studies could be done. In principal, quantitative estimates of the costs and benefits extracted from two or more studies can be pooled using a meta-analysis. There are currently no agreed-upon methods for combining data collected from multiple full economic evaluation studies using a meta-analysis, or other quantitative synthesis methods.

Synthesis involves the collation, combination and summary of the findings of individual studies included in the systematic review. Synthesis can be done quantitatively using formal statistical techniques such as meta-analysis, or if formal pooling of results is inappropriate, through a narrative approach. As well as drawing results together, synthesis should consider the strength of evidence, explore whether any observed effects are consistent across studies, and investigate possible reasons for any inconsistencies. This enables reliable conclusions to be drawn from the assembled body of evidence.

Narrative and quantitative approaches are not mutually exclusive. Components of narrative synthesis can be usefully incorporated into a review that is primarily quantitative in focus and those that take a primarily narrative approach can incorporate some statistical analyses such as calculating a common outcome statistic for each study.

Essentially, there are three options for the synthesis of economic data: results are presented in a narrative summary; results are presented in tables of results; or results can be summarised using a permutation matrix.

Synthesis should begin by constructing a clear descriptive summary of the included studies. This is usually done by tabulating details about study type, interventions, numbers of participants, a summary of participant characteristics, outcomes and outcome measures. An indication of study quality may also be given in tables.

The descriptive process should be both explicit and rigorous and decisions about how to group and tabulate data should be based on the review question and what has been planned in the protocol.

Synthesis should begin with descriptive comparisons of the study question, methods and results. It may be useful to include summary tables which present key information relating

to population, country, perspective, comparison of interventions, measure of benefit and incremental cost-effectiveness ratios.

The range of incremental cost-effectiveness ratios should be presented and the reliability and generalizability of the estimates should be explored. The analytical approaches used in the studies should be compared and their robustness discussed.

It is useful to report in the same table the interventions examined, the adopted perspective, the type of economic evaluation and the main results together with reviewer's comments.

Table 1. Results

<b>Author country year</b>	<b>Diagnosis</b>	<b>Intervention</b>	<b>Perspective</b>	<b>Type of Economic Evaluation</b>	<b>Primary Outcomes</b>	<b>Results</b>	<b>Reviewer Comments</b>

Sometimes it is important to report in the same table details on study design, sample size, types of patients and effectiveness results.

Table 2. Effectiveness Results

<b>Intervention</b>	<b>Country</b>	<b>Study period</b>	<b>Sample size/Study Design</b>	<b>Comparator</b>	<b>Patients</b>	<b>Effectiveness Results</b>	<b>Reference</b>

It is important to report information on sponsors of economic studies.

Table 3. Results

<b>References</b>	<b>Year of publication</b>	<b>Sponsoring company</b>
Study 1		
Study 2		
Study 3		

Results for different search terms are sometimes reported in systematic reviews.

Table 4. Search Results

Search Term	Search Term 1	Search Term 2	Search Term 3	Search Term 4
Total number of hits				
Total number of titles/abstracts screened				
Number of studies eligible for full review				
Number of studies selected				

In some systematic reviews, different disease classification systems are used. It is important to report the studies that used different systems.

Table 5. Disease Classifications used in the Review

Disease	Disease Classification	References	Reviewer Comments/Notes
Disease 1			
Disease 2			
Disease 3			
Disease 4			

A way to present the quality of included economic studies.

Table 6. Results

Question	Study 1	Study 2	Study 3
Did the analysis provide a full economic comparison of health care strategies?			
Was a broad enough view point adopted?			
Were all relevant clinical strategies compared?			
Was clinical effectiveness established?			
Were costs measured accurately?			
Was appropriate allowance made for uncertainties in the analysis?			
Are estimates of cost and outcomes related to the baseline risk in the treatment population?			
How much does allowance for uncertainty change the results?			

Another way to report the quality of included studies.

Table 7. Results

	<b>Study 1</b>	<b>Study 2</b>
Study/Authors/Country/Year		
Choice of design was justified		
All costs were measured and valued appropriately		
The outcome measures were measured and valued appropriately		
Comparisons between interventions were made using a ratio of incremental costs and outcomes		
The study question/scope of evaluation was clearly defined		
The study design was clearly described		
Assumptions and uncertainties were made explicit		
The effect that assumptions and uncertainties had on the results was transparent		
Sensitivity analyses were performed and choice of sensitivity analyses was justified		
Future costs and outcomes were discounted where necessary		
The study question/scope of evaluation was relevant		
All relevant costs were included		
The outcome measures were relevant		
The results were of relevance to decision-makers, or the implications of the results in terms of economic impact were clear		

For reporting results of critical appraisal/quality assessment it is useful to use specific tables.

Table 8. Results

<b>Question</b>	<b>Study 1</b>	<b>Study 2</b>
Purpose of study explained?		
Study perspective mentioned?		
Comparative treatments relevant/appropriate?		
Source of clinical outcomes data stated?		
Method of eliciting utility values stated?		
Relevant costs included?		
Sources of costs and healthcare resource use stated?		

*(continued)*

Table 8. Results (*Continued*)

Question	Study 1	Study 2
Unit costs provided?		
Year of costing provided?		
Discounting applied appropriately?		
Sensitivity analysis conducted?		
Sensitivity analysis performed on key variables and justification given for range of values?		
Incremental analysis conducted?		
Discussion of results provided, including study limitations, comparison with previous studies addressing similar issues, etc.?		
Source of funding disclosed in published article?		
Conclusions valid?		

It is possible to use tables in order to report specific details regarding the quality of included studies.

Table 9. Methodological Quality Results

	Study 1	Study 2
Is the study population clearly described?		
Are competing alternatives clearly described?		
Is a well-defined research question posed in answerable form?		
Is the economic study design appropriate to the stated objective?		
Is the chosen time horizon appropriate in order to include relevant costs and consequences?		
Is the actual perspective chosen appropriate?		
Are all important and relevant costs for each alternative identified?		
Are all costs measured appropriately in physical units?		
Are costs valued appropriately?		
Are all important and relevant outcomes for each alternative identified?		
Are all outcomes measured appropriately?		
Are outcomes valued appropriately?		
Is an incremental analysis of costs and outcomes of alternatives performed?		

(*continued*)

Table 9. Methodological Quality Results (*Continued*)

	<b>Study 1</b>	<b>Study 2</b>
Are all future costs and outcomes discounted appropriately		
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?		
Do the conclusions follow from the data reported?		
Does the study discuss the generalisability of the results to other settings and patient/ client groups?		
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?		
Are ethical and distributional issues discussed appropriately?		

It is useful to report in tables the details of included studies (design, sample, endpoints)

Table 10. Results Characteristics of included studies

	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Study ID			
Authors			
Country			
Design			
Sample			
Follow-up			
Perspective			
Endpoints			

Systematic reviews of economic evidence should include synthesis tables reporting details of included studies.

Table 11. Results

	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Study			
Type of economic evaluation			
Country			
Condition/Disease			
Interventions			

(*continued*)

Table 11. Results (*Continued*)

	Study 1	Study 2	Study 3
Primary Outcome measures			
Cost components used			
Study methodological quality			
Results			
Year of costing			

Reporting of effectiveness in terms of effect sizes is very important in systematic review of economic evidence.

Table 12. Effectiveness Results

Study	Treatment/Regimen	Treatment duration/timepoint	Effectiveness (% of patients)	Effectiveness Results (Effect Size; 95%CI)
Study 1				
Study 2				

For economic models it is important to report for example the basic health states, the model cycle length, the transitions probabilities, and the year of costing.

Table 13. Model Details Results

Model Aspect	Study 1	Study 2	Study 3
<b>Country/ Year of costing</b>			
Model Cycle Length			
Basic Health States			
Other factors incorporated			
Costs included			
Population			
Transitions probabilities			
Resources use and unit costs			
Annual Discounting			
Incremental cost per patient			
QALY gained per patient			
Cost per QALY gained			

Tables could be used to report details on economic models used in included studies.

Table 14. Results

	<b>Number of studies</b>	<b>References</b>
Studies that met the inclusion criteria		
Markov models		
Markov models Included data on modeling and cost effectiveness		
Markov models Included modeling data only		
Dynamic models Included data on both modeling and cost effectiveness		
Dynamic models Included modeling data only		
Hybrid models Included data on modeling and cost effectiveness		
Duplicate studies		
Studies that did not meet the study inclusion criteria		

It is important to compare studies in terms of types of costs included and year of costs estimates.

Table 15. Results

<b>Authors</b>	<b>Country</b>	<b>Year of costs estimates</b>	<b>Types of Costs included</b>	<b>Primary data sources</b>	<b>References</b>	<b>Reviewer Comments/Notes</b>

In some systematic reviews is important to report costs of informal care, sick leave and early retirement.

Table 16. Results

<b>Costs Components</b>	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Outpatient care			
Inpatient care			

*(continued)*

Table 16. Results (*Continued*)

<b>Costs Components</b>	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Rehabilitation			
Drug use			
Medical procedures			
Informal care			
Transportation			
Sick leave			
Early retirement			
Premature mortality			

An important comparison is for direct healthcare costs and indirect costs.

Table 17. Results

<b>Study/ Year/ Country</b>	<b>Estimated cases</b>	<b>Currency</b>	<b>Total cost</b>	<b>Direct healthcare costs</b>	<b>Indirect costs</b>	<b>Reviewer comments/Notes</b>

It is important sometimes to compare cost of medical procedures or cost of outpatient care or cost of drugs.

Table 18. Results

<b>Costs</b>	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>	<b>Study 4</b>
Cost of hospitalization				
Cost of outpatient care				
Cost of drugs				
Cost of medical procedures				
Cost of devices				
Cost of social services				

(*continued*)

Table 18. Results (*Continued*)

<b>Costs</b>	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>	<b>Study 4</b>
Cost of transportation				
Cost of informal care				
Cost of premature mortality				
Cost of short-term absence				
Cost of early retirement				

Incremental analysis results are useful for example incremental cost per patient and incremental cost per event avoided.

Table 19. Results

<b>Study (year of costing)</b>	<b>Country</b>	<b>Incremental cost per patient</b>	<b>Incremental cost per event avoided</b>
Study 1			
Study 2			
Study 3			

A different way of reporting is the presentation of incremental cost per life year gained.

Table 20. Results

<b>Study (year of costing)</b>	<b>Life-expectancy data sources</b>	<b>Incremental cost per patient (\$)</b>	<b>Incremental cost per life-year gained (LYG) (\$)</b>
Study 1 (Year)			
Study 2 (Year)			
Study 3 (Year)			

It is useful in analysis to report not only the incremental direct cost per patient but also for example the incremental cost per life year gained.

Table 21. Results

<b>Study (year of costing)</b>	<b>Country</b>	<b>Clinical events</b>	<b>Incremental Direct cost per patient</b>	<b>Incremental Direct cost per life-year gained (LYG)</b>
Study 1				
Study 2				

In the special case of economic studies of vaccines it is important to report for example vaccine delivery costs included, productivity changes and the results of sensitivity analysis.

Table 22. Results

Study (Year)	Country	Decision Analytical Model	Effectiveness Results	Treatment Costs	Vaccine Delivery Costs Included	Productivity Changes	Sensitivity Analysis

Some studies report average values, for example average length of stay in hospital or average treatment cost of a case.

Table 23. Results

	Study 1	Study 2	Study 3
Study (Year)			
Monetary value of a life			
Lifetime productivity loss			
Average length of stay in hospital			
Average treatment cost of a case			
Discounted lifetime treatment cost of a sequelae case			

It is important to synthesize the information on articles reporting specific positive or negative economic or clinical outcomes.

Table 24. Results

Category	Number (%) of articles
Positive economic outcomes	
Positive medical/clinical outcomes	
Negative economic outcomes	
Negative medical/clinical outcomes	

Results of cost-effectiveness studies could be reported in synthesis tables.

Table 25. Results

<b>Conclusion</b>	<b>Number (%) of articles</b>
Intervention saves money	
Intervention saves time and money	
Intervention cost effective only if a certain threshold achieved	
More research needed to determine cost-effectiveness	
Intervention does not save money	
Other	

Total costs and absolute differences and the statistical significance of the results could be reported in tables.

Table 26. Results Cost Data

	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Study ID Authors Country			
Total Cost Intervention			
Total Cost Comparator			
Absolute Difference And (%) Difference			
P-value/95%CI			

Very important are tables reporting the incremental cost, incremental effectiveness and ICERs.

Table 27. Results

	<b>Study 1</b>	<b>Study 2</b>
Study ID Authors Country Year		

*(continued)*

Table 27. Results (*Continued*)

	Study 1	Study 2
Primary Outcome		
Incremental cost		
Incremental effectiveness		
ICER		

Useful tables report also the perspective of the study and the time horizon of the study for different interventions examined in different economic studies.

Table 28. Results

	Study 1	Study 2
Study/Year of costing		
Study type		
Country/Currency		
Interventions/Treatments		
Perspective		
Time Horizon		
Main Outcomes		

Very important are tables reporting effects on morbidity, mortality and quality of life.

Table 29. Results

	Study 1	Study 2
Study details (Authors, Year)		
Design		
Interventions		
Subjects		
Summary of effects on morbidity		
Summary of effects on mortality		
Summary of effects on quality of life		
Life years saved (LYS)		
Incremental cost per LYS		
Incremental cost per patient		

It is useful to report papers/articles showing specific conclusions.

Table 30. Results

	<b>Intervention 1</b>	<b>Intervention 2</b>
Number of papers		
Number of papers showing net savings		
Number of papers showing no net savings		
Number of papers showing no effects		
Reviewer Conclusions		

For policy makers sometimes it is important to know specific reported results such as cost per successfully treated patient and healthcare cost reduction per patient per year.

Table 31.

	<b>Study 1</b>	<b>Study 2</b>
Study References		
Country		
Study duration		
Cost per successfully treated patient		
Intervention Total Cost per patient per year		
Comparator Total Cost per patient per year		
Healthcare cost reduction per patient per year		
P-value/95% CI		

In Cost-Benefit studies tables could be used to report for example the estimated incremental cost, estimated incremental benefit and the cost/benefit ratio.

Table 32.

	<b>Study 1</b>	<b>Study 2</b>
Study References		
Interventions <b>Comparators</b>		
Estimated Incremental Benefits		
Estimated Incremental Cost		
Cost/Benefit Ratio		
Sensitivity Analysis Results		

## Narrative summary of results

All systematic reviews should contain text and tables to provide an initial descriptive summary and explanation of the characteristics and findings of the included studies. However simply describing the studies is not sufficient for a synthesis. The defining characteristic of narrative synthesis is the adoption of a textual approach that provides an analysis of the relationships within and between studies and an overall assessment of the robustness of the evidence.

A narrative synthesis of studies may be undertaken where studies are too diverse (either clinically or methodologically) to combine in a meta-analysis, but even where a meta-analysis is possible, aspects of narrative synthesis will usually be required in order to fully interpret the collected evidence.

Narrative synthesis is inherently a more subjective process than meta-analysis; therefore, the approach used should be rigorous and transparent to reduce the potential for bias. The idea of narrative synthesis within a systematic review should not be confused with broader terms like narrative review, which are sometimes used to describe reviews that are not systematic.

## Examples of narrative summary of economic evidence

In a systematic review (Dixon et al., 2004) on economic evaluations of treatments for systemic fungal infections authors provided for example the following narrative summary of economic evidence:

*“Collection of healthcare resource use data (e.g. length of stay) in many studies was undertaken retrospectively from case notes or hospital billing systems.<sup>[23,25,27,29,31]</sup> Others used trial based clinical datasets, and so could in theory be better designed for the purpose of accurate costings required for economic evaluations.<sup>[21,22,28,30,32]</sup> Some studies attempted to produce more detailed costs by supplementing routine sources with professional opinion. . . . Although not reported in the same detail, several studies covered the key components of the costs of drug acquisition, laboratory tests, hospitalisation and treatment of infections.<sup>[20–22,28,33]</sup> . . . Five studies were based on randomised controlled trials.<sup>[20,22,28,30,33]</sup> Such studies are likely to have greater internal validity than the studies where effectiveness is derived from non-experimental studies.<sup>[22–27,31,33]</sup> The studies by Wakerly et al.<sup>[33]</sup> and Flynn et al.<sup>[22]</sup> combined trial-based and model-based methods, which allowed . . . to be easily combined with other data in order to investigate changes in costs and effects in other settings.”*

In a systematic review (Getsios et al., 2005) of economic evaluations of pharmacological management of overactive bladder authors provided for example the following narrative summary of economic evidence:

*“Two studies have been published on patients’ willingness to pay to obtain various outcomes.<sup>[40,58]</sup> A Swedish study administered questionnaires to 461 individuals with OAB, with either urge or mixed incontinence. The contingent valuation method was used to determine how much they would be willing to pay to reduce the number of micturitions and urinary leakages they experienced by either 25% or 50%.<sup>[58]</sup> The median and mean willingness to pay for a 25% reduction were SEK240 per month and SEK530 per month (1996 values), respectively. For a 50% reduction, both median and mean willingness to*

pay doubled. A similar approach was used in the US,<sup>[40]</sup> with 495 questionnaires completed. The median and mean willingness to pay for a 25% reduction in symptoms were \$US27 and \$US87 per month (1997 values), respectively. Median and mean estimates nearly tripled for a 50% reduction. A UK study, which looked at incontinence in general, also calculated willingness to pay as part of a broader study.<sup>[59]</sup> Willingness to pay of patients with urinary symptoms was between £74 and £92 per year (1999/2000 values) for complete continence with no adverse effects, substantially lower than in the Swedish<sup>[58]</sup> and US<sup>[40]</sup> studies. Individuals without symptoms valued this outcome at only between £14 and £21 per year.”

In a systematic review (Halton and Graves, 2007) of economic evaluation of catheter-related bloodstream infections authors provided for example the following narrative summary of economic evidence:

*“In the 6 evaluations where the intervention was cost-saving,<sup>[23,24,26,27,29,30]</sup> the conclusions were robust to the sensitivity analyses. In the 2 evaluations where an incremental cost-effectiveness ratio could be calculated,<sup>[25,28]</sup> different conclusions were drawn in different scenarios . . . Scenario analyses used in 6 evaluations<sup>[23,24,26,27,29,30]</sup> indicated internal consistency in the models, i.e., they behaved logically and as expected. However, only 1 evaluation<sup>[27]</sup> made an explicit statement on internal consistency about checks performed during the model construction and analysis. Authors of 7 evaluations discussed caveats to their work.<sup>[23–27,29,30]”</sup>*

**Permutation matrix**

It is possible to use a permutation matrix following the method proposed by Nixon et al (2001) for reporting the possible outcomes of economic evaluations included in the systematic reviews of economic evidence.

Table 33.

	<b>Incremental Effectiveness Poorer</b>	<b>Incremental Effectiveness Same</b>	<b>Incremental Effectiveness Better</b>
Incremental Costs Better	Number of studies Study References	Number of studies Study References	Number of studies Study References
Incremental Costs Same	Number of studies Study References	Number of studies Study References	Number of studies Study References
Incremental Costs Poorer	Number of studies Study References	Number of studies Study References	Number of studies Study References

From the data extraction forms, specifically the outcomes data extraction matrix, reviewers are able to generate a permutation matrix in order to classify the economic evaluation studies

included in the review with regards to incremental effectiveness and the incremental costs of the intervention under examination. Effectiveness of the intervention under examination in each included study could be considered the same, poorer or better in comparison with the comparator. In the same time, for each included study the results for costs of the intervention under examination could be considered as the same, poorer or better in comparison with the comparator. In each cell of the permutation matrix are specified the number of studies in the respective class and the study references, for example, the number of studies and the references of studies that provided evidence that the effectiveness is better and the costs are the same. In the original method proposed by Nixon et al. (2001) only number of studies are specified in the matrix cells.

Interpretation of the results of a review of health economics studies is dependent on the specific economic questions and context of relevance to a given decision regarding the provision of health care.

## Conclusion

Synthesis involves the collation, combination and summary of the findings of individual studies included in the systematic review. Essentially, there are three options for the synthesis or of economic data: results are presented in tables of results, results are presented in a narrative summary; or results can be summarised using a permutation matrix.



# Chapter 7:

## *Developing a systematic review report*

**H**igh-quality systematic review reports should accurately document all of the steps and judgments in the systematic review process.

The methodological quality of systematic reviews is distinct from reporting quality.

Incomplete documentation of the systematic review process makes it impossible to evaluate its methodological quality, so it is impossible to tell whether a step in the systematic review process was performed correctly but not reported, performed inadequately, or not performed at all and therefore not reported.

The title should identify the review report as a systematic review. This may improve the indexing and identification of systematic reviews in bibliographic databases. The title should also reflect the review questions addressed in the review in order to help the reader understand the scope of the review.

The executive summary is the most important part of the report because potentially it is the only section that many readers will actually read. It should present the findings of the review clearly and concisely and allow readers to quickly judge the quality of the review and the generalizability of its findings. The executive summary is usually the last section to be written so that full consideration can be given to all relevant aspects of the review.

Systematic reviews final reports should be critically reviewed by peer reviewers to ensure accuracy and clarity and to identify any potential methodological flaws. The original protocol for the systematic review including any amendments should be made available to the peer reviewers.

A systematic review report is the final outcome of a review. To a large extent, the components of the systematic review report will mirror the content of the original protocol. As with the protocol, there should be a comprehensive background that justifies conducting the review, a description of the objectives of the review, an account of the criteria that were used for considering studies for the review, the search strategy used and methods utilised for critical appraisal, extraction and synthesis of data.

The review report includes both a flow chart describing the search, selection and inclusion process and a description of the studies that includes the type and number of papers identified. The number of papers included and excluded with brief explanation for exclusion are stated. The report also provides a summary of the overall quality of the literature identified. The results section must be organised in a meaningful way based on the objectives of the review and the criteria for considering studies. Particular consideration should be given to the types of interventions and outcomes.

The discussion must include an overview of the results and a discussion about any limitations and issues arising from the results of the review. The conclusions focuses on the implications

for practice and for research. These should be detailed and must be based on the documented results, not author opinion.

Where evidence is of a sufficient level, appropriate recommendations are also made. Recommendations must be clear, concise and unambiguous. As in the initial protocol, the final review report should include references and appendices. The references should be appropriate in content and volume and also include background references.

The appendices should include: Critical appraisal form(s), Data extraction form(s), Table of included studies, Table of excluded studies with justification for exclusion.

A statement should be included in every review report that either declares the absence of any conflict of interest or describes a specified conflict of interest.

### **Proposed structure of a systematic review report**

- Title of the systematic review
- Details on review authors
- Executive summary  
*(Background; Review Objectives/questions, Types of participants; Types of Interventions/Comparators; Types of Outcomes; Types of studies, Search strategy, critical appraisal, data extraction, data synthesis, results, conclusions, implications for practice, implications for research)*
- Background
- Review Objectives/Questions
- Inclusion Criteria  
*(Types of participants; Types of Interventions/Comparators; Types of Outcomes; Types of studies)*
- Search strategy
- Methods of the Review (critical appraisal, data extraction, data synthesis)
- Results (description of studies, methodological quality, results)
- Discussion
- Conclusions
- Implications for practice
- Implications for research
- Appendices (critical appraisal tools, data extraction tools; excluded studies, included studies)

## **Conclusion**

A systematic review report is the final outcome of a review. A systematic review report should provide enough detail that a knowledgeable reader could reproduce the systematic review. For systematic reviews to be trustworthy enough to inform healthcare decisions, accurate, thorough, and transparent reporting are essential.

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