**Problem Structuring in Economic Evaluation**

Rita Faria

# Summary

Economic evaluation provides a framework to help inform decisions on which technologies represent the best use of healthcare resources (i.e. are cost-effective) by bringing together the available evidence about the benefits and costs of the alternative options. Critical to the economic evaluation framework is the need to accurately characterise the decision problem – this is the problem structuring stage. Problem structuring encompasses the characterisation of the target population; identification of the decisions options to compare in the model (e.g. using the technology in different ways, standard of care, others); and the development of the conceptual model, which maps out how the decision options relate to the costs and benefits in the target population. Problem structuring is central to the application of the economic evaluation framework and to development of the analysis, as it determines the specific questions that can be addressed and affects the relevance and credibility of the results. The methodological guidelines discuss problem structuring to some extent, although the practical implications warrant further consideration. With respect to the target population, questions emerge about how to define the target population, whether and which sources of heterogeneity to consider, and when and in whom to consider spillovers. Relating to the specification of decision options, about how to identify and select relevant decision options, including restricting the comparison to standard of care, sequences of tests and/or treatments and do-nothing approaches. There are also issues relating to the role and the process of development of the conceptual model. Based on a review of methodological guidelines and reflections on their implications, various recommendations for practice emerge. The process of developing the conceptual model, and how to use it to inform choices and assumptions in the economic evaluation are two areas where further research is warranted.

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# Introduction

Economic evaluation in the form of cost-effectiveness (or cost-utility) analysis can inform the optimal decision choice between alternative technologies, by establishing the associated costs and consequences of the technologies and quantifying the expected improvement of one technology over the alternatives (M. F. Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). Technologies refer the various interventions which can be evaluated, such as drugs, diagnostic tests, medical devices, care pathways, etc. The evidence, assumptions and judgements used to inform an economic evaluation are never perfect; therefore, uncertainty and the need for further research to help inform the decision is an important consideration (Fenwick et al., 2020; Rothery et al., 2020).

The first stage of an economic evaluation is in its design, also known as structuring the decision problem. At this stage, analysts consider the demands on the economic evaluation so that it can inform the decision problem and meet the decision makers’ requirements (e.g. perspective, outcome measures, and discounting). At the same time, analysts decide the specific elements of the economic evaluation to address the decision problem, within the decision makers’ requirements. That is, given the perspective, outcome of interest, and discounting rates, who are the people that the technology is aimed at (the *target population*), in whom costs and outcomes may differ (*subpopulations*) and others who may be affected (*spillover effects*); what are the relevant *decision options* given the technology and other ways to address the problem; and how to reflect all the important consequences of all the options on the total costs and outcomes for the target population – this is the *conceptual model* underpinning the evaluation. The decisions at the problem structuring stage determine the specific questions that can be addressed by the economic evaluation, and ultimately determine the relevance and credibility of the cost-effectiveness results.

This chapter discusses the methodological guidance in economic evaluation for decision-making in healthcare for their recommendations around three areas of problem structuring for economic evaluation: population, decision options and conceptual modelling. Under each area, the methodological guidance is summarised, and its implications for practice are discussed. The chapter concludes with recommendations for practice and research. These three areas were selected because they are at the start of many applied economic evaluations, given that the decision makers’ requirements are often already established *a priori*. In this author’s experience, the choices about the target population, decision options and conceptual model are often not discussed in detail in the reports of economic evaluations (e.g. journal articles and health technology assessment reports). For example, a review of economic evaluations of diagnostic tests in the UK setting found that 19/38 (50%) studies specified the reasons for the exclusion of decision options from the evaluation (Yang, Abel, Buchanan, Fanshawe, & Shinkins, 2019), and a review of economic evaluations of treatments for venous leg ulcers noted that the quality of the reporting about the model structure is variable (Layer, McManus, & Levell, 2020). As a result, analysts and decision-makers may not be fully aware of the considerations in making such choices or appreciate the impact of these early decisions on the results.

The methodological guidance documents considered in this chapter were chosen for their role as reference materials that set out the guiding principles for economic evaluation in healthcare decision-making, either as country-specific guidance to inform decision-making, recommendations by international organisations, textbooks in economic evaluation and consensus statements. The focus is on methodological guidance by health technology assessment agencies and expert consensus reports in the literature, which were identified by targeted searches in the websites of health technology assessment agencies and professional organisations, rather than a comprehensive systematic review of the literature. For an overview of the guidance documents reviewed here, see Further Reading.

The methodological guidance reviewed here includes:

* The National Institute for Health and Care Excellence (NICE) “Guide to the methods of technology appraisal 2013” termed henceforth as NICE Guideline (National Institute for Health and Care Excellence (NICE), 2013), and associated NICE Decision Support Unit Technical Support Documents (NICE Decision Support Unit, n.d.);
* The Canadian Agency for Drugs and Technologies in Health (CADTH) “Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition)”, termed henceforth as the CADTH Guideline (Canadian Agency for Drugs and Technologies in Health, 2017);
* The Australia’s Pharmaceutical Benefits Advisory Committee (PBAC) “Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (version 5.0)”, termed henceforth as the PBAC Guideline (Pharmaceutical Benefits Advisory Committee, 2016);
* The European Network for Health Technology Assessment (EUnetHTA) report “Methods for health economic evaluations – a guideline based on current practices in Europe”, termed henceforth EUnetHTA Guideline (European Network for Health Technology Assessment (EUneHTA), 2015);
* The Bill and Melinda Gates Foundation report “Methods for Economic Evaluation Project”, henceforth referred to as Gates Guideline (NICE International, 2014);
* The Drummond et al textbook “Methods for economic evaluation of health programmes (4th edition)”, henceforth referred to as the Drummond et al book (M. F. Drummond et al., 2015);
* The 2016 book “Cost-effectiveness in health and medicine” by the second US panel on the topic, henceforth referred to US Panel report (Kuntz et al., 2016; Meltzer, Basu, & Sculpher, 2016; Owens, Siegel, Sculpher, & Salomon, 2016)
* The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task forces reports of economic evaluation using decision models, specifically “Modeling good research practices - Overview: A report of the ISPOR-SMDM modeling good research practices task force-1” and “Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2”, referred henceforth as ISPOR taskforce reports (Caro, Briggs, Siebert, & Kuntz, 2012; Roberts, Russell, Paltiel, Chambers, & McEwan, 2012)).

# Population

The target population is the group of individuals for whom the technology is intended (Owens et al., 2016). The economic evaluation aims to determine the expected costs and outcomes of the technology and alternative courses of action for the average individual in the target population.

Patients in the same population may vary in ways that affect the magnitude of benefits they may achieve from a technology or in their costs. Of interest to economic evaluation, is the variation in benefits or costs that can be explained by information known at the time of deciding which option to use. This variation is referred to as ‘*heterogeneity’*. Offering a technology only in the subpopulations [[1]](#endnote-1) in whom it is expected to be cost-effective means that the health care service gets the most value of the technology (Coyle, Buxton, & O’Brien, 2003). For more details on heterogeneity in economic evaluation, see Heterogeneity in Cost-Effectiveness Analysis (Kohli-Lynch & Briggs, 2019).

Some technologies may also have consequences to people beyond the target population, in terms of their health outcomes, other non-health outcomes (e.g. consumption, employment, wellbeing, etc.) and costs. These are known as *spillover* *effects* (Owens et al., 2016). Examples of spillover effects are curing or preventing an infectious disease (also known as externalities; see The Economics of Infectious Diseases (Hauck, 2018)), which has benefits to people who do not have the disease but who are at risk of being infected, and consequences to caregivers and family members (see The Economics of Informal Care (Van Houtven et al., 2019) and The Economics of Families and Health (Averett & Kohn, 2018)).

The target population, subpopulations and spillover populations should be considered at the problem structuring stage. This is because these aspects have implications not only to the data collection to inform the economic evaluation but also to the choice of decision options to include in the evaluation, given that the options should be relevant to the target population and subpopulations, and to the development of the conceptual model, so that it can adequately map the relationships between the options and their consequences on costs and health outcomes.

## Recommendations In Methodological Guidelines

### Recommendations On Target Population

The recommendations are summarised in Table 1. Four guidelines define the target population as the people for which the technologies are to be used within their specific setting (Canadian Agency for Drugs and Technologies in Health, 2017; Owens et al., 2016; Pharmaceutical Benefits Advisory Committee, 2016; Roberts et al., 2012).

### Recommendations On Heterogeneity

The guidelines acknowledged a wide variety of sources of heterogeneity (see Table 1). The source of heterogeneity mentioned the most is heterogeneity in the treatment effect (Canadian Agency for Drugs and Technologies in Health, 2017; M. F. Drummond et al., 2015; National Institute for Health and Care Excellence (NICE), 2013; NICE International, 2014; Owens et al., 2016; Pharmaceutical Benefits Advisory Committee, 2016). Five guidelines mention heterogeneity in the absolute level of risk (Canadian Agency for Drugs and Technologies in Health, 2017; National Institute for Health and Care Excellence (NICE), 2013; NICE International, 2014; Owens et al., 2016; Roberts et al., 2012). Four guidelines mention heterogeneity in costs (Canadian Agency for Drugs and Technologies in Health, 2017; National Institute for Health and Care Excellence (NICE), 2013; NICE International, 2014; Owens et al., 2016). Other sources of heterogeneity are demographics (Canadian Agency for Drugs and Technologies in Health, 2017; Roberts et al., 2012), socio-economic characteristics (Canadian Agency for Drugs and Technologies in Health, 2017; Owens et al., 2016), preferences (Owens et al., 2016), quality of life weights (Canadian Agency for Drugs and Technologies in Health, 2017), etc. The NICE Guideline (National Institute for Health and Care Excellence (NICE), 2013), the CADTH Guideline (Canadian Agency for Drugs and Technologies in Health, 2017), the Gates Guideline (NICE International, 2014) and the US panel (Owens et al., 2016) all note that some sources of heterogeneity may give rise to ethical and equity concerns. Of all the guidelines, only the NICE Guideline states that heterogeneity in treatment costs related to social characteristics or related to geographical location are not relevant to the assessment (National Institute for Health and Care Excellence (NICE), 2013).

All guidelines recommend that heterogeneity is explored by presenting results for subpopulations whenever there is reason to expect that the health benefits and/or the costs differ. The EUnetHTA Guideline notes that 15 countries recommend analysis by subpopulation (Austria, Belgium, Croatia, England, Finland, France, Hungary, Ireland, Italy, Norway, The Netherlands, Poland, Slovakia, Spain, Sweden), six countries allow it (Czech Republic, Estonia, Latvia, Germany, Portugal, Scotland), whereas in four countries there was no information available (Denmark, Russia, Slovenia, Switzerland) (European Network for Health Technology Assessment (EUneHTA), 2015).

The NICE Guideline, the PBAC Guideline and the EUnetHTA Guideline ask for the analysis by subpopulations to be justified on the basis of a clinical rationale (European Network for Health Technology Assessment (EUneHTA), 2015; Pharmaceutical Benefits Advisory Committee, 2016), a pharmacological or biological mechanism (National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016), social characteristics (National Institute for Health and Care Excellence (NICE), 2013), and robustness of the evidence (National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016).

### Recommendations On Spillover Effects

Spillover effects are not explicitly referred to in the NICE Guideline, although, under the section on perspective, there is a recommendation that direct health effects should be included in the base-case, whether for patients or other people (e.g. carers) (National Institute for Health and Care Excellence (NICE), 2013). This suggests that spillover effects should be considered, although only if they are direct health effects. The CADTH Guideline explicitly recommends that spillover effects should be considered and addressed in a non-reference case analysis (Canadian Agency for Drugs and Technologies in Health, 2017). Similarly, the PBAC Guideline allows supplementary analyses where the beneficiaries of the technology are broader than the treated (target) population (Pharmaceutical Benefits Advisory Committee, 2016). The US Panel discusses spillover effects under the scope of the evaluation, in the chapter on designing a cost-effectiveness analysis (Owens et al., 2016). Here, the US Panel recommends that the analysis should include all populations where there are “*notable*” effects (p.24), and that the analyst should define and justify the inclusion/exclusion criteria (Owens et al., 2016). In another chapter, on identifying and quantifying the consequences of interventions, the US Panel recommends considering the recipients of the technology, their formal and informal carers, and the larger community (Salomon, Trikalinos, Sanders, & Mandelblatt, 2016). The ISPOR taskforce also recommends that effects in people who are not in the target population should be considered (Roberts et al., 2012). The EUnetHTA Guideline, the Gates Guideline, and Drummond et al do not discuss spillover effects; effects on families and carers are touched on under perspective but focussing on the question of whether to include costs outside the health care budget (M. F. Drummond et al., 2015; European Network for Health Technology Assessment (EUneHTA), 2015; NICE International, 2014).

*Table 1: Summary of recommendations on target population, subpopulations and spillover effects*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Recommendations | NICE Guideline (National Institute for Health and Care Excellence (NICE), 2013) | CADTH Guideline (Canadian Agency for Drugs and Technologies in Health, 2017) | PBAC Guideline(Pharmaceutical Benefits Advisory Committee, 2016) | EUnetHTA Guideline(European Network for Health Technology Assessment (EUneHTA), 2015) | Gates Guideline (NICE International, 2014) | Drummond et al (M. F. Drummond et al., 2015) | US Panel (Owens et al., 2016; Salomon et al., 2016) | ISPOR taskforce(Roberts et al., 2012) |
| Recommendations on the definition of the target population | | | | | | | | |
| Target population=people who will use technologies in practice. | ND | R | R | ND | ND | ND | R | R |
| Recommendations on identification and selection of subpopulations | | | | | | | | |
| Subpopulations are relevant where health benefits and/or costs are expected to differ | R | R | R | R | R | R | R | R |
| Justified based on clinical basis |  |  | R | R |  |  |  |  |
| Justified based on pharmacological or biological mechanism | R |  | R |  |  |  |  |  |
| Justified based on social characteristics | R |  |  |  |  |  |  |  |
| Justified based on robustness of evidence | R |  | R |  |  |  |  |  |
| Examples for potential sources of heterogeneity | | | | | | | | |
| Demographics |  | R |  |  |  |  |  | R |
| Socio-economic characteristics | NR[[2]](#endnote-2) | R |  |  |  |  | R |  |
| Preferences |  |  |  |  |  |  | R |  |
| Geographical location | NR6 | R |  |  | R |  |  |  |
| Risk of disease, of events, of progression | R | R |  |  | R |  | R | R |
| Quality of life weights |  | R |  |  |  |  |  |  |
| Treatment effect | R[[3]](#endnote-3) | R | R |  | R | R | R |  |
| Adherence to treatment |  | R |  |  |  |  |  |  |
| Typical treatment patterns |  | R |  |  |  |  |  |  |
| Treatment setting/provision |  | R |  |  | R |  |  |  |
| Resource use and/or costs | R | R |  |  | R |  | R |  |
| Recommendations on spillover effects | | | | | | | | |
| Whether to include | R[[4]](#endnote-4) | R | R |  |  |  | R | R |
| R: Recommended; NR: not recommended. ND: not discussed. | | | | | | | | |

## Practical Implications

### Who Should Constitute The Target Population?

There is consensus in the methodological guidelines that the target population is the people for whom the technology is intended. In the context of health technology assessment of new drugs, the target population typically follows from the marketing authorisation. This is usually straightforward, although there may be uncertainty when the marketing authorisation is broader than the clinical trials which underpin it. For example, the NICE guidance on rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease is an example where the recommendation was restricted to the trial population due to concerns about the generalisability of trial population to the population in clinical practice (National Institute for Health and Care Excellence (NICE), 2019).

Identifying the target population can be challenging when economic evaluation is applied to technologies other than drugs. Examples are economic evaluations of diagnostic tests, surgical procedures, public health, and social care technologies. For example, the NICE scope for the technology appraisal of the EOS 2D/3D X-ray system defined the patient population as children, adolescents and adults with spinal deformity, children and adolescents with leg length discrepancy and alignment, and adults with loss of sagittal and coronal balance (National Institute for Health and Care Excellence (NICE), 2010). So that the economic evaluation was tractable, clinical experts were asked to characterise the target population in more detail; and to understand the consequences of uncertainty on the target population, a threshold sensitivity analysis was conducted to the patient throughput that would be required for the technology to be considered cost-effective (Rita Faria et al., 2013). More generally, economic evaluation can have a useful role in exploring the magnitude of uncertainty around decisions in wider populations that those where the evidence exists, and to help prioritise further research to inform decision-making in that population.

### Whether And Which Sources Of Heterogeneity To Consider?

The guidelines agree that economic evaluations should consider heterogeneity in costs and health benefits, although there are differences about which sources of heterogeneity to consider. None of the texts make recommendations about how to select the sources of heterogeneity to consider for specific decision problems. Given the wide ranges of possible sources of heterogeneity, the number of subpopulations can quickly explode to a number that is difficult to parametrise, compute and interpret. For example, an economic evaluation of direct-acting antivirals for chronic hepatitis C defined subgroups according to whether patients had been previously treated or not (2 categories: yes and no), whether they were eligible for peg-interferon (2 categories: yes and no, although those who were ineligible were assumed to not be previously treated) and by viral genotype (4 categories: 1, 2, 3 and 4) (R. Faria et al., 2016). As a result, 14 subgroups were evaluated (= 2 x 2 x 4 - 2). Had another category been considered, say 2 age groups, the number of subpopulations would have increased to 28.

Kohli-Lynch and Briggs suggest that clinical feasibility, statistical validity and equity should be considered when identifying subpopulations (Kohli-Lynch & Briggs, 2019). Clinical feasibility refers to the practicalities of implementing different decisions by subpopulation. For example, NICE, CADTH and PBAC recommended alirocumab and evolocumab in subpopulations who have low-density lipoprotein cholesterol level above a certain threshold, and in those with familial hypercholesterolaemia and/or prior history of cardiovascular disease. These are indicators for the magnitude of risk of cardiovascular disease, which are known at the time of the treatment decision (Varghese, Ohlow, & Kumar, 2019).

Some of the information required to stratify patients into subpopulations may involve costs. As recommended by Kohli-Lynch and Briggs, “*the additional costs incurred stratifying patients based on these characteristics must be accounted for in cost-effectiveness analyses*” (p24). This is also recommended by the NICE Guideline (National Institute for Health and Care Excellence (NICE), 2013). The stratification of patients into subpopulations may be itself uncertain, such as when it is based on the results of a test and the test is not perfect. In this situation, the stratification should be considered in terms of the relevant options and the consequences of incorrect stratification (or diagnosis) accounted for in the cost-effectiveness analysis. In its simplest form, assuming two subpopulations and two decision options, it means including the costs and outcomes of those who were correctly stratified and managed with the cost-effective option as well as those who were incorrectly stratified and managed with the cost-ineffective option.

Statistical validity refers to the risk of finding characteristics that vary by subpopulation by chance. In subgroup analysis of clinical trials, the standard approach is to pre-specify subgroups at the clinical trial design, and to assess consistency, biological plausibility and replicability (Committee for Medicinal Products for Human Use (CHMP), 2019). Kohli-Lynch and Briggs suggest that economic evaluations could pre-specify subpopulations according to a clinical or economic rationale. Fletcher et al note that, without the final economic model, it may be difficult to prespecify all relevant subpopulations; hence they recommend “*a degree of flexibility*” in defining the subpopulations, as long as the process of identification and selection is transparent and fully described (Fletcher, Chuang-Stein, Paget, Reid, & Hawkins, 2014).

An additional consideration is the expected impact on the cost-effectiveness. This can be informed by previous economic evaluations in the same population (and ideally the same or similar technologies) and based on consultation with stakeholders (e.g. clinicians, patients, healthcare managers). For example, an economic evaluation of omalizumab for severe asthma selected the sources of heterogeneity based on results of previous evaluations, which in turn were based on clinical feedback (Rita Faria, McKenna, & Palmer, 2014). Some care is required to avoid prior errors perpetuating if basing choices on previous evaluations. Additionally, choices regarding subpopulations may involve developing a preliminary economic model (Fletcher et al., 2014) or developing the conceptual model of economic evaluation to a sufficient detail in order to inform qualitative judgements on the expected differences in costs and effects between subpopulations.

### When And In Whom To Consider Spillovers?

Most guidelines recommend that spillover populations should be considered when applicable, although there is little guidance how to identify and select them. The US Panel (p.24) notes “*Spillover effects ripple out from every technology designed to improve health. The question is how far to follow such ripples*” and advises that deciding on whether to include spillover effects depends on their magnitude relative to the effects in the target population (Owens et al., 2016). In another chapter, the US Panel formulates this concept as “*the rule of reason*” (p.13): “*Consequences that are expected to be trivially small in the context of the analysis, and thus have little effect on the results, can reasonably be excluded at the analyst’s discretion. This exclusion should, however, be explicitly noted and justified*” (Salomon et al., 2016). However, the US Panel offers no guidance on the practicalities of making such judgements.

There is some methodological literature on spillover effects in economic evaluation, generally related to the spillover to family members and carers. The topics include whether spillover effects should be included in an economic evaluation from a normative standpoint (see, for example, (Basu & Meltzer, 2005), (Brouwer, 2019), (McCabe, 2019)), how to measure and value such effects (e.g. (Al-Janabi, Van Exel, Brouwer, Trotter, et al., 2016; Basu & Meltzer, 2005; Dixon & Round, 2019; Weatherly, Faria, & Van den Berg, 2014)), and how to include them in an economic evaluation (e.g. (Al-Janabi, Van Exel, Brouwer, & Coast, 2016; Dixon & Round, 2019)). When and in whom to consider spillover effects have been less examined, although Al-Janabi et al suggested that health spillover effects are likely to be more relevant when the spillover on gains diverges from the spillover on losses (via the opportunity cost) (Al-Janabi, Van Exel, Brouwer, & Coast, 2016). Prosser and Wittenberg commented in an editorial to a PharmacoEconomics themed issue on spillover effects that this is an area where future research is needed (Prosser & Wittenberg, 2019). Applied economic evaluations vary in their consideration for spillover effects, and often it is focussed on the costs. For example, a systematic review on economic evaluations of Alzheimer’s Disease interventions found that 44/63 (70%) studies considered some spillover effects, of which 36 studies included the cost of informal carer time (Lin et al., 2019), while a systematic review on economic evaluations in children found that 120/142 (85%) studies considered family spillover effects, of which 98 studies considered time costs (Lavelle et al., 2019). In order to decide whether to consider spillover populations, and similarly to the approach for subpopulations, a practical approach is to review previous cost-effectiveness analyses, consulting stakeholders, and to lean on the conceptual model to infer the magnitude of gains and benefits in people who could be affected by the technology other than the target population.

# Decision Options To Evaluate

The decision options refer to the alternative courses of action that could be taken to address the problem (M. Drummond, Stoddard, & Torrance, 2005). As economic evaluation is comparative, the additional costs and benefits of the technology depend on the costs and benefits of the alternative that it is compared against. The exclusion of alternatives may affect the comparative benefits or costs of the technology, and the economic evaluations may erroneously conclude that a technology is cost-effective when that is not the case.

Decision options could be considered as simply the new technology and the standard of care in the absence of the new technology. Additionally, decision options can comprise care pathways, which may include combinations of the technology and the alternative courses of action in its absence (e.g. standard of care as first line then the new technology as second line; standard of care in combination with the new technology; the new technology at different intensities or durations; stop-and-start rules, etc.).

## Recommendations In Methodological Guidelines

Table 2 summarises the recommendations on how to identify and select the decision options for an economic evaluation.

*Table 2: Summary of recommendations on identification and selection on the options to include in the evaluation in the methodological guidelines*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Recommendations | NICE Guideline (National Institute for Health and Care Excellence (NICE), 2013) | CADTH Guideline (Canadian Agency for Drugs and Technologies in Health, 2017) | PBAC Guideline(Pharmaceutical Benefits Advisory Committee, 2016) | EUnetHTA Guideline(European Network for Health Technology Assessment (EUneHTA), 2015) | Gates Guideline (NICE International, 2014) | Drummond et al (M. F. Drummond et al., 2015) | US Panel (Owens et al., 2016; Salomon et al., 2016) | ISPOR taskforce(Roberts et al., 2012) |
| General recommendations on the options to include in the evaluation in addition to the new technology | | | | | | | | |
| Standard care | R[[5]](#endnote-5) |  | R | R |  |  |  |  |
| Technology most likely to be replaced |  | R[[6]](#endnote-6) | R |  |  |  |  |  |
| All relevant alternatives |  | R |  |  | R | R | R | R |
| Examples and specific options stated in the literature | | | | | | | | |
| Routine or current care | R | R | R | R | R |  | R | R |
| Technologies currently available | R | R | R |  | R | R | R |  |
| The technology considered to be best practice |  |  |  |  | R |  |  |  |
| The technology most likely to be replaced |  | R | R |  | R |  |  |  |
| Technologies available in the near future |  | R |  |  |  |  |  |  |
| Technologies available but unlicensed | R[[7]](#endnote-7) |  |  |  |  |  |  |  |
| Technologies in different intensities |  |  |  |  | R | R | R |  |
| Treatment continuation rules | R |  |  |  |  | R | R |  |
| Technologies in sequences | R | R |  |  | R | R | R |  |
| Co-dependent technologies |  | R |  |  |  |  |  |  |
| Technologies in combination |  | R |  |  |  |  |  |  |
| Technologies as a class | R[[8]](#endnote-8) |  |  |  |  |  |  |  |
| Do nothing or best supportive care | R | R | R |  | R | R | R | R |
| R: Recommended; NR: not recommended. ND: not discussed. | | | | | | | | |

### Identification Of Decision Options

There is no consensus on which decision options should be compared in an economic evaluation. Some guidelines recommend that the new technology is compared against the alternative considered to be standard care (Pharmaceutical Benefits Advisory Committee, 2016) (European Network for Health Technology Assessment (EUneHTA), 2015). Others recommend that the new technology is compared against all alternatives for the condition (NICE International, 2014) (M. Drummond et al., 2005) (Owens et al., 2016) (Roberts et al., 2012). The NICE Guideline recommends that all potentially relevant options to the technology (termed ‘comparators’) should be identified at the scoping stage, and taken forward to the analysis (National Institute for Health and Care Excellence (NICE), 2013). The CADTH Guideline distinguishes the situation where a new technology is under evaluation for a reimbursement decision, where the other decision options are the technologies that could be replaced, from the situation where the objective is to identify the most efficient way of managing a condition, where all decision options should be included (Canadian Agency for Drugs and Technologies in Health, 2017).

All guidelines recommend that “do-nothing” approaches (also referred as best supportive care) should be included. Most guidelines specify routine care and the technologies available at the time of the economic evaluation. Other decision options suggested by one or more documents are: technologies in sequences, the technology most likely to be replaced, technologies in different intensities, treatment continuation rules, the technology considered best practice, technologies available in the near future, co-dependent technologies (e.g. new technology with companion diagnostic test in a subpopulation or without companion diagnostic test in a broader population), and technologies in combination.

The EUnetHTA Guideline recommends standard care as the alternative to the new technology. To inform this recommendation, a review of the guidelines in the EUnetHTA members was conducted. This review found some variation: five countries recommend that all options in the efficiency frontier should be compared (Belgium, France, Germany, Norway if standard care is not cost-effective, Slovenia), seven countries recommend that the new technology should be compared against all alternatives in routine use (Croatia, Czech Republic, England, Ireland, Italy, Russia, Scotland), three countries also consider alternatives recommended by the HTA process or in the reimbursement list (Czech Republic, England, Russia), three countries recommend that the new technology is recommended against one single alternative considered to be best practice or the most effective (Croatia, Finland, and Spain), ten countries recommend that the new technology is compared against one single alternative considered to be standard care (Estonia & Latvia, Ireland, Norway, The Netherlands, Poland, Portugal, Slovakia, Sweden, Switzerland).

### Selection Of Decision Options

Six guidelines recommend that analysts first identify all alternatives to address the decision problem, then to select the relevant options to be evaluated (Canadian Agency for Drugs and Technologies in Health, 2017; M. F. Drummond et al., 2015; European Network for Health Technology Assessment (EUneHTA), 2015; Owens et al., 2016; Roberts et al., 2012). In the NICE process, the committee has the role of selecting the most appropriate decision options to compare to the new technology (National Institute for Health and Care Excellence (NICE), 2013). Across the guidelines, the criteria for selection include relevance to clinical practice (National Institute for Health and Care Excellence (NICE), 2013) (Canadian Agency for Drugs and Technologies in Health, 2017) (European Network for Health Technology Assessment (EUneHTA), 2015), which technologies are likely to be displaced by the new technology (Canadian Agency for Drugs and Technologies in Health, 2017; Pharmaceutical Benefits Advisory Committee, 2016), natural history of the condition without suitable treatment (National Institute for Health and Care Excellence (NICE), 2013), existing guidance (National Institute for Health and Care Excellence (NICE), 2013), the licensing status of the technologies (National Institute for Health and Care Excellence (NICE), 2013), the resources for the economic evaluation (Owens et al., 2016), the feasibility of the alternatives being used in practice (Owens et al., 2016), the likelihood that the alternatives will be considered by decision-makers (Owens et al., 2016), and likelihood that the alternative is cost-effective (M. F. Drummond et al., 2015).

## Practical Implications

### Should Economic Evaluations Compare The New Technology Only To Standard Care?

Some guidelines recommend that the new technology is only compared against the alternative considered to be standard care (Pharmaceutical Benefits Advisory Committee, 2016) (European Network for Health Technology Assessment (EUneHTA), 2015). Comparing the new technology against standard care has the advantage of directly informing the decision of whether to replace standard care by the new technology and simplifies the economic evaluation. However, comparing the new technology against standard care may lead to biased results if standard care does not consist of the cost-effective course of action in the absence of the new technology.

Standard care may not be cost-effective if the intervention used as standard care is not the cost-effective option among those available, or if standard care includes the use of a variety of options. In this situation, some economic evaluations define a hypothetical decision option that comprises the outcomes and costs of each option, weighted by their use – this is known as a blended comparator. A blended comparator is appropriate only if it can be assumed that the options in the blended comparator will be displaced in the same proportion as their current use (Wailoo, Trowman, & Stevens, n.d.). If this is not the case, a blended comparator may lead to biased results as it is necessarily not cost-effective compared to the cost-effective option in its blend.

Another issue of comparing a new technology only with the standard care is that standard care may be in flux as new technologies are adopted into practice. If the economic evaluations only consider the technologies available at the time, their relevance may be short-lived. Furthermore, by not comparing technologies directly, the technology which entered the market first may benefit from a positive recommendation even if it is not cost-effective compared to technologies that entered the market subsequently. To avoid this limitation, Canada’s Guideline recommends including technologies likely to be available in the near future (Canadian Agency for Drugs and Technologies in Health, 2017). The challenge is that effectiveness studies may not have reported yet or their results are not available to analysts.

### How To Identify And Select The Relevant Decision Options?

To know which option is cost-effective, that is, the decision option which offers the most benefits net of the benefits forgone due to the opportunity cost, one would ideally compare all relevant options. Applying this principle in practice can be challenging. The first challenge is how to identify all options, given that there may be many possible ways of using the new technology. The types of options mentioned in the guidance documents provide a starting point: standard care, the technologies currently available, the technologies available in the near future, technologies in sequences, co-dependent technologies, technologies in combination, do nothing approaches, technologies in different intensities and different treatment continuation rules.

The second challenge is in selecting the relevant decision options for inclusion in the evaluation once all options were identified. Apart from excluding options on the basis of prior evidence that such options are not cost-effective, all other criteria may result in a cost-effective option being excluded from the economic evaluation. Conversely, including all possible options may be unfeasible within the resource constraints of the evaluation.

The next challenge is analytical. A consequence of aiming to include all relevant options is that it may lead to a large number of options being compared, which increases the demands on parameterisation and model programming. The results of an economic evaluation with a large number of options are harder to interpret and validate by analysts, as well as by stakeholders and decision-makers.

The downside of not comparing all relevant options is the risk of biasing the results of the economic evaluation. In the economic evaluation of direct acting antivirals for hepatitis C, the net benefit of the cost-effective single line option for people with chronic hepatitis C viral genotype 4 was 10.20 quality-adjusted life years (QALYs, at a cost-effectiveness threshold of £20,000/QALY and using list prices) (R. Faria et al., 2016). Including treatment sequences, the cost-effective option was instead a treatment sequence with an expected net benefit of 10.31 QALYs. The difference, at 0.11 QALYs per patient treated, represents the loss in health from restricting the options in this specific evaluation.

### When To Consider Sequences Of Treatments And/Or Of Tests?

Sequences of treatments refer to options that a number of treatments in a specific order. Treatment switches can occur due to clinical reasons, such as loss of effect, disease progression, side effects, etc. Zheng et al recommend that sequences of treatments should be included as options if the selection, effectiveness and/or the cost of subsequent treatments are affected by the earlier choices; or if the decision problem relates to the optimal positioning of a specific treatment in a treatment pathway (Zheng, Pan, & Sorensen, 2017). Whether to include treatment sequences may be restricted by a drug’s marketing authorisation if it specifies where the drug fits within a treatment sequence.

Sequencing of tests refers to having a number of tests in a specific order and following a specific result. Depending on the accuracy and costs of the tests, tests can be combined in sequences to improve their combined accuracy at a lower cost. For example, template mapping biopsy is considered to be a perfect test to diagnose prostate cancer, but it is costly and too resource intensive for routine use. Transrectal-ultrasound guided biopsy and magnetic resonance imaging are imperfect but less costly. By combining these two imperfect tests in a sequence, the diagnostic pathway can achieve higher accuracy than by using the imperfect tests alone and at a fraction of the costs of the perfect test (Rita Faria et al., 2018).

As individual treatments and/or tests are added to the options, the number of sequences increases. For example, an economic evaluation of treatments for psoriasis which identified 13,699 sequences from 7 unique drugs (Woolacott et al., 2006). By assuming that the treatments did not alter disease progression and that effectiveness was independent from treatment history, the economic evaluation calculated the expected net benefit per unit of time. If these assumptions do not apply, such as in evaluations where the treatments alter the risk of progression or of events, or where the diagnostic performance of the subsequent test depends on the first test, the sequences will need to be evaluated separately. Parameterisation may be an issue, given that there may not be direct evidence on the effectiveness (for treatments) (Zheng et al., 2017) or diagnostic accuracy (for tests) in all positions of the sequence (Novielli, Sutton, & Cooper, 2013).

### What Does A “Do-Nothing” Option Represent?

All but the EUnetHTA Guideline recommend that “*do-nothing*” is considered as an option for the economic evaluation, although there is variation of what the “do-nothing” option should represent. Some define it as “best supportive care” (National Institute for Health and Care Excellence (NICE), 2013) (Canadian Agency for Drugs and Technologies in Health, 2017) (Pharmaceutical Benefits Advisory Committee, 2016) (NICE International, 2014); the PBAC Guideline also uses the term “conservative management” (Pharmaceutical Benefits Advisory Committee, 2016); the ISPOR taskforce mentions the “natural” disease course (Roberts et al., 2012); whereas the US panel and Drummond et al do not define what is “do-nothing” (M. F. Drummond et al., 2015; Owens et al., 2016). The interpretation of what “do-nothing” represents can have implications to the costs and health benefits of a new technology depending on the costs and health effects of subsequent management. If do-nothing is interpreted as complete absence of treatment until a severe event occurs, and the probability of a severe event is relatively high, “do-nothing” may result in low quality-adjusted life expectancy. Alternatively, “do-nothing” could be interpreted as watchful waiting with some technology being given as soon as disease progresses. The cost-effectiveness of a new drug compared to the more ‘laisse-faire’ “do-nothing” is more likely to be more favourable rather than a watchful waiting “do-nothing” approach.

# Conceptual Model Of The Evaluation

All economic evaluations are underpinned by a conceptual model of how the decision options affect the target population in their costs and outcomes. The conceptual model of the evaluation refers to the relationships between the effects of the decision options to the outcomes of interest (i.e. health outcomes and costs) in the target population (and, if relevant, subpopulations and spillover populations) under each decision option. In a within-trial economic evaluation, the randomised controlled trial (or other source of individual-level data, such as an observational study) is the vehicle for the economic evaluation. Therefore, the conceptual model of the evaluation assumes that the trial includes all relevant options, was conducted in the target population, with a follow-up which represents the time horizon of interest, and that it comprises all available evidence to inform the decision – as these are the conditions for a within-trial evaluation to be an appropriate design for an economic evaluation (M. J. Sculpher, Claxton, Drummond, & McCabe, 2006). In a model-based economic evaluation, the decision model calculates the costs and outcomes of the target population, for each decision option, based on a set of inputs and how they are thought to affect costs and outcomes. Therefore, in the context of a model-based economic evaluation, the conceptual model of the evaluation also includes the relevant inputs and their relationships to costs and outcomes. This conceptual model underpins the structure of the decision model, which is ultimately implemented.

## Recommendations In Methodological Guidelines

### Terminology

The guidelines vary in the terminology relating to conceptual modelling. The NICE Guideline and the PBAC Guideline do not use the term “*conceptual model*” or related terms, although there are some recommendations on model structure and structural assumptions (National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016). The NICE DSU TSD13 uses the term ‘conceptual modelling’ interchangeably with ‘model structuring’. It defines conceptual modelling as: “*activity related to translating the understanding of the decision problem towards a mathematical model-based solution*” (p18) (Kaltenhalter, Tappenden, Paisley, & Squires, 2011). In the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 13, conceptual modelling is placed after the stage of “*understanding the decision problem*” and before the implementation of the model within a software platform, as per Chilcott et al (Chilcott et al., 2010). Understanding the decision problem includes “*activities including immersion in research evidence, defining the research question, engaging with clinicians, decision-makers and methodologists, and understanding what is feasible”* (p.18).

The CADTH Guideline uses a similar terminology to the NICE DSU TSD13, describing model conceptualisation as “*(…) the development of a model structure that is defined by specific states or events and the relationships among them that together constitute the clinical or care pathway for the condition of interest and the technologies being compared*” (p.33) (Canadian Agency for Drugs and Technologies in Health, 2017).

Drummond et al also uses the term “*conceptualising a decision model*” for the process of deciding the model structure – this is the third stage in model development (M. F. Drummond et al., 2015). For Drummond et al, the first stage in the development of a model is to define the decision problem, i.e. specifying the research question in terms of the target population and relevant options. The second stage is defining the boundaries of the model, which include the perspective, the outcomes, time horizon, effects to consider and whether to include spillover populations.

The US Panel uses the term “*conceptualisation*” in two ways. In Owens et al, the conceptual model refers to the analysts’ understanding of the sequence of events from the use of each option to the outcomes of interest (Owens et al., 2016). Kuntz et al uses the term “*conceptualisation”* in the context of *“conceptualisation of the decision problem*” (Kuntz et al., 2016). This stage generally corresponds to what the NICE DSU TSD13 classifies as the stage of understanding of the decision problem (Kaltenhalter et al., 2011), and to the first two stages by Drummond et al of defining the decision problem and defining the boundaries of the model (M. F. Drummond et al., 2015).

The ISPOR Taskforce uses the terms “*problem conceptualisation*” and “*model conceptualisation*” (Roberts et al., 2012). Problem conceptualisation is the process of understanding the decision problem (Roberts et al., 2012); this refers to the similar stage as the NICE DSU TSD13 (Kaltenhalter et al., 2011) and Drummond et al’s ‘*defining the decision problem*’ and ‘*defining the boundaries of the model*’ (M. F. Drummond et al., 2015). According to the ISPOR Taskforce, model conceptualisation is the process by which the components of the problem are represented using a specific modelling approach (Roberts et al., 2012). Hence it includes the process of designing the model structure to planning its implementation using a specific technique.

### Recommendations On Conceptual Model And/Or Model Structuring

Table 3 summarises the types of recommendations on conceptual modelling and/or model structuring. All the guidelines offer recommendations on modelling bar the Gates Guideline (NICE International, 2014). The topics covered include the situations where modelling is likely to be required (M. F. Drummond et al., 2015; Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016), the process of model development (Canadian Agency for Drugs and Technologies in Health, 2017; M. F. Drummond et al., 2015; Kaltenhalter et al., 2011; Kuntz et al., 2016; Pharmaceutical Benefits Advisory Committee, 2016; Roberts et al., 2012), standards for the model structure (Canadian Agency for Drugs and Technologies in Health, 2017; M. F. Drummond et al., 2015; Kuntz & Goldie, 2002; National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016; Roberts et al., 2012), on the issues for consideration when developing a model (M. F. Drummond et al., 2015; Kaltenhalter et al., 2011; Kuntz et al., 2016; Pharmaceutical Benefits Advisory Committee, 2016; Roberts et al., 2012), and on the impact of the model design on the decision (National Institute for Health and Care Excellence (NICE), 2013).

Regarding when modelling is likely to be required, the situations most often mentioned are: when the trial collected data on intermediate outcomes (M. F. Drummond et al., 2015; Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016), when the costs and/or benefits of the options under comparison extend beyond the trial follow-up (M. F. Drummond et al., 2015; Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016), when all the relevant options are not compared in a single trial (M. F. Drummond et al., 2015; Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013), and when the trial population is not generalisable to the decision setting (M. F. Drummond et al., 2015; National Institute for Health and Care Excellence (NICE), 2013; Pharmaceutical Benefits Advisory Committee, 2016). The NICE Guideline adds when there was crossover in the trial which would not occur in clinical practice (National Institute for Health and Care Excellence (NICE), 2013). Drummond et al also recommend modelling when the way that the outcomes were measured in the trial differs from clinical practice or when there is relevant evidence beyond a single trial (M. F. Drummond et al., 2015). The US Panel recommend modelling for when the decision problem requires extrapolation; extrapolation refers to not only extrapolation beyond the trial follow-up or from intermediate to final outcomes, but also to other subpopulations not observed in the primary studies, from diagnostic outcomes to long-term outcomes and to other options not compared in the trial (Kuntz et al., 2016). Furthermore, the US Panel al recommend modelling to assess the implications of uncertainty (Kuntz et al., 2016).

The guidelines are generally silent on the process of conceptual modelling, apart from a recommendation of starting with a literature review of economic evaluations, clinical trials, clinical guidelines, epidemiology and burden of disease studies (Canadian Agency for Drugs and Technologies in Health, 2017; Pharmaceutical Benefits Advisory Committee, 2016) as well as having input from content experts (Kuntz et al., 2016; Roberts et al., 2012) . The exception is the NICE DSU TSD13, which proposes a two-stage process to conceptualise the model, with the literature review and expert input being sources of evidence (Kaltenhalter et al., 2011). It advises to start with the problem-oriented conceptual model, then to develop the design-oriented conceptual model. The problem-oriented conceptual model aims to develop, share and test the analysts’ understanding of the decision problem and the system in which it exists through mapping out the underlying disease process and treatment pathways. The design-oriented conceptual model draws together the problem-oriented models with the aim of setting out the model structure, its assumptions and parameterisation.

There are few recommendations on any standards that the model structure should meet. The NICE Guideline even states that “*Providing an all-embracing definition of what constitutes a high-quality model is not possible*” (p.47) (National Institute for Health and Care Excellence (NICE), 2013). The most frequently stated recommendation is that the model structure should be consistent with the current understanding of the clinical pathway of the condition and the expected effect of options under evaluation (Canadian Agency for Drugs and Technologies in Health, 2017; Kaltenhalter et al., 2011; Kuntz et al., 2016; Pharmaceutical Benefits Advisory Committee, 2016). The two other recommendations mentioned by more than one guideline are that model conceptualisation should address the decision problem (Canadian Agency for Drugs and Technologies in Health, 2017; Roberts et al., 2012); and that the baseline natural history should be representative of the target population (Canadian Agency for Drugs and Technologies in Health, 2017; M. F. Drummond et al., 2015).

Only the NICE DSU TSD13 and Drummond et al discuss the issues to consider when developing a model (M. F. Drummond et al., 2015; Kaltenhalter et al., 2011). The NICE DSU TSD13 is the most exhaustive, devoting a few pages listing the issues to consider (see p.23-28) (Kaltenhalter et al., 2011). Examples include which are the relevant events, whether these can be discretised into mutually exclusive health states, what are the relationships between states, events, and health-related quality of life. Some examples from Drummond et al are whether events are one-off or recurrent, whether an event influences the risk of experiencing subsequent events, and the evidence supporting the link between intermediate to final outcomes (M. F. Drummond et al., 2015).

Most guidelines recommend sensitivity analysis to test the impact of alternative assumptions (Canadian Agency for Drugs and Technologies in Health, 2017; European Network for Health Technology Assessment (EUneHTA), 2015; Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013; Roberts et al., 2012). The PBAC Guideline also recommends scenario analyses to alternative model structures (Pharmaceutical Benefits Advisory Committee, 2016) . The NICE Guideline requests sensitivity analysis to the surrogate-to-final endpoint relationship and to the duration of treatment effect during the extrapolation phase (also recommended by the US Panel) (Kuntz et al., 2016; National Institute for Health and Care Excellence (NICE), 2013).

Only the NICE Guideline discusses the impact of the model structure on the decision as part of the Committee’s judgements on cost-effectiveness: “*The robustness and appropriateness of the structure of the economic models. In particular, the Committee considers carefully whether the model reflects the decision problem at hand and the uncertainties around the assumptions on which the model structure is based*” (p.66) (National Institute for Health and Care Excellence (NICE), 2013).

*Table 3: Types of recommendations on conceptual modelling and/or model structuring*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Recommendations | NICE Guide(National Institute for Health and Care Excellence (NICE), 2013) | CADTH Guide(Canadian Agency for Drugs and Technologies in Health, 2017) | PBAC Guide(Pharmaceutical Benefits Advisory Committee, 2016) | EUnetHTA guideline(European Network for Health Technology Assessment (EUneHTA), 2015) | Gates Guide(NICE International, 2014) | Drummond et al (M. Drummond et al., 2005) | US Panel (M. J. Sculpher, Basu, Kuntz, & Meltzer, 2016) | ISPOR taskforce(Husereau et al., 2013)(Roberts et al., 2012) |
| 1. On the situations when modelling is likely to be required | R |  | R | [[9]](#endnote-9) |  | R | R |  |
| 1. On the process | DSU | R | R |  |  | R | R | R |
| 1. On standards | R | R | R |  |  | R | R | R |
| 1. On the issues for consideration | DSU |  | R |  |  | R | R | R |
| 1. On sensitivity analysis to the model structure | R | R | R | R |  |  | R | R |
| 1. On implications of the model structure for the decision | R |  |  |  |  |  |  |  |
| R: Recommended; DSU, recommended in the NICE DSU TSD13 (Kaltenhalter et al., 2011). | | | | | | | | |

## Practical Implications

### What Is The Role Of The Conceptual Model?

Conceptual modelling has had relatively little attention in the economic evaluation literature as a standalone topic, although it is often discussed implicitly in the literature around modelling approaches (e.g. (H Haji Ali Afzali & Karnon, 2014; Stahl, 2008)) and in the literature on the assessment of the validity and quality of models (e.g. (Chilcott et al., 2010; Jaime Caro et al., 2014; Peñaloza Ramos, Barton, Jowett, & Sutton, 2015; Philips et al., 2004; M. Sculpher, Fenwick, & Claxton, 2000)). The reporting standards guidelines, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), recommend that the model structure and assumptions should be reported, but do not mention the conceptual model (Husereau et al., 2013). Therefore, the conceptual model, as well as the process to develop it and that has led to the implemented model structure, may be missed from the published study.

To this author’s knowledge, the first study discussing conceptual modelling in detail was Chilcott et al (Chilcott et al., 2010). Chilcott et al defined five stages in the model developing process: (1) understanding the decision problem, (2) conceptual modelling, (3) model implementation, (4) model checking and (5) engaging with the decision. Chilcott et al defined “*conceptual modelling [as] the process of sharing, testing, questioning and agreeing this formulation of the problem; concerned with defining the scope of a model and providing the inputs to the process of systems analysis and design associated with defining a solution to the proble*m” (p29) (Chilcott et al., 2010). According to Chilcott et al, the conceptual model describes the analysts’ understanding of the system where the decision problem sits, whereas the implemented model is a subset of the conceptual model. Furthermore, the conceptual model is a resource to help check the implemented model and to confirm the validity of the assumptions and simplifications.

The NICE DSU TSD13 (Kaltenhalter et al., 2011), and subsequently Tappenden (P. Tappenden, 2014; Paul Tappenden, Chilcott, Brennan, Squires, & Stevenson, 2012) , developed the methodology of conceptual modelling, building on the Chilcott et al work (Chilcott et al., 2010). Here, the goal of conceptual modelling is to translate the analysts’ understanding of the decision problem towards a mathematical solution. Having an explicit conceptual model is seen as essential to justify the appropriateness of the chosen model structure, and the impact of assumptions and simplifications.

Afzali et al discussed the model structuring, of which conceptual modelling was a structural aspect (Haji Ali Afzali, Bojke, & Karnon, 2018). Here, conceptual modelling related to the appropriateness of the model structure in reflecting the natural history of the disease and the impact of each option on the disease progression.

### How To Develop A Conceptual Model?

Chilcott et al asked analysts experienced in modelling for economic evaluation to explain their approach to the process of conceptual modelling (Chilcott et al., 2010). For some, conceptual modelling was not an explicit stage in the modelling work and instead it was done in parallel with model building. For those who saw conceptual modelling as an explicit stage in the modelling work, the methods employed included developing written documentation of the proposed model structure and assumptions, the use of diagrams to represent the disease and care pathways, developing mock-ups, and written interpretations of the evidence (p.23-24).

Of the guidance documents, only the NICE DSU TSD13 (and subsequently Tappenden) discuss the process of developing a conceptual model in detail (Kaltenhalter et al., 2011; P. Tappenden, 2014; Paul Tappenden et al., 2012). The first step is to develop the problem-oriented conceptual model by learning about the disease and its management insofar as it is relevant to the decision problem, as well as the impact of each option. To this goal, there are two types of problem-oriented conceptual model: the disease process model is concerned with the disease whereas the service pathways model is concerned with the process of managing the disease, such as technologies, resources and costs. The second step is to develop the design-oriented conceptual model, based on the problem-oriented conceptual model, and considering the available evidence, timelines, and resources. The output of the design-oriented conceptual model is one or more model structures, which will ultimately be implemented, as well as a list of evidence requirements. This approach to conceptual modelling was developed in the context of whole disease modelling, that is simulating the full course of the disease and its care pathway (Paul Tappenden et al., 2012). Examples of its application are in colorectal cancer (Paul Tappenden et al., 2013), in prostate cancer (Lord et al., 2013) and in schizophrenia (Jin, Tappenden, MacCabe, Robinson, & Byford, 2020).

Squires et al developed the methodology of conceptual modelling in the context of economic evaluations of public health technologies (Squires, Chilcott, Akehurst, Burr, & Kelly, 2016). They defined four stages in conceptual modelling:

1. “*Aligning the framework with the decision-making process*”, which involves setting out the relevant modes to engage with stakeholders, approaches for searching evidence, and the timelines and resourcing available.
2. “*Identifying relevant stakeholders*”, stakeholder being anyone who impacts on or who is impacted on by the technology.
3. “*Understanding the problem*”, which includes developing the conceptual model of the problem, developing the research question, and describing the care pathways.
4. “*Developing and justifying the model structure*”, which involves reviewing existing models, choosing the technology and the comparators, determining the scope of the model, the populations and subpopulations, perspective and outcomes, determining the level of detail in the modelling of each relationship, choosing the modelling approach, and qualitatively describing the model which will ultimately be implemented.

The Squires et al approach was applied in the development of an economic model to simulate the impact of public health technologies to change the amount of physical activity and/or diet on quality-adjusted survival and health and social care costs (A. D. M. Briggs, Cobiac, Wolstenholme, & Scarborough, 2019).

Publishing the conceptual models for economic evaluation is not common practice but there are a few examples (Hossein Haji Ali Afzali et al., 2019; Alemao et al., 2018; Gonzalez-McQuire et al., 2019; Ramos et al., 2011). In general, these conceptual models were informed by a review of the clinical and/or economic evaluation literature to understand the disease process and its care pathway and how previous models have represented it. Additionally, clinical and economic experts were consulted (e.g. as an advisory group or Delphi panel) to review and refine the conceptual model. For example, Tabberer et al developed a conceptual model for the economic evaluation of therapies for chronic obstructive pulmonary disease (COPD) (Tabberer et al., 2017). To do this, they conducted a literature review of conceptual models, economic evaluation models and studies on the progression of COPD; asked a group of researchers with expertise in COPD to develop a draft conceptual model based on the literature review; tested this draft conceptual model on a Delphi Panel; and finally refined the conceptual model based on the results of the Delphi Panel and given the available data to parameterise it. This conceptual model was the basis for the development of a statistical model to predict COPD progression and outcomes (A. H. Briggs et al., 2017; Exuzides et al., 2017) and for economic evaluations of a new therapy for COPD (Ismaila et al., 2019; Schroeder et al., 2019).

# Recommendations

The design of an economic evaluation – or problem structuring - involves defining the target population, subpopulation and spillover populations; selecting the relevant decision options; and developing the conceptual model, all given the requirements of the decision makers whose decision the economic evaluation aims to inform. The problem structuring stage involves mapping out what should be included in the economic evaluation, investigating whether it can be included in practice, and deciding on what the economic evaluation will formally consider as well as the impact of any exclusions. The next stage – the implementation of the economic evaluation – is conditional on the decisions made at the problem structuring stage. To this end, it is useful to separate out the problem structuring stage from the implementation stage, not only in terms of its conduct but also in the reporting. This separation ensures that the choices are transparent and their impact on the cost-effectiveness results, as well as their applicability to the decision, is explicit to decision-makers and other users of the economic evaluation.

From the review of methodological guidelines and reflections on their practical implications, a number of recommendations emerge:

1. The target population should represent all people for whom the technology is intended for in practice.
2. The target population may be constrained by the evidence base, and particularly in the case of drugs, by their marketing authorisation. Nevertheless, the economic evaluation can explore the assumptions required to expand the target population and identify the key uncertainties, which may be subject to future research.
3. Subpopulations should be considered where there is the expectation that there will be important differences in costs and outcomes, and that their implementation in practice is likely to be considered ethical and feasible as a basis for making separate decisions.
4. A priori definition of subpopulations may involve reviewing previous cost-effectiveness evidence, consultation with stakeholders and development of the conceptual model in order to understand how subpopulation effects propagate to final outcomes.
5. Choices regarding spillover populations should consider of the expected impact on the cost-effectiveness results, both in terms of magnitude and its direction. As with (2), this may be based on previous cost-effectiveness studies, stakeholder feedback and using the conceptual model to infer the expected impact on the results.
6. In setting out the relevant decision options, analysts should bear in mind that the role of an economic evaluation is to quantify the costs and benefits of alternative courses of action, whilst noting any issues which have not been possible to quantify, such as value judgements, ethical concerns, or effects which could not be explicitly considered.
7. Economic evaluations should start by listing all potentially relevant options to the new technology. Depending on the specific decision problem, the options may comprise other currently available technologies, do-nothing approaches, technologies in sequence, technologies in different intensities, technologies in combination and technologies available in the near future.
8. The selection of decision options should primarily consider the risk of biasing the results if an option is excluded. The risk is low for options which are thought to have a small probability of being cost-effective, and for options which are thought to have the similar costs and benefits to other included options.
9. The selection of decision options may also consider clinical practice, technologies likely to be displaced, existing guidance, licensing status, acceptability and feasibility of the economic evaluation given its resources. It may not be feasible to include options for which there is no or very low-quality evidence.
10. The characterisation of “do-nothing” options should be relevant to the decision problem and context so that it reflects what the absence of active treatment consists of in clinical practice.
11. The problem-oriented disease process model should set out the analysts’ understanding of the underlying natural history of the disease and the key disease-specific factors, while the problem-oriented treatment pathways model should define the treatment pathway at the time of the economic evaluation.
12. The design-oriented conceptual model should define the relationships between the effects of the decision options to the costs and consequences of interest to decision makers in the target population.
13. Developing the conceptual model should involve gaining an understanding the clinical and economic evidence and feedback from stakeholders.
14. Stakeholders, such as clinicians, health care managers, patients, and decision makers, should be involved in the process of problem structuring so that the decision problem and its context is appropriately reflected.
15. The choices made at the problem structuring stage should be reported, alongside their justification and their expected impact on the cost-effectiveness results.

Further research is warranted on (i) the process of developing the conceptual model and (ii) how the conceptual model can be used to inform choices in the selection of decision options, subpopulations and spillovers; to inform assumptions and simplifications in the conduct of the economic evaluation; and to shed light on uncertainties, particularly structural uncertainties, and inform sensitivity analyses. The existing literature is mostly in the context of whole disease modelling or public health modelling, where the goal is to represent the whole system, either the disease (in whole-disease modelling) or the public health concern (in public health modelling), and generally relates to the development of the model structure and its parameterisation. Many economic evaluations are on whether a new technology should be offered/reimbursed by the healthcare service at a specific point of the care pathway. Although the recommendations in the literature are applicable, their recommended process for model conceptualisation and problem structuring requires sufficient timelines and resources. Therefore, approaches to expedite model conceptualisation and prioritise areas for stakeholder involvement may be useful in resource constrained settings or when timelines are short. Secondly, there is little discussion on how the conceptual model can be used to inform choices at problem structuring, model design, parameterisation, and sensitivity analysis. In particular, explicit conceptual modelling can provide a process for understanding structural uncertainties prior to model implementation, and to plan structural sensitivity analyses to address them. Given the impact of such choices on the economic evaluation, the development of methods and/or criteria to inform them has the potential to improve the conduct of economic evaluations and their enhance their value to decision-makers.

## Conclusion

An economic evaluation aims to elucidate the trade-offs in the consequences between the alternative courses of action and inform decisions regarding adoption of new technologies and future research. Inevitably, an economic evaluation cannot consider all individuals potentially affected by it, nor compare all possible options, nor account for all relationships that affect costs and consequences. Problem structuring is the stage at which such choices are made, given the decision maker requirements, the available evidence, stakeholder feedback and resource constraints. Thoughtful consideration of problem structuring, and thorough documentation of the process are important to the transparency, credibility, and value of economic evaluations.

# Further Reading

## Methodological Guidelines

* The NICE “Guide to the methods of technology appraisal 2013” is the methodological guide for economic evaluations to inform decisions on the funding of new technologies by the UK National Health Service (NHS) (National Institute for Health and Care Excellence (NICE), 2013). It is supplemented by the NICE Decision Support Unit Technical Support Documents (NICE DSU TSD), as relevant (NICE Decision Support Unit, n.d.). At the time of writing, the NICE guideline was under review.
* The “Guidelines for the Economic Evaluation of Health Technologies: Canada (4th edition)” is the methodological guideline for Canada’s CADTH, which is responsible for providing evidence to help funding decisions about new drugs, diagnostic tests, and medical, dental, and surgical devices and procedures. (Canadian Agency for Drugs and Technologies in Health, 2017).
* The “Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (version 5.0)” is the methodological guideline to inform funding decisions on new drugs by Australia’s PBAC (Pharmaceutical Benefits Advisory Committee, 2016).
* The EUnetHTA guideline is the 2015 report “Methods for health economic evaluations – a guideline based on current practices in Europe” (European Network for Health Technology Assessment (EUneHTA), 2015). EUnetHTA is a network of health technology assessment agencies in European countries.
* The Gates guideline is the report “Methods for Economic Evaluation Project” on the development of the Gates Reference Case for the Bill and Melinda Gates Foundation on economic evaluations in low- and middle-income countries that is commissions (NICE International, 2014).
* The Drummond et al textbook “Methods for economic evaluation of health programmes (4th edition)” is a key textbook for economic evaluation and has been cited over 15,000 times (M. F. Drummond et al., 2015).
* The 2016 book “Cost-effectiveness in health and medicine” by the second US panel on the topic (Neumann, Sanders, Russell, Siegel, & Ganiats, n.d.). This book updates the recommendations by the first US panel on cost-effectiveness of health and medicine, which greatly influenced the conduct of economic evaluations worldwide (Neumann, Sanders, Russell, Siegel, & Ganiats, 2016). This chapter mostly uses the US Panel Report chapter “Designing a Cost-Effectiveness Analysis” (Owens et al., 2016), with some information from the chapter “Identifying and Quantifying the Consequences of Technologies” (Salomon et al., 2016) and “Decision Models in Cost-Effectiveness Analysis” (Kuntz et al., 2016).
* The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task forces consensus reports. ISPOR was founded in 1995 to advance the policy, science and practice of research on the effects of health care technologies on costs and patients well-being (‘About ISPOR’, n.d.). Of the various task forces convened to issue guidance, those relevant to this thesis are the reports on economic evaluation using decision models by Caro et al (Caro et al., 2012) titled “Modeling good research practices - Overview: A report of the ISPOR-SMDM modeling good research practices task force-1” and by Roberts et al (Roberts et al., 2012) titled “Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2” . All other taskforce reports are recommended as further reading as state-the-art guidance on economic evaluation and related topics (ISPOR, n.d.).

## Other Further Reading

### On Subpopulations And Heterogeneity

Kohli-Lynch, C. N., Briggs, A. H., Kohli-Lynch, C. N. & Briggs, A. H. Heterogeneity in Cost-Effectiveness Analysis. in Oxford Research Encyclopedia of Economics and Finance (2019). doi:10.1093/acrefore/9780190625979.013.101

### On Spillover Populations

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### On Conceptual Modelling

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**Notes**

1. Throughout this chapter, and following the terminology by the European Medicines Agency (Committee for Medicinal Products for Human Use (CHMP), 2019), the term subpopulation refers to a subset of the target population whereas the term subgroup refers to a subset of the population in a primary research study (e.g. a clinical trial). [↑](#endnote-ref-1)
2. The NICE Guideline states upfront that heterogeneity in treatment costs related to social characteristics or related to geographical location are not relevant to the assessment (National Institute for Health and Care Excellence (NICE), 2013). [↑](#endnote-ref-2)
3. Although the NICE Guideline allows exploration of heterogeneity in the treatment effect, there is a strong preference for pre-specified subgroup analysis with a clear rationale for differential effectiveness; it advises caution against post hoc subgroup analysis due to the risk of finding differential treatment effect caused by chance. [↑](#endnote-ref-3)
4. The NICE Guideline does not mention spillover effects explicitly but recommends that the perspective on outcomes is all direct health effects, whether for patients or other people. [↑](#endnote-ref-4)
5. The NICE Guideline defines the comparator as the “*the standard technology against which the technology under appraisal is compared*” (p.80) but advices that, at the scoping stage, all potentially relevant comparators are identified. The Committee is tasked with selecting the most appropriate comparators given established clinical practice in England, natural history of the condition without suitable treatment, existing NICE Guidance, cost-effectiveness and licensing status of the comparator. [↑](#endnote-ref-5)
6. The CADTH Guideline suggests that the options should include the technologies which will be replaced by the new technology if the evaluation aims to inform a reimbursement decision; but the options should include all currently available, relevant technologies if the evaluation aims to inform efficient practice (p.24). [↑](#endnote-ref-6)
7. The NICE Guideline accepts unlicensed technologies as options only if used in the NHS as standard practice. [↑](#endnote-ref-7)
8. The NICE Guideline accepts technologies to be evaluated as a therapeutic class only in exceptional circumstances. [↑](#endnote-ref-8)
9. The EUnetHTA Guideline recommends the use of models for economic evaluation. [↑](#endnote-ref-9)