



**Health  
Information  
and Quality  
Authority**

An tÚdarás Um Fhaisnéis  
agus Cáilíocht Sláinte

# **Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland**

**September 2014**

***Safer Better Care***

## **About the Health Information and Quality Authority**

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive high quality and safe care for people using our health and social care services. HIQA's role is to promote sustainable improvements, safeguard people using health and social care services, support informed decisions on how services are delivered, and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting directly to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

**Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.

**Supporting Improvement** – Supporting health and social care services to implement standards by providing education in quality improvement tools and methodologies.

**Social Services Inspectorate** – Registering and inspecting residential centres for dependent people and inspecting children detention schools, foster care services and child protection services.

**Monitoring Healthcare Quality and Safety** – Monitoring the quality and safety of health and personal social care services and investigating as necessary serious concerns about the health and welfare of people who use these services.

**Health Technology Assessment** – Ensuring the best outcome for people who use our health services and best use of resources by evaluating the clinical and cost effectiveness of drugs, equipment, diagnostic techniques and health promotion activities.

**Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

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## Foreword

The Health Information and Quality Authority (the Authority) has a statutory remit to evaluate the clinical and cost-effectiveness of health technologies, providing advice to the Minister for Health and to the Health Service Executive (HSE). It is also recognised that the findings of a health technology assessment (HTA) may have implications for other stakeholders in the Irish healthcare system, including patient groups, the general public, clinicians, other healthcare providers, academic groups and the health technology industry.

To ensure consistency in the HTAs undertaken by the Authority and others, the Authority continues to develop guidelines on the conduct of HTA in Ireland. These guidelines provide an overview of the principles and methods that are used in assessing health technologies. They are intended to be a guide for all those who are involved in the conduct or use of HTA in Ireland, promoting the production of assessments that are timely, reliable, consistent and relevant to the needs of decision makers and key stakeholders in Ireland.

This document is part of the series of guidelines that also includes the *Guidelines for Economic Evaluation of Health Technologies in Ireland (2014)*, *Guidelines for Budget Impact Analysis of Health Technologies in Ireland (2014)*, *Guidelines for Stakeholder Engagement in Health Technology Assessment in Ireland (2014)* and the *Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland (2014)*.

This document is limited to guidance on the retrieval and interpretation of economic evaluations and is intended to promote best practice in this area. The purpose of these guidelines is to assist those conducting or using HTA in Ireland. They are intended to inform technology assessments conducted by, or on behalf of the Health Information and Quality Authority, the National Centre for Pharmacoeconomics, the Department of Health and the HSE, to include health technology suppliers preparing applications for reimbursement. They are also intended to support clinical guideline developers as well as other practitioners within the HSE tasked with the appraisal of the cost-effectiveness of the technologies.

These guidelines have been developed in consultation with the HTA Scientific Advisory Group of the Authority. Providing broad representation from key stakeholders in healthcare in Ireland, this group includes methodological experts from the field of HTA. The Authority would like to thank the members of the Scientific Advisory Group and its Chairperson, Dr Michael Barry from the National Centre for Pharmacoeconomics, and all who have contributed to the production of these guidelines.

Dr Máirín Ryan

Director of Health Technology Assessment  
Health Information and Quality Authority

## **Process and acknowledgements**

This document is a complementary document to previously published guidelines. The guidelines are limited to guidance on retrieval and interpretation of economic evaluation literature in health technology assessment and are intended to promote best practice in this area. They will be reviewed and revised as necessary, with updates provided online through the Authority's website, [www.hiqa.ie](http://www.hiqa.ie). This document forms part of a series of national guidelines for health technology assessment (HTA) in Ireland that the Authority has developed and will continue to expand and review.

The Guidelines have been developed by the Authority in consultation with its HTA Scientific Advisory Group (the Group). This group includes methodological experts from the field of HTA. The Group provides ongoing advice and support to the Authority in its development of national HTA guidelines. The terms of reference for this group are to:

- contribute fully to the work, debate and decision-making processes of the Group by providing expert technical and scientific guidance at Scientific Advisory Group meetings, as appropriate
- be prepared to occasionally provide expert advice on relevant issues outside of Scientific Advisory Group meetings, as requested
- support the Authority in the generation of guidelines to establish quality standards for the conduct of HTA in Ireland
- support the Authority in the development of methodologies for effective HTA in Ireland
- advise the Authority on its proposed HTA Guidelines Work Plan and on priorities, as required
- support the Authority in achieving its objectives outlined in the HTA Guidelines Work Plan
- review draft guidelines and other HTA documents developed by the Authority and recommend amendments, as appropriate
- contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process, as required.

Following review by the Scientific Advisory Group, the draft guidelines were made available for public consultation. Feedback was sought by open consultation through the Authority's website and by targeted consultation with stakeholders in Irish healthcare. The draft guidelines have been revised as appropriate and approved by the Board of the Authority before publication.

**The membership of the Scientific Advisory Group is as follows:**

**Chairperson:** Professor Michael Barry,  
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## Record of updates

Date	Title / Version	Summary of changes
September 2014	Guidelines for the retrieval and interpretation of economic evaluations of health technologies in Ireland	First national retrieval and interpretation guidelines

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This document is one of a series that describes the methods and processes for conducting health technology assessment in Ireland.

Other guidelines in the series include:

- Guidelines for Economic Evaluation of Health Technologies in Ireland (2014)
- Guidelines for Budget Impact Analysis of Health Technologies in Ireland (2014)
- Guidelines for Stakeholder Engagement in Health Technology Assessment in Ireland (2014)
- Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland (2014).

## List of abbreviations and acronyms

BMJ	British Medical Journal
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CHEC-LIST	Consensus on Health Economic Criteria List
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPI	consumer price index
CMA	cost-minimisation analysis
CRD	Centres for Reviews and Dissemination
CUA	cost-utility analysis
DES	discrete-event simulation
DRG	diagnosis related group
EUnetHTA	European Network of Health Technology Assessment
HRQoL	health-related quality of life
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NHS EED	National Health Service Economic Evaluation Database
PICO	Participants, Intervention, Comparison, Outcome
PPP	purchasing power parity
PSA	probabilistic sensitivity analyses
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAG	Scientific Advisory Group
SIGN	Scottish Intercollegiate Guidelines Network
VAS	visual analogue scale

## **1 Introduction**

Health technology assessment (HTA) has been described as 'a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner'.<sup>(1)</sup> The scope of the assessment depends on the technology being assessed, but may include any, or all of these issues. The purpose of HTA is to inform health policy decisions that promote safe, effective, efficient and patient-focussed healthcare.

The primary audience for HTAs in Ireland is decision makers within the publicly-funded health and social care system. It is recognised that the findings of a HTA may also have implications for other stakeholders in the system. These include patient groups, the general public, clinicians, other healthcare providers, academic groups and the manufacturing industry.

The Authority continues to develop a series of methodological guidelines that are intended to assist those that conduct HTA for or on behalf of the Health Information and Quality Authority, the National Centre for Pharmacoeconomics, the Department of Health and the Health Service Executive (HSE). They should, additionally, prove to be valuable for clinical guideline developers preparing national guidelines for quality assurance by the National Clinical Effectiveness Committee and subsequent endorsement by the Minister for Health. Their purpose is to promote the production of health technology assessments and clinical guidelines that are timely, reliable, consistent and relevant to the needs of decision makers and other stakeholders.

The series of HTA guidelines is intended to be applicable to all healthcare technologies, including pharmaceuticals, procedures, medical devices, broader public health interventions, and service delivery models. The Guidelines are therefore broad in scope and some aspects may be more relevant to certain health technologies than others.

The *Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies* represent one component of the overall series. Their aim is to provide guidance on the retrieval of economic evaluation literature of healthcare technologies and the interpretation of this literature in the context of the Irish healthcare system. These guidelines are intended to be viewed as a complementary document to the existing economic evaluation, budget impact analysis, clinical effectiveness evaluation and stakeholder engagement guidelines in Ireland.

These guidelines have drawn on published research and will be reviewed and revised as necessary following consultation with the various stakeholders, including those in the Scientific Advisory Group.

## **1.1 Guidelines for the retrieval and interpretation of economic evaluations of health technologies**

The aim of economic evaluations of health technologies is to compare the costs and consequences of new or existing health technologies (such as drugs, diagnostics, devices, and so on) with one or more relevant alternatives (often referred to as the comparator[s]). The type of economic evaluation undertaken is considered to be a factor in its value to decision makers. Economic evaluations fall into two major categories:

- cost-effectiveness analysis (including cost-utility analysis as a particular sub-type)
- cost-benefit analysis.

Although they employ similar methods to define and evaluate costs, the methods differ in how the consequences are assessed and, therefore, in the conclusions that are drawn. A brief description of these evaluation types including a description of cost-minimisation analysis and the particular circumstances for its use is included in Appendix 1.

The results for cost-effectiveness analysis are typically presented as incremental cost-effectiveness ratios (ICERs). ICERs present the cost per unit of outcome, for example, the expected additional total cost to the expected additional quality-adjusted life years (QALYs) and are calculated as follows:

$$\text{ICER} = \frac{(\text{cost A} - \text{cost B})}{(\text{outcome of A} - \text{outcome of B})}$$

As the cost per unit of outcome (ICER) becomes larger, the intervention is said to be less cost-effective.<sup>(2)</sup>

Non-comparative costing studies, 'burden of disease' studies and 'cost of illness' studies are studies that consider only the costs and not the consequences of health technologies.

Although increasingly common as a prerequisite to reimbursement, the cost-effectiveness of health technologies, particularly non-pharmaceuticals, is only assessed in a limited number of countries. Directly applying results from international literature in Ireland may pose a challenge as the funding and organisation of the healthcare system differs between countries. Specific concerns in relation to the

transferability of clinical and economic data to HTAs or clinical guidelines in the Irish healthcare setting are the:

- extent to which the clinical efficacy data are representative of the likely effectiveness that can be achieved in Ireland
- extent to which economic data is representative of the likely costs and resource utilisation incurred in Ireland
- generalisability of the economic and clinical data across different patient populations (such as age, gender, ethnicity) within Ireland
- generalisability of data due to local and regional differences in healthcare practice within Ireland.

The recognised gold standards for the retrieval of literature are referenced and summarised here in order to facilitate the reader and to provide a comprehensive single reference point on how to conduct and interpret the findings from a systematic review of the economic evaluation literature.

## **1.2 Document layout**

For ease of use, a list of the guideline statements that summarise the key points of the guidance is included at the end of this chapter. Each of the guideline statements is also included in italics at the end of the relevant section in Chapters 2, 3 and 4.

## **1.3 Explanation of terms**

A number of terms used in the guidelines may be interpreted more broadly elsewhere or may have synonymous terms that could be considered interchangeable. The following outlines the specific meanings that may be inferred for these terms within the context of these guidelines and identifies the term that will be used throughout the guidelines for the purpose of consistency.

'Technology' includes any intervention that may be used to promote health, to prevent, diagnose or treat disease, or that is used in rehabilitation or long-term care. These include: pharmaceuticals, devices, medical equipment, medical and surgical procedures including disease detection mechanisms and diagnostic testing, and the organisational and supportive systems within which healthcare is provided. Within the context of these guidelines, the terms 'intervention' and 'technology' should be considered to be interchangeable, with the term 'technology' used throughout for the purpose of consistency.

'Economic evaluation' refers to an analysis that evaluates the costs and consequences of health technologies. It includes cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). The term 'economic

evaluation' should be considered to be interchangeable with any of the terms CEA, CUA or CBA, with the term 'economic evaluation' used throughout these guidelines for the purpose of consistency.

'Transferability' refers to the extent to which one can apply or extrapolate results obtained in one setting or population to another. A trial, study or model is considered transferable if it can be used to produce unbiased inferences to another specified healthcare system (such as from overseas to Ireland). The term transferability is also referred to as applicability, exchangeability, extrapolation, external validity, generalisability, portability, relevance and transportability. However, distinctions have been drawn between these terms by some researchers depending on whether a study can be applied without adjustment, or needs to be adapted to apply, to another setting.<sup>(3)</sup>

#### **1.4 Summary of guideline statements**

**Study question (Section 2.1.1).** The study question should be framed into a detailed question to enable a search strategy to be developed. The detailed question should clearly define the participants, intervention, comparison and outcome of interest.

**Search strategy (Section 2.1.2).** The search strategy should be clearly documented in order that it can be reproduced, with any search limits, exclusion and inclusion criteria explicitly stated.

**Databases (Section 2.2.1).** The search should be conducted in both generic and specialised databases with searches of grey literature sources clearly documented.

**Economic filters (Section 2.3.1).** Validated search filters for economic evaluation studies should be used as appropriate.

**Screening studies (Section 2.4.1).** All retrieved literature should be stored using reference management software. A preliminary assessment of the health questions covered by the retrieved studies should be undertaken to eliminate those studies that are clearly not relevant.

**Assessing relevance (Section 3.1.1).** Each study should be examined in detail to assess its relevance against the defined exclusion and inclusion criteria. Ideally this should be performed independently by two or more reviewers.

**Data extraction (Section 3.2.1).** All relevant data should be extracted into evidence tables and presented in the report. Ideally data extraction should be performed independently by two or more reviewers.

**Assessing quality (Section 3.3.1).** For all relevant studies, an assessment of their quality should be determined using an appropriate checklist for economic evaluation studies. Ideally this should be performed independently by two or more reviewers.

**Assessing transferability (Section 4.1.1).** The transferability of the study results should be considered for all relevant studies that have an acceptable quality. This should be conducted using a defined framework; any reasons for a lack of transferability should be clearly documented and any expected differences in the Irish setting explicitly stated (for example, intervention to prevent transmission of infection would be less cost-effective due to a lower disease prevalence).

**Transferability factors (Section 4.2).** The following key factors should be considered when assessing the transferability of results: perspective, time horizon, clinical effectiveness, health-related quality of life, costing approaches, modelling approach, discount rate, results of any sensitivity analyses and the implications of the cost-effectiveness result relative the notional threshold used in Ireland.

**Clear structured report (Section 4.3.1).** A well structured report should be provided that summarises the available literature and its relevance to the Irish context, with information provided on each of the elements outlined in the guidelines.

## **2 Searching for economic evaluation literature**

This chapter will summarise the issues involved when conducting an economic literature search. These include defining the question, formulating the search strategy, and the initial screening of the retrieved studies. The material presented in this chapter summarises the relevant issues covered in the Cochrane Handbook for Systematic Reviews of Interventions<sup>(4)</sup> and the CRD's guidance for undertaking reviews in healthcare.<sup>(5)</sup> For further details on the issues outlined here, readers are directed to these texts. It should be noted that the results from an economic literature search will not be sufficient for a review of the clinical effectiveness, and where this is required, the clinical evidence should be retrieved and synthesised separately.

The search for economic evaluation literature should be undertaken using a systematic approach. Systematic reviews seek to collate all evidence that fits pre-specified eligibility criteria in order to address a specific research question.<sup>(6)</sup> The use of a systematic approach will reduce the likelihood of bias. The literature search should be reproducible, thorough and transparent. A clear description of the process used to obtain relevant information should be provided. The study question to be addressed should be defined in advance along with clear inclusion and exclusion criteria. A clear protocol should be prepared outlining the steps of the review. The typical steps in a systematic review are as follows:<sup>(5)</sup>

- formulate the review question
- define inclusion and exclusion criteria
- develop search strategy
- identify studies
- select studies for inclusion
- assess study quality
- extract data
- analyse and present results
- interpret results.

When undertaking a literature search, it may be useful to get assistance from a librarian or other information specialist who has experience in this area (service providers may already have access to these specialists on site, particularly in hospital libraries, or through their local /regional /national office). Clinical librarians can assist with literature searches, devising a search strategy for key resources, or provide training on literature search techniques for systematic reviews.

### **2.1 Generic searching methodology**

The health problem that the search is anticipated to inform is the starting point. It is vital to have a well formulated question to create the search strategy.<sup>(7)</sup> This should

be framed into a detailed question that should be clearly specified and potentially answerable.<sup>(5)</sup>

A well formulated question consists of four elements:

- participants – who is involved? what is the setting?
- intervention – pharmaceutical, diagnostic testing, screening test, surgical method, health services?
- comparator – what are the alternatives to the intervention?
- outcome – what are the relevant clinical endpoints?

These factors are frequently abbreviated to PICO: Participants, Intervention, Comparison and Outcome. Frequently 'study design' is added as a factor to be considered (that is, PICOS). The study design should be clearly specified, that is to say if limited to full economic evaluations (those that include both the costs and consequences of the technology) or if kept broader, so as to also include non-comparative costing studies. The study question is the basis for the literature search, the initial abstract sorting, the critical appraisal of the articles and the quality assessment of the evidence.<sup>(5)</sup>

### **Example**

In the clinical question used in the HTA of intermittent pneumatic compression for severe peripheral arterial disease – “What is the clinical effectiveness of intermittent pneumatic compression in patients with severe peripheral arterial disease who are not suitable for surgery or percutaneous transluminal angioplasty?” – the PICO analysis used to structure the search strategy was as follows:<sup>(8)</sup>

**Participants:** Patients with critical limb ischemia (defined per TASC II guidelines as patients with chronic ischaemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease) who are ineligible for surgical revascularisation or PTA. This corresponds to Rutherford stage 4, 5 or 6 and Fontaine stage III or IV.

**Intervention:** Intermittent pneumatic compression (single or sequential) plus standard medical care.

**Comparator:** Standard medical care only.

<b>Outcome:</b>	<b>Primary outcomes</b>	<b>Measures of effect</b>
	1. All cause mortality.	Difference in median survival or mortality rates at equivalent intervals.
	2. Major adverse	Relative risk of a major adverse

cardiovascular event (MACE) rates.	cardiovascular event in different treatment groups over an equivalent time period.
3. Limb amputation rate and amputation-free survival.	Relative risk of amputation in different treatment groups; amputation-free survival by differences in mean time to amputation or death.
4. Quality of life or pain changes.	Difference between groups only if measured using a validated tool.
5. Wound healing rates.	Differences in mean wound healing times or healing rates at equivalent intervals using an objective wound healing measure.
6. Change in clinical status.	Changes in clinical status measured per the Society for Vascular Surgery (SVS) reporting guidelines.
7. Initial and absolute claudication distance.	Differences in the mean change in distance achieved.
8. Adverse events and complication rate.	The number and severity of complications in different treatment groups. Complications to be included were limited to those specified in the SVS reporting guidelines.
<b>Secondary outcomes</b>	<b>Measures of effect</b>
9. Differences in ankle brachial pressure index or toe pressure.	Mean change in pressure between groups.
10. Treatment adherence and persistence rates for IPC.	Compliance rates measured by both adherence (to the daily treatment sessions) and persistence (duration of compliance with the course of treatment).
11. Costs.	Total cost of provision of the treatment from a patient or health service perspective.
12. Hospitalisation rates.	Difference in the frequency or length of stay of hospital admission.

**Study design:** Randomised controlled trials (RCTs), non-randomised control trials (NRCTs) and controlled before-and-after (CBA) studies were considered the best source of evidence for the effectiveness of this treatment. Cohort studies, trials with historical controls, cross-sectional studies and case series provide less reliable information on the effects of such interventions, primarily due to the inability to control allocation or ensure that treatment and comparison groups are equivalent in terms of their prognosis at baseline. However,

findings from these types of studies were synthesised and discussed in the absence of better evidence, with due consideration of their methodological limitations. Studies that were only reported in conference abstracts were excluded.

### **2.1.1 Study question**

*The study question should be framed into a detailed question to enable a search strategy to be developed. The detailed question should clearly define the participants, intervention, comparison and outcome of interest.*

The search strategy should clearly outline the search terms to be used, how they will be combined (AND, OR, NOT, NEAR, NEXT, ADJ, WITH, and so on), all search limits (such as language, population, year) and databases to be searched.<sup>(7)</sup> It needs to be detailed enough that it can be reproduced and the same results obtained. It is important to remember that each database requires its own search strategy, as search terms and methods of combining them differ.<sup>(7)</sup>

Clear and unambiguous inclusion and exclusion criteria should be decided upon before searching begins to ensure that a systematic and transparent process is used when deciding whether to include or exclude studies and thus reduces bias. Inclusion and exclusion criteria are defined based on the key question and the PICO. The search strategy should be defined to minimise publication bias where possible. English language bias and citation bias are forms of publication bias in which studies with negative findings are more likely to appear in non-English language publications and are less likely to be cited, respectively. It is of critical importance that the search strategy is as comprehensive as possible.

### **2.1.2 Search Strategy**

*The search strategy should be clearly documented in order that it can be reproduced, with any search limits, exclusion and inclusion criteria explicitly stated.*

## **2.2 Databases**

For health economic evaluations searches, the main specialised databases and their host websites are listed in Table 2.1. The NHS EED is populated through extensive, sensitive searching of a number of generic databases along with hand-searching of journals.<sup>(9)</sup> Undertaking searches in the specialised databases should guarantee a comprehensive cross-section of economic evaluations.<sup>(5)</sup> There are problems with

currency, however, because of time delays between the identification of studies and publication of the full abstracts in the databases.<sup>(9)</sup> Thus, along with searching the specialised databases, a search should be performed using the major health search engines such as MEDLINE<sup>®</sup>, EMBASE<sup>™</sup>, PsycInfo<sup>®</sup>, and CINAHL<sup>®</sup> and Web of Science.

**Table 2.1 Main Specialised Economic Evaluation Databases**

Database	Websites
Database of Abstracts of Reviews of Effects	<a href="http://www.crd.york.ac.uk/CRDWeb">www.crd.york.ac.uk/CRDWeb</a>
NHS Economic Evaluation Database (EED)	<a href="http://www.crd.york.ac.uk/CRDWeb">www.crd.york.ac.uk/CRDWeb</a>
Health Technology Assessment Database	<a href="http://www.crd.york.ac.uk/CRDWeb">www.crd.york.ac.uk/CRDWeb</a>
Cochrane Central Register of Controlled Trials	<a href="http://www.thecochranelibrary.com">www.thecochranelibrary.com</a>
Cochrane Database of Systematic Reviews	<a href="http://www.thecochranelibrary.com">www.thecochranelibrary.com</a>

Searches conducted in bibliographic databases might frequently be complemented with information retrieved in the 'grey literature'. This covers material which is typically not included in bibliographic databases, such as conference abstracts, reports, unpublished studies and reports from specialist networks, for example, national HTA agencies).<sup>(7)</sup> Search engines such as, Google<sup>™</sup> Scholar can also be useful to supplement bibliographic database searching.

### 2.2.1 Databases

*The search should be conducted in both generic and specialised databases with any additional searches of grey literature sources clearly documented.*

### 2.3 Economic filters

Search filters are sets of search terms used to limit retrieved literature. They can be developed to retrieve literature using a particular study design or topic, or by some other characteristic.<sup>(9)</sup> Glanville et al.<sup>(9)</sup> showed there are a number of filters that can be used when searching for economic evaluations in MEDLINE<sup>®</sup>. These have varying levels of sensitivity. Those with the highest sensitivity may return a large number of studies. For researchers undertaking rapid reviews or scoping studies, Glanville et al. identified filters that have lower, but acceptable levels, of sensitivity.<sup>(9)</sup> A number of economic search filters are available on [www.york.ac.uk/inst/crd/intertasc/econ.htm](http://www.york.ac.uk/inst/crd/intertasc/econ.htm) that have been developed for use in the CINAHL<sup>®</sup>, EMBASE<sup>™</sup>, MEDLINE<sup>®</sup> and PsycINFO<sup>®</sup> databases. It should be noted that these are English language search filters and as such will bias towards the English literature. Appendix 2 provides an example of an economic search filter for CINAHL<sup>®</sup>, used by SIGN, which is an

adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination (CRD) at the University of York.

### **2.3.1 Economic filters**

*Validated search filters for economic evaluation studies should be used as appropriate.*

## **2.4 Screening studies**

When a systematic literature search is finished, the result is frequently a vast quantity of material including a variety of different study types.<sup>(7)</sup> Papers that do not address the study question should be eliminated. The use of specialised bibliographic software for instance Reference Manager<sup>®</sup>, EndNote<sup>®</sup> or Zotero to manage and record references will make the identification and deletion of duplicated references easier and it can be used to record inclusion and exclusion decisions.<sup>(5)</sup> These specialised software packages also have the ability to import electronic references from databases, and can be used to create references list or bibliographies in word processing packages.<sup>(5)</sup> Care must be taken to ensure any databases created are stored and backed-up appropriately.

Each article must be screened to assess its relevance to the study question and to ensure it answers a clearly specified and relevant problem. For best practice, two or more reviewers should be involved in the selection process using a predefined protocol to maximise transparency and objectivity. The two reviewers should initially work independently. The mechanisms used to resolve disagreement should be clearly outlined for instance through discussion or arbitration by a third party. A log of the ineligible studies should be maintained including a rationale for their individual exclusion in relation to the study question. This log can be incorporated into the reference database. This ensures robustness of the search and selection process.<sup>(10)</sup> Many papers are eliminated in this step.

### **2.4.1 Screening studies**

*All retrieved literature should be stored using reference management software. A preliminary assessment of the health questions covered by the retrieved studies should be undertaken to eliminate those studies that are clearly not relevant.*

## **3 Reviewing the Evidence**

Once the initial screening of studies has been completed, the remaining references will need to be retrieved in full. Each article retrieved during the search should be critically assessed, with consideration given to the following questions: Is it relevant? Are the results reliable? Is the study of reasonable quality?<sup>(7)</sup>

This chapter will describe the issues involved in assessing the relevance of economic evaluation literature, extracting the data and checklists that can be used when considering the quality of the relevant studies.

### **3.1 Assess relevance to current study setting**

Once the full articles have been retrieved each article will need to be assessed against the inclusion and exclusion criteria. Each element of the review question (participants, intervention[s], comparator[s] and outcomes) should be considered when assessing the relevance of studies in the review.<sup>(5)</sup>

#### 1) Is the population similar?

Consideration should be paid to the relevant demographic characteristics (such as age and gender, nationality, ethnicity), risk factors (such as average blood pressure, cholesterol, and body mass index levels), behaviours (such as smoking and adherence to treatment), details of the condition (such as stage and severity and past and current treatments), the setting and any relevant comorbidities.<sup>(3)</sup>

#### 2) Is the intervention the same?

As well as the actual technology used, consideration should be paid to the full care pathway for the intervention described in the literature and how this compares to the intervention under consideration. This should include how it is administered; the dose; duration of treatment (or protection for a vaccine); skill level and behaviour of provider; post-treatment monitoring and care; and duration of follow up.<sup>(3)</sup> For medical devices, which can change substantially over time in terms of design, the evidence should not be generalised to other similar devices or subsequent generations of a device unless it can be shown that they are at least equivalent and that the synthesised evidence is appropriately adjusted to account for differences.

#### 3) Is the comparator(s) relevant?

All aspects of the comparator should be assessed that is, who did what, to whom, where, and how often.<sup>(11)</sup> Consideration should be given to whether all relevant

comparators were considered, and how well does background care in the model match the standard care in Ireland?

4) Are the outcomes relevant?

Are both the clinical and economic outcomes relevant? Is the timing of the outcome assessment appropriate? Have relevant adverse effects been considered?<sup>(5)</sup>

Studies for which the answer is 'No' to one or more of the above questions should be excluded. If any limitations based on study design were specified in the search strategy, then studies that do not meet these criteria should also be eliminated at this stage. For best practice, two or more reviewers should be involved in the selection process using a predefined protocol to maximise transparency and objectivity. The mechanisms used to resolve disagreement should be clearly outlined. A log of the ineligible studies should be maintained including a rationale for their individual exclusion in relation to the study question. This ensures robustness of the selection process.<sup>(10)</sup>

### **3.1.1 Assessing relevance**

*Each study should be examined in detail to assess its relevance against the defined exclusion and inclusion criteria. This should be performed independently by two or more reviewers.*

## **3.2 Data extraction and evidence tables**

Data extraction is the way that researchers obtain the required information on study characteristics and results from the included economic evaluations.<sup>(5)</sup> Data extraction requirements will be specific to each literature review, but will include the following:<sup>(5)</sup>

- study question, population, intervention, comparator and setting
- modelling methods
- sources and quality of clinical data
- sources and quality of cost data
- study outcomes, and methods used to synthesise them
- methods for dealing with uncertainty
- study results.

The key factors (such as perspective, time horizon, discount rate and methods employed in undertaking the economic analysis) that can influence the results of an economic evaluation should also be captured in the data extraction. Data extraction

requirements typically vary between reviews and the extraction tables need to be adapted to the specific review question.<sup>(5)</sup> It may be helpful to consider the care pathway when structuring the data extraction.<sup>(5)</sup>

All relevant data should be extracted into standardised data extraction tables which enables consistency of reporting, aids reproducibility, and so reduces bias.<sup>(5)</sup> These evidence tables should be presented in the report. An example of an evidence table is provided in Appendix 3.

Data extraction should be as reliable and unbiased as possible. It is however, susceptible to human error and subjective decisions are frequently required. The number of reviewers performing data extraction will be influenced by time and resource constraints. Ideally two or more reviewers will independently conduct the data extraction. Any disagreements need to be documented and resolved among reviewers or with an additional independent reviewer.<sup>(5)</sup> The data extraction is linked to the quality assessment of the economic evaluation in that both are often conducted at the same time.<sup>(5)</sup>

### **3.2.1 Data extraction**

*All relevant data should be extracted into evidence tables and presented in the report. Data extraction should be performed independently by two or more reviewers.*

### **3.3 Assessing the quality of the evidence**

When reviewing a number of studies it is essential to assess the quality of the studies. A review should be based on the highest quality evidence available. Whatever study designs are included, it cannot be assumed that studies with the same design are all equally well-conducted. A study may be of genuinely poor quality due to inadequate study design, or it may be poorly reported irrespective of the actual study quality. It can be anticipated that a poor quality study will generate a biased estimate of effect. Quality assessment should ultimately help to answer the question: Are the economic evaluations sufficiently robust to guide treatment or policy decisions?<sup>(5)</sup>

Economic evaluations may run alongside a clinical trial, where the patient outcomes and associated costs generated in the trial are used to populate the economic model, rather than data being collated from multiple trials or gathered in a systematic review. In such cases there are a number of risks of bias (such as protocol-driven costs, lack of longer-term follow-up data, inappropriate outcomes) that can impact on the results. A poorly reported study may be of good quality, but there is

insufficient information to safely draw that conclusion. However, a well designed study will typically adhere to good reporting guidelines. Bias may also be introduced where some studies are sponsored by the technology manufacturer. In such trials there is a risk that the comparator technology may be applied in a sub-optimal manner to show the sponsor's treatment in a more favourable light.

All studies should be examined for stated conflict of interest or study funding that might indicate potential sponsorship bias.

Quality assessment will tend to concentrate on the following factors all of which can have an important influence on the overall validity of the results:

- methods of deriving and sources of the effectiveness data
- measurement and valuation of resource and health benefits (utilities) data
- modelling techniques (if used)
- sensitivity analysis
- transferability of the results.

Assessing the quality of the effectiveness data depends on the data used; whether it was sourced from a meta-analysis of RCTs, from a single study or from expert opinion.<sup>(5)</sup> Where the effectiveness data is created from a range of sources, consideration should be given to the literature review including: which databases or sources were included in the search, the inclusion and exclusion criteria applied and whether enough information was provided on the included studies.<sup>(5)</sup>

Assessing the quality of the cost analysis should focus on which costs were included in the study (this will depend on the perspective adopted), and how the associated resource quantities were measured and valued (costs assigned).<sup>(5)</sup>

For modelling studies a key aspect is the validity of the model. It should be clear how the internal and external validity of the model was tested. The external validity of the model can be tested in a number of ways including a comparison of the results with those generated by other models. Where differences exist, they should be clearly described and justified. Calibration of the model using independent data may also be used, again with discrepancies in the findings explained. Counterintuitive results generated by the model should also be justified. Probabilistic sensitivity analyses (PSA) can be used in model-based economic evaluations to account for parameter uncertainty. PSA considers the uncertainty in a parameter value through assigning a probability distribution to each parameter. Assessing the quality in this instance should concentrate on whether suitable distributions were used and whether relevant assumptions were investigated.

Documenting the strengths and limitations of included studies indicates whether the results are unduly influenced by features in the study conduct or design. It is important to do this in a way that is relatively objective, reproducible and documented. Given the unavoidable subjectivity among reviewers, it is considered good practice to use a specified tool when performing a quality assessment of the papers.<sup>(7)</sup> There are a number of quality scoring systems which can be used to assess the quality of an economic evaluation, for example the Quality of Health Economic Studies (QHES) list,<sup>(12)</sup> and the Pediatric Quality Appraisal Questionnaire (PQAQ).<sup>(13)</sup> These generally involve completing checklists, assigning a value to each of the different questions and adding up the values to obtain a final score, to indicate the quality of the economic evaluation. None of the currently published quality scoring systems are considered sufficiently valid or reliable to use for quality assessment. Instead, presenting a descriptive critical assessment or a checklist – which describes the methods, results, strengths and limitations of the economic evaluation and its conclusions – is preferred.<sup>(5)</sup> Checklists can help ensure that the design, objectives, and study methods are of an acceptable standard. They may be useful in preparing a report to obtain an overview of the reviewed literature.<sup>(7)</sup> There are a number of reliable, comprehensive, and easy to use checklists available that can be used to aid in the critical appraisal of economic evaluation studies. While no checklist has a published a formal validation, the CHEC-List<sup>(14)</sup> and the BMJ checklist<sup>(11)</sup> have received more examination than most.<sup>(14;15;15)</sup> These two checklists and the Philips<sup>(15)</sup> checklist are described in detail in the next sections of this report.

On completion of the quality review, a decision will need to be made on whether the quality is too poor and thus the study should be excluded from any summary of the literature, or whether it should be included, but with clear caveats presented. This decision is likely to be a pragmatic one particularly where there is limited available evidence.

### **3.3.1 Consensus on Health Economic Criteria (CHEC)-list**

The CHEC-list was developed by a consortium of international experts as a tool to facilitate assessment of the methodological quality of economic evaluations in systematic reviews.<sup>(14)</sup> The aim of the project was to identify a core set of items that could be used to assess the quality of economic evaluations that are being considered for inclusion in a systematic review. While recognised as a minimum set (inclusion of other criteria may be appropriate in specific circumstances), it was proposed that use of the tool would increase the transparency and comparability of systematic reviews, thus facilitating their interpretation and usefulness.<sup>(14)</sup>

The CHEC-list is suitable for systematic reviews that include full economic evaluation studies based on clinical studies (cohort studies, case-control studies, randomised

controlled trials). The focus on clinical studies was due to practical considerations, e.g. the CHEC-list cannot be used in studies based on modelling or scenario-analysis, as other methodological criteria are relevant when using these designs. Furthermore, the criteria list is limited to systematic reviews based on full economic evaluation studies, that is, studies that compare two or more alternatives, and in which both costs (inputs) and consequences (outputs) of the alternatives are examined. Finally, the criteria list does not consider the more general design characteristics of clinical trials (such as blinding and protocol deviation).<sup>(14)</sup>

The Cochrane handbook recommends using the *British Medical Journal* (BMJ) checklist (see below) and the CHEC-list to inform critical appraisal of the methodological quality of full economic evaluations carried out alongside effectiveness studies, and use of a subset of applicable checklist items, to inform critical appraisal of partial economic evaluations.<sup>(4;14)</sup> A copy of the CHEC-list is included in Appendix 4.

### **3.3.2 *British Medical Journal* (BMJ) checklist**

The BMJ checklist for authors and peer reviewers of economic submissions is one of the most commonly used checklists. It focuses on full economic evaluations considering both costs and consequences and comparing two or more healthcare technologies.<sup>(11)</sup>

Two versions are available: a full 35-item version and a shorter 10-item version. Additionally, a 36<sup>th</sup> question relating to generalisability can be added where it is relevant. This checklist lacks detailed coverage of modelling issues, thus if the review of health economic evaluation studies includes modelling studies, it may be necessary to supplement the checklist by using specific items, for instance, model type, time horizon, structural assumptions and health states.<sup>(5)</sup> Alternatively, a checklist created to consider the quality of models in economic evaluations may be used for the critical appraisal of the methodological quality, since the BMJ checklist is relevant, but inadequate for modelling studies.<sup>(4;14)</sup>

As noted above, the Cochrane handbook recommends using the BMJ checklist and the CHEC-list to inform critical appraisal of the methodological quality of full economic evaluations carried out alongside effectiveness studies, and use of a subset of applicable checklist items, to inform critical appraisal of partial economic evaluations.<sup>(4;14)</sup> A copy of the BMJ checklist is included in Appendix 4.

### **3.3.3 Philips checklist**

There are a wide range of methods used in economic evaluations; the methodological rigour can vary with some methods used inappropriately which can

influence the quality and the validity of the findings.<sup>(5)</sup> Philips et al.<sup>(15)</sup> developed a checklist for the critical appraisal of economic modelling studies. The list comprises three categories of questions relating to the model structure, data and consistency. For modelling studies the checklist developed by Philips<sup>(15)</sup> is more detailed and addresses modelling aspects more thoroughly than either the BMJ or the CHEC-list tools.

The Cochrane handbook recommends using the Philips checklist to inform critical appraisal of the methodological quality of economic modelling studies.<sup>(4;14)</sup> A copy of the Philips checklist is included in Appendix 4.

### **3.3.1 Assessing quality**

*For all relevant studies, an assessment of their quality should be determined using an appropriate checklist for economic evaluation studies. This should be performed independently by two or more reviewers.*

## **4 Summarising and Interpretation**

Once all the relevant literature of sufficient quality has been selected, the scope for transferability of the results to the Irish setting must be considered. There is considerable overlap between the quality assessment and an assessment of the transferability of results. Thus, the quality assessment may be a useful starting point in helping to interpret and explain disparities in results across economic evaluations.

This chapter will look at frameworks which can be used to assess study transferability, followed by a review of the key elements to be considered regardless of the framework used.

### **4.1 Assessing applicability and transferability**

Although increasingly common as a prerequisite to reimbursement, the cost-effectiveness of health technologies, and in particular non-pharmaceuticals, is only assessed in a limited number of countries. With an increasing demand for evidence, but limited resources and a scarcity of evidence created in the Irish setting, there is a need to maximise the use of available international studies. This poses a question. Is it possible to transfer results of an economic evaluation across jurisdictions to assist in making market access and reimbursement decisions in a timely fashion? The key question becomes whether the results of the study are applicable to your particular country. Numerous reasons exist why the economic evaluations of health technologies may vary between countries, including differences in the availability of healthcare resources, the incidence of the disease, relative prices and clinical practice patterns.<sup>(16)</sup> In a review of economic evaluations of medicines carried out in Western Europe, there was up to a two-fold difference in the estimate of the incremental cost-effectiveness ratio (ICER)<sup>(16)</sup> – with potential implications for the reimbursement decision if an evaluation was adopted without consideration of its transferability to the Irish setting.

A reasonable amount of literature exists on methods for the critical appraisal of the transferability potential of economic evaluations. Following a systematic review of the literature, Goeree et al.<sup>(17)</sup> provided an overview of the approaches and tools used for assessing the transferability potential and for transfer of economic evaluations. They identified seven distinct tools, flow charts and checklists that specifically considered transferability. All of the studies provided a checklist of factors for consideration and most identified a set of factors critical to assessing study transferability potential. These critical factors mostly relate to the study quality, the level of reporting of methods and results, the transparency of methods, and the relevance of comparators. Some studies suggested using a flow chart, with others suggesting an initial assessment of the critical criteria, before assessing other non-

critical factors. Use of a quantitative score to measure the transferability potential was also proposed.

Three of the most commonly used and user-friendly tools are those developed by EUnetHTA,<sup>(18)</sup> Welte et al.<sup>(19)</sup> and ISPOR<sup>(3)</sup> which are discussed in the following sections.

#### **4.1.1 EUnetHTA model**

The European Network of Health Technology Assessment (EUnetHTA) has developed a Core Model for HTA that aims to define and standardise elements of HTA.<sup>(18)</sup> By reducing differences in content across reports, this Core Model could facilitate future automated and international use of HTA. A review of the transferability of each assessment element and the extent to which transferability of that element is important is included in the Core Model.

A series of checklists, resources and questions has been created to help researchers select potentially relevant information for their jurisdiction. The toolkit consists of two parts:<sup>(18)</sup>

- 1) Speedy sifting – a tool for quick screening to consider the relevance of an economic evaluation for adaptation.
- 2) Main toolkit – a comprehensive checklist with questions on relevance, reliability and issues regarding transferability.

Speedy sifting:

- 1) Are the policy and research questions being addressed relevant to your questions (Yes / No)?
- 2) What is the language of this HTA report? Is it possible to translate this report into your language? (Yes / No)?
- 3) Is there a description of the health technology being assessed (judgment needed)?
- 4) Is the scope of the assessment specified (judgment needed) (study question, alternatives considered, perspective, endpoints and so on)?
- 5) Has the report been externally reviewed (judgment needed)?
- 6) Is there any conflict of interest (judgment needed)?
- 7) When was the work that underpins this report done? Does this make it out of date for your purposes (judgment needed)?
- 8) Have the methods of the assessment being described in the HTA (judgment needed)?

Using the results of the speedy sifting, researchers can decide whether to create a new HTA report, seek further data or continue to the main section of the toolkit. The speedy sifting questions are comparable to critical criteria suggested in other systems.<sup>(17)</sup>

The main section of the toolkit consists of five domains (technology use, safety, effectiveness or efficacy, economic evaluation and organisational features). Each domain consists of a series of questions to assess specific relevance, reliability and transferability. The answers aid users in extracting information from the HTA report, and incorporating it within a local HTA report. The data may need to be updated and or supplemented with local contextual data. The main toolkit can be used either in its entirety for five domains or can be useful in adapting information within one or a subset of domains.<sup>(17)</sup> If, after using the toolkit, the data under assessment is found to be unreliable and or untransferable, then creating a local HTA report should be considered.

In the context of a review of economic evaluations, the questions in the economic evaluation domain of the EUnetHTA model combine a quality assessment, an assessment of relevance and an assessment of the transferability. The economic evaluation domain comprises 26 questions covering the reliability and relevance with three questions addressing the transferability. For the transferability, the following 15 key parameters are identified:<sup>(18)</sup>

- perspective
- preferences
- relative costs
- indirect costs
- discount rate
- technological context
- personnel characteristics
- epidemiological context (including genetic variants)
- factors which influence incidence and prevalence
- demographic context
- life expectancy
- reproduction
- pre- and post-intervention care
- integration of technology in healthcare system
- incentives.

Each parameter is considered and the following question asked: Are there differences in the parameters? If differences exist, how likely is it that each factor would impact on the results? In which direction? To what magnitude? Taken together, how would

they impact on the results and to what magnitude? Given these potential differences, how would the conclusions likely change in the target setting? Are you able to quantify this in any manner?<sup>(18)</sup>

A copy of the reliability, relevance and transferability questions for the economic evaluation domain of the EUnetHTA core model are included in Appendix 5.

#### **4.1.2 Welte model**

Welte et al.<sup>(19)</sup> created a framework examining the transferability of international studies. It allows both an assessment of the transferability of the economic evaluation results and an identification of both the factors which require most adjustment and what measures could improve transferability. Hence, it aids in prioritising adjustments and determines what data should be gathered. It demonstrates that the more complex an economic evaluation is, the more effort is needed to consider the transferability.

The proposed approach to transferability consists of five steps:<sup>(19;20)</sup>

1. Consider general knock-out criteria which assess the eligibility for transferability.
2. Consider the specific knock-out criteria.
3. Estimate the relevance of a specific knock-out criteria.
4. Estimate correspondence between two countries relating to these specific knock-out criteria.
5. Estimate the effect on the ICER of the decision country.

Welte et al.<sup>(19)</sup> begins with three general knock-out criteria that identify studies that are not considered transferable. If the answer to any of the following questions is yes, then the study should not be transferred.

1. Evaluated technology not comparable to the one used in decision country?
2. Comparator is not comparable to decision country?
3. Study does not possess an acceptable quality?

After the general knock-out criteria are met, a checklist of 'specific knock-out' criteria is then considered. Welte's<sup>(19)</sup> specific knock-out criteria comprises 14 factors grouped into three categories:

- Methodological characteristics
  - perspective
  - discount rate
  - medical cost approach
  - productivity cost approach

- Healthcare characteristics
  - absolute and relative prices
  - practice variation
  - technology variation
- Population characteristics
  - incidence/prevalence
  - casemix
  - life expectancy
  - health-status preferences
  - acceptance, compliance and incentives to patients
  - productivity and work-loss time
  - disease spread.

Each of the 14 transferability factors should be reviewed in turn with consideration first given to the relevance of the factor (ranging from not relevant, very low relevance to very high relevance) to the study in question. If it is considered relevant, the correspondence between the two countries is then estimated (rated from very low to very high) and then finally the likely effect on the ICER of the decision country is estimated (unbiased, too low, too high). If a factor cannot be assessed, due to insufficient data from either the study or the decision country, it is noted that this may constitute a special knock out criterion.<sup>(17)</sup>

The checklist by Welte et al. is a pragmatic rather than a purely scientific approach, as it a descriptive estimate of the transferability factors' relevance and correspondence. Thus, it is in general suitable only for 'ad hoc' advice.<sup>(19)</sup>

#### **4.1.3 ISPOR model**

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has developed a questionnaire to assess the relevance and credibility of modelling studies for informing healthcare decision making.<sup>(3)</sup> It considers both the credibility and the relevance of economic evaluation models and aims to answer the question: can this economic evaluation be used to inform healthcare decisions?

The ISPOR questionnaire consists of 15 questions related to the relevance and credibility of a modelling study. The questionnaire begins with the following four questions to assess the relevance of the study:<sup>(3)</sup>

1. Is the population relevant?
2. Are any critical interventions missing?
3. Are any relevant outcomes missing?
4. Is the context (settings and circumstances) applicable?

Each of these four questions is supported by helper questions to aid users. Based on the responses to these questions, a study is considered to be either sufficient or insufficient to answer the healthcare decision. If the relevance of a modelling study is considered to be sufficient, then the assessment proceeds to the next set of questions.

The credibility of the study is then captured with questions in the following seven domains: validation, design, data, analysis, reporting, interpretation, and conflict of interest. Based on responses to the individual questions, each domain is assessed as a strength, neutral, weakness, or fatal flaw. If a response triggers a 'fatal flaw' indicator, the domain is marked as a fatal flaw, indicating that the modelling study has serious credibility issues. Based on the domain assessments, the overall credibility of the modelling study is judged as sufficient or insufficient.<sup>(3)</sup>

A copy of the ISPOR questionnaire is included in Appendix 5 and also available on line at <http://www.ispor.org/modeling-health-study-use-guideline.pdf> .

The ISPOR questionnaire is considered the most user-friendly of the three tools that have been described in this section and may be the most suitable for those with limited experience. Each question is accompanied by helper questions to aid understanding and there is also an interactive version of the tool available on-line at <https://www.healthstudyassessment.org/> which allows users to save their responses and to store the relevant articles.

#### **4.1.1 Assessing transferability**

*The transferability of the study results should be considered for all relevant studies that have an acceptable quality. This should be conducted using a defined framework; any reasons for a lack of transferability clearly documented and any expected differences in the Irish setting explicitly stated (such as intervention to prevent transmission of infection would be more cost-effective due to a higher disease prevalence).*

#### **4.2 Factors to consider when assessing transferability**

Transferability factors are factors that may impact on the results of an economic evaluation and should be considered when attempting to transfer results of economic evaluation studies between countries. The key factors mentioned vary considerably in the literature, depending upon the level of detail and categories used.<sup>(19)</sup> Some factors that limit transferability include: basic demography and epidemiology of disease (age structure of the population, incidence of various diseases, and so on), availability of health resources and variation in clinical practice (range of treatments, clinical guidelines), incentives to healthcare professionals and institutions (physicians fee-for-service or salary; hospital input or output based), relative prices or costs

(process do not reflect costs, difference in relative prices affect CEA) and population values (value of health state preferences may vary by demographic area). The clinical effectiveness is unlikely to limit transferability, as biological differences between countries are often small. A good understanding of the most relevant factors and their potential influence on the ICER is necessary when considering the transferability of economic evaluations.

The following sections discuss some of the key factors to be considered when assessing transferability of results.

#### **4.2.1 Perspective**

The perspective of an economic evaluation is the viewpoint from which the evaluation is conducted (such as public payer, individual, society) and defines whose costs, resources and consequences should be examined.

The preferred perspective, for the reference case, in Ireland is that of the publicly funded health and social care system with a view to providing advice that maximises health gain for the population and represents the most efficient use of the finite resources available within the health services budget.<sup>(21)</sup> Consistent with this outlook, all health effects accruing to individuals (QALYs, life-years gained, and so on) should be included in the outcomes for the reference case. Only costs and resource requirements relevant to the HSE should be included in the analysis. If the inclusion of a wider societal perspective is expected to impact significantly on the results of the analysis, this may be presented as a secondary analysis in addition to the reference case analysis.

Other jurisdictions, however, may recommend a societal perspective to be used, for example, the Netherlands and Germany. Adopting a societal perspective that captures all relevant costs and consequences of the technologies in question, regardless on whom these costs and consequences fall, is considered the most comprehensive approach that can be taken.<sup>(22)</sup> These may include direct and indirect costs, including productivity costs, as well as additional costs, savings or other benefits such as non-resource effects (for instance, improved educational attainment) that may accrue to other public sector agencies, patients or their carers as a result of a technology.

Where the perspective used in the literature differs, this may impact on the measurement of both the cost and effectiveness elements of the ICER.<sup>(19)</sup> A technology might be cost-effective from a societal perspective, but not from a narrower health services perspective. For example, a health technology may lead to higher hospital costs, initially, but these may be offset by cost savings elsewhere, for instance an earlier return to work.<sup>(7)</sup> However, it is possible for the opposite to occur

where a societal perspective is less cost-effective; for instance, an accelerated treatment regime could save certain hospital costs if patients are discharged quicker. This might mean, however, that the cost of care for the interval between the faster and usual discharge dates may be passed on to care homes or relatives. For studies that adopt a societal perspective, it is possible that the data may be presented in a disaggregated form showing the analysis from several perspectives, so that the researcher may transfer the relevant cost data.<sup>(11)</sup>

#### **4.2.2 Time Horizon**

Health economic evaluations frequently need a long time horizon to capture all the relative costs and benefits of the interventions compared.<sup>(20)</sup> A lifetime horizon is usually considered appropriate as the majority of technologies have costs and outcomes that impact over a patient's lifetime. This is particularly pertinent for chronic diseases such as diabetes. A shorter time frame may be considered when the costs and outcomes relate to a relatively short period of time, such as in an acute infection, and when mortality is not expected to differ between the competing technologies.

The use of extrapolation modelling is typically required when adopting a lifetime horizon as long-term primary data on the safety and effectiveness of a new technology will only be available after the product has been in routine clinical use for some time. When extrapolating data beyond the duration of the clinical trials, assumptions regarding future treatment effects and disease progression will be made. Consideration needs to be paid to whether these assumptions are valid and if they would differ in the Irish setting; it may be helpful to discuss these assumptions with clinicians or patient representatives. Where for practical reasons, such as a lack of available evidence, the time horizon is reduced, any possible bias introduced as a result should be considered.<sup>(11)</sup>

#### **4.2.3 Clinical Effectiveness**

Clinical effectiveness is generally considered to be transferable across jurisdictions. However, there are aspects to the effectiveness estimates that need review. The applicability of the effectiveness data, which may be sourced from a clinical trial or meta-analysis must be considered. (See clinical effectiveness guidelines for further details.) Is the study population that the clinical effectiveness data was based on sufficiently similar? For example, in countries with a small pharmaceutical market, there is usually less interest in including patients in Phase IIIb or Phase IV clinical trials. In such situations, jurisdiction-specific data on effectiveness would be unavailable.<sup>(16)</sup> Are compliance rates reasonable? Clinical trials may typically have unrealistically high compliance rates.<sup>(11)</sup> Is persistence with the healthcare intervention longer than would be expected in practice? Where a specific device is

used, then this should not be generalised to other similar devices or subsequent generations of a device unless it can be shown that they are at least equivalent and that the synthesised evidence is appropriately adjusted to account for differences.

Any differences in clinical practice, for instance the treatment setting or care pathway, should be noted and consideration given to how this would affect both the cost and effectiveness.

#### **4.2.4 Health-related quality of life**

Health-related quality of life (HRQoL) has been defined as a broad theoretical construct developed to explain and organise measures concerned with the evaluation of health status, attitudes, values and perceived levels of satisfaction and general wellbeing with respect to either specific health conditions or life as a whole from the individual's perspective.<sup>(23)</sup>

A quality-adjusted life year (QALY) is a measure of an individual's length of life that has been adjusted for the health-related quality of that life. Gains or losses in the quantity of life (mortality) and quality of life (morbidity) are therefore combined into a single health outcome measure.<sup>(23)</sup> Use of the QALY as an outcome measure has two main advantages: it incorporates a measure of value or preference for different health states; and as a single generic outcome measure, it facilitates comparisons between different health programmes as it is universally applicable to all patients and diseases. Adopting QALYs as the preferred outcome measure facilitates comparisons with previous HTAs conducted in Ireland.

Weighted measures of HRQoL (utilities) are used to calculate QALYs. This weighting of HRQoL usually comprises two elements: a description of the health state and a valuation of that description. The preferences captured can include that of the patient or the informed general public. Utilities may be measured directly (using standard gamble or time trade-off) or through a generic tool such as the EQ-5D<sup>(24)</sup> or SF-6D.<sup>(25)</sup> The generic tools use data on the HRQoL obtained from patients, but generate a utility score using preference values obtained from an 'informed' general public. Despite the apparent advantages of the QALY, its valuation may be inconsistent as utility weights used in its calculation are instrument dependent.

The transferability of health-state preferences is unknown. EQ-5D is often used and was developed to compare preferences across countries, with 15 (additive) value sets available. While the impact of using any of the value sets on the utilities is known, the impact on incremental utilities is unknown. There are differences between national EQ-5D value sets and as such it may not always be advisable to transfer utilities between countries - currently there are no value sets available for Ireland. An extended version of the EQ-5D, the EQ-5D-5L, which contains five levels

within each of the five dimensions, has recently been produced and has been used both nationally and internationally. The differences in value sets are due both to the methodological issues in how the value sets were constructed (time-trade-off, visual analogue scale [VAS]) and cultural differences. Thus the source and relevance to an Irish population of any QALYs used should be noted, and consideration paid to any differences among studies.

#### **4.2.5 Costing approaches**

How the various cost elements are valued (charges or fees, per diem costs [costs for each day], market prices, the approach to the inclusion of overheads, capital costs and maintenance) will affect the potential transferability of results, so the potential influence of all cost elements should be considered. For example, for a hospital interested in the cost-effectiveness of a new diagnostic device, the results from an economic evaluation that used only per diem costs would not be suitable due to the high aggregation level of the costs.<sup>(19)</sup>

Productivity costs are usually measured using the friction cost method or the human-capital approach. These methods lead to similar results only where the duration of the productivity loss is less than, or equal to the estimated friction time. Where it is higher, the human-capital approach results in higher productivity costs. Additionally, the productivity loss could be valued differently. Frequently used approaches are wages for paid work and substitution costs for unpaid work for instance housework.<sup>(19)</sup> In Ireland, the preferred perspective is that of the HSE, and as such the guidelines do not currently specify a suggested approach for measuring productivity costs.

#### **4.2.6 Modelling**

There are a number of different modelling techniques which may be used, and the decision regarding which method is appropriate will depend on the research question being investigated. These include decision-tree analysis, state-transition or Markov models, and discrete-event simulation (DES). Decision trees can be useful for relatively simple models, or decision problems with special characteristics (such as very short time horizons). State-transition or Markov models are useful where the disease or treatment pathway can be represented as a series of mutually exclusive states. Cohort Markov models generally do not depend on past history, which can be disadvantageous although this can be addressed by the use of individual-level simulations. When the disease or treatment pathway includes interactions between individuals and or their environment, discrete-event simulation methods are preferable. These models are also useful when variable rather than fixed-time intervals are used.<sup>(26)</sup>

A model is a simplification of reality, how suitable this simplification is will need to be considered.<sup>(11)</sup> The inputs and outputs of the model should reflect the nature of the decision problem and the model structure should reflect the true nature of the disease process being modelled as closely as possible. For state transition models such as Markov models, the cycle length should be sufficiently short to ensure that multiple changes in disease, treatment decisions or costs do not occur within a single cycle. Limitations in data may constrain choices regarding the model structure. Differences within the modelled population in terms of event probabilities, outputs and costs should be minimised where possible by splitting the population into biologically or clinically plausible subgroups. For example, cancer patients at different stages of disease at diagnosis may follow different care pathways (and thus incur different costs) and have different survival probabilities.

Consideration should be given to whether the model structure, the assumptions which underpin it, and all data inputs adequately reflect the Irish situation.

#### **4.2.7 Discounting**

Costs and health outcomes that occur in the future should be discounted to present values to reflect society's rate of time preference. Accordingly, costs or outcomes occurring beyond one year should be discounted using standard methods. The appropriate discount rate is debatable, and should reflect the relevant national economic conditions,<sup>(16)</sup> frequently 3 or 5% (both for costs and outcomes) is recommended in international guidelines.<sup>(20)</sup> Some jurisdictions allow for differential discounting, whereby a (typically) lower rate of discounting is applied to benefits. For interventions where the potential benefits are not realised for a long time, for instance an immunisation programme, some jurisdictions use a non-constant rate of discounting.<sup>(27)</sup> In Ireland, a standard rate of 5% per annum for costs and outcomes is recommended.<sup>(28)</sup>

Different discount rates might have a considerable impact on the ICER of interventions where the intervention is associated with future effects or costs.<sup>(19)</sup> For instance, a vaccination programme will have immediate costs, but projected future savings. Therefore, if considering the transferability of a study that uses a discount rate higher than the 5% currently recommended in Ireland, the estimated benefits will be reduced, leading to an overestimate of the ICER (that is to say, the technology would be considered less cost-effective) in the Irish setting. It should be noted that the longer the time horizon, the larger the impact of differences in the discount rate.

#### **4.2.8 Sensitivity analysis**

The primary purpose of sensitivity analysis is to inform the decision maker regarding the certainty and robustness of the results and conclusions of the economic analysis. It involves the systematic examination of the influence of the variables and assumptions used in an evaluation.<sup>(29)</sup> In a sensitivity analysis, critical component(s) in the calculation are varied through a relevant range or from worst case to best case, and the results recalculated. Sensitivity analysis may also include the use of alternate model structures, where structural uncertainties are present.

Models will frequently require numerous additional parameters which may be directly or indirectly related to the effectiveness of a technology (for example, uptake rate, disease severity). The values for these sorts of parameters will often be informed by local data on disease prevalence, service utilisation and expert opinion. As they are not typically derived from systematic review, care must be taken to adequately address potential bias in the parameter estimates and to take into account the uncertainty or lack of precision in the estimates. As such, a sensitivity analysis should also include these parameters. Where expert opinion is used, it should be sought in a manner which minimises bias and the process should be documented in sufficient detail.<sup>(30)</sup>

The results of a sensitivity analysis can prove particularly useful when considering the transferability of study results to the Irish setting. The results of a sensitivity analysis should highlight which variables have the greatest influence on the ICER. If the sensitivity analysis encompasses parameter values relevant to the Irish healthcare setting, it can provide useful information on the applicability of the results to Ireland.

Frequently, only uncertain parameters are investigated in the sensitivity analysis, however, it is important to remember that the certain parameters are no less critical when considering transferability.<sup>(19)</sup>

#### **4.2.9 Threshold**

One of the implications of making comparisons regarding the cost-effectiveness of different technologies is that a reference value for the ICER is required, above which technologies are considered not to be cost-effective. This is because the additional cost for an additional unit of effect is considered too high and below which they are considered to be cost-effective.<sup>(31)</sup> This reference value is referred to as the cost-effectiveness threshold. The principle of what a cost-effectiveness threshold represents and how it should be used in decisions regarding the allocation of healthcare resources has been a source of significant debate in other countries. The threshold will vary by jurisdiction. Within jurisdictions, it may vary over time and may

also differ in certain circumstances, for example in the case of ultra-orphan drugs.<sup>(32)</sup> The issue of orphan drugs in Ireland is discussed in more detail in the National Rare Disease Plan for Ireland 2014-2018.<sup>(33)</sup> Thus, it is important to consider the actual ICER reported in an economic evaluation rather than whether it is considered cost-effective.

In Ireland, in line with the current agreement between the Irish Pharmaceutical Healthcare Association (IPHA) and the Department of Health, pharmaceuticals reimbursed through the Primary Care Reimbursement Service (PCRS), with an ICER of less than €45,000 per QALY are reimbursed as specified. This threshold does not apply, however, to non-pharmaceuticals. Historically, the threshold in Ireland has varied between €20,000 and €45,000 per QALY, although reimbursement below these levels was not guaranteed and technologies above these thresholds have been adopted. For reporting purposes, it is pragmatic to report the probability of cost-effectiveness at thresholds of €20,000 and €45,000 per QALY.

#### **4.2.1 Transferability Factors**

The following key factors should be considered when assessing the transferability of results: perspective, time horizon, clinical effectiveness, health-related quality of life, costing approaches, modelling approach, discount rate, results of any sensitivity analyses and the implications of the cost-effectiveness result relative the notional threshold used in Ireland.

### **4.3 Summarise the literature**

The report should be well structured with information provided on each of the elements outlined in these guidelines. The characteristics and limitations of the studies included in the review should be clearly documented and a summary table of results should be included. To aid comparisons across studies, disaggregated costs and QALYs should be presented where available and all costs should be reported in euro. Retrospective costs should be inflated to the most recent calendar year using the Consumer Price Index for health (see Appendix 6 for an example).<sup>(34)</sup> If transferring costs from another country, the inflation should be calculated using the Consumer Price Index for the local currency prior to conversion to the Irish equivalent in euro using Purchasing Power Parity (PPP) indices (see Appendix 7 for an example).<sup>(35)</sup> PPP indices are used to convert local currency into international currencies by taking into account the difference in price level and purchasing power between countries. The PPP theory uses the long-term equilibrium exchange rate of two currencies to equalise their purchasing power. This purchasing power exchange rate equalises the purchasing power of different currencies in their home countries for a given basket of goods.

The report should address the needs of the target audience, that is, to provide sufficient information to them to critically evaluate the validity of the report and its findings. The review might be restricted to only include economic studies that used clinical evidence from a high quality source (such as from a systematic review or an RCT). Other considerations may include, for instance, whether to exclude economic evaluations which take a societal perspective.<sup>(5)</sup> Any conclusions should be clear, for instance, where the purpose of review is to consider whether a local HTA is necessary or if current literature is sufficient for the Irish context.

#### **4.3.1 Clear structured report**

*A well structured report should be provided which summarises the available literature and its relevance to the Irish context, with information provided on each of the elements outlined in the guidelines.*

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## 6 Glossary of terms and abbreviations

Some of the terms in this glossary will not be found within the body of these guidelines. They have been included here to make the glossary a more complete resource for users.

**Bias:** systematic (as opposed to random) deviation of the results of a study from the 'true' results.

**Baseline:** a term used to describe the initial set of measurements taken at the beginning of a study (after a run-in period, when applicable).

**Blinding:** when study participants, caregivers, researchers and outcome assessors are kept unaware about the technologies that the people have been allocated to in a study.

**Capital costs:** the costs of buying land, buildings or equipment (such as medical equipment) to provide a service (such as healthcare).

**CBA:** cost-benefit analysis.

**CCA:** cost-consequences analysis.

**CEA:** cost-effectiveness analysis.

**CMA:** cost-minimisation analysis.

**Comparator:** the alternative against which the intervention is compared.

**Consumer Price Index:** this index maintained by the Central Statistics Office measures the change in the average price levels (including all indirect taxes) paid for consumer goods and services by all private households in Ireland and by foreign tourists holidaying in the country.

**Cost:** the value of opportunity forgone, as a result of engaging resources in an activity (see opportunity cost). There can be a cost without the exchange of money; the range of costs (and benefits) included in a particular economic evaluation depends on perspective taken. Average costs are average cost per unit of output (that is to say total costs divided by total number of units produced). Incremental costs are extra costs associated with intervention compared to alternative; marginal cost is cost of producing one extra unit of output.

**Cost, financial:** the monetary value of providing a resource accounted for in the budget of the provider.

**Cost analysis:** a partial economic evaluation that only compares the costs in monetary units of the proposed technology with its main comparator(s).

**Cost-benefit analysis (CBA):** an economic evaluation that compares the proposed technology with its main comparator(s) in which both costs and benefits are measured in monetary terms to compute a net monetary gain/loss or benefit gain/loss.

**Cost-consequences analysis (CCA):** an economic evaluation that compares the proposed technology with its main comparator(s) as an array of all material costs and outcomes measured in their natural units rather than a single representative outcome as presented in a cost-effectiveness analysis.

**Cost-effective (value for money):** a proposed technology is considered cost-effective for a specified main indication if the incremental benefits of the proposed technology versus its main comparator(s) justify its incremental costs and harms.

**Cost-effectiveness:** a comparison of both the costs and health effects of a technology to assess whether the technology provides value for money.

**Cost-effectiveness analysis (CEA):** an economic evaluation that compares, for example, a proposed technology with its main comparator(s) having common clinical outcome(s) in which costs are measured in monetary terms and outcomes are measured in natural units (for example, reduced mortality or morbidity).

**Cost-minimisation analysis (CMA):** an economic evaluation that finds the least costly alternative technology, for example, after the proposed technology has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and adverse events.

**Cost-utility analysis (CUA):** an economic evaluation that compares the proposed technology with its main comparator(s) in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension (such as using quality-adjusted life years [QALYs]).

**Critical appraisal:** a strict process to assess the validity, results and relevance of evidence.

**CUA:** cost-utility analysis.

**Data synthesis:** combining evidence from different sources.

**Decision tree:** a graphical representation of the probable outcomes following the various decision options in a decision analysis.

**Direct costs:** the fixed and variable costs of all resources (goods, services, and so on) consumed in the provision of a technology as well as any consequences of the intervention such as adverse effects or goods or services induced by the intervention. These include direct medical costs and direct non-medical costs such as transportation or child care.

**Direct medical costs:** Medical costs that vary with the healthcare provided (such as doctors' salaries).

**Direct non-medical costs:** the non-medical costs of treating a patient (such as transportation provided to and from a medical appointment).

**Disability-adjusted life years (DALYs):** a unit of healthcare status that adjusts age-specific life expectancy by the loss of health and years of life due to disability from disease or injury. DALYs are often used to measure the global burden of disease.

**Discounting:** the process used in economic analyses to convert future costs or benefits to present values using a discount rate. Discounting costs reflects societal preference for costs to be experienced in the future rather than the present. Discounting benefits reflects a preference for benefits to be realised in the present rather than at a later date.

**Discount rate:** the interest rate used to discount or adjust future costs and benefits so as to arrive at their present values (such as 4%). This is also known as the opportunity cost of capital investment.

**Discrete-event simulation (DES):** a collection of techniques for modelling one or more phenomena of interest in a system that change value or state at discrete points in time. DES allows all characteristics of the system to be represented. Unlike Markov models, the primary focus in DES is on the occurrence of events rather than transitions or states. (See also **Markov Model**.)

**Economic evaluation:** application of analytical methods to identify, measure, value, and compare costs and consequences of alternatives being considered. It addresses issue of efficiency to aid decision making for resource allocation. It is an umbrella term covering CBA, CEA, CMA and CUA.

**Economic model:** economic models provide a means of bringing together different types of data from a range of sources and provide a framework for decision making under conditions of uncertainty. Modelling may be used to combine different data sets changing the information collected from a clinical trial into a form that can be used to extrapolate short-term clinical data to the longer term; to link intermediate with final endpoints; to generalise from clinical trial settings to routine practice; and to estimate the relative effectiveness of technologies where these have not been directly compared in clinical trials.

**Effectiveness:** the extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) in routine clinical practice (contrast with **Efficacy**).

**Efficacy:** the extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) when studied under controlled research conditions (contrast with **Effectiveness**).

**EQ-5D:** the EQ-5D is a standardised instrument (questionnaire) used to measure health outcomes. The instrument is applicable to a wide range of health conditions and treatments and can be used to generate a single index value for health status. The EQ-5D questionnaire describes five attributes (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) each of which has three levels (no problems, some problems, and major problems). This combination defines 243 possible health states which added to the health states 'unconscious' and 'dead', allow for 245 possible health states. Each EQ-5D health state (or profile) provides a set of observations about a person by way of a five-digit code number. This EQ-5D health state is then converted to a single summary index by applying a formula that attaches weights to each of these levels in each dimension and subtracting these values from 1.0. Additional weights that are applied are a constant (for any deviation from perfect health) and a weight if any of the dimensions are at level three (major problems). The scores fall on a value scale that ranges from 0.0 (dead) to 1.0 (perfect health). For further information on EQ-5D see: [www.euroqol.org](http://www.euroqol.org).

**External validity:** the extent to which one can generalise study conclusions to populations and settings of interest outside study.

**Extrapolation:** prediction of value of model parameter outside measured range or inference of value of parameter of related outcome (such as extrapolation of reduction in rate of progression to AIDS from improvement in HIV viral load).

**Final outcome:** a health outcome that is directly related to the length of life (for instance, life-years gained or quality-adjusted life years).

**Follow up:** the observation over a period of time of study/trial participants to measure changes in outcomes under investigation.

**Generalisability:** the extent to which one can apply or extrapolate results obtained in one setting or population to another; term may also be referred to as 'transferability', 'transportability', 'external validity', 'relevance', or 'applicability'.

**Grey literature:** research reports that are not found in traditional peer reviewed publications (such as government agency monographs, symposium proceedings, and unpublished company reports).

**Gross or macro costing:** costing approach that uses large components as basis for costing, such as cost per hospital day; compare with **Micro-costing**.

**Health outcome:** a change (or lack of change) in health status caused by a therapy or factor when compared with a previously documented health status using disease-specific measures, general quality of life measures or utility measures.

**Health-related quality of life (HRQoL):** a combination of the physical, social and emotional aspects of an individual's life that are important for their wellbeing.

**Health technology:** the application of scientific or other organised knowledge – including any tool, technique, product, process, method, organisation or system – in healthcare and prevention. In healthcare, technology includes drugs, diagnostics, indicators and reagents, devices, equipment, and supplies, medical and surgical procedures, support systems and organisational and managerial systems used in prevention, screening diagnosis, treatment and rehabilitation.

**Health technology assessment (HTA):** this is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value.

**Incidence:** the number of new cases of a disease or condition that develop within a specific time frame in a defined population at risk. It is usually expressed as a ratio of the number of affected people to the total population.

**Incremental costs:** the absolute difference between the costs of alternative management strategies of the same medical condition, disease or disorder.

**Indirect costs:** the cost of time lost from work and decreased productivity due to disease, disability, or death. (In cost accounting, it refers to the overhead or fixed costs of producing goods or services.)

**Indirect preference measurement:** use of instruments (such as Health Utilities Index and EQ-5D) to measure preferences, without undertaking direct measurement.

**Intangible costs:** the cost of pain and suffering resulting from a disease, condition, or intervention.

**Internal validity:** a trial has internal validity if, apart from possible sampling error, the measured difference in outcomes can be attributed only to the different therapies assigned.

**Literature review:** a summary and interpretation of research findings reported in the literature. This may include unstructured qualitative reviews by single authors as well as various systematic and quantitative procedures such as meta-analysis.

**Markov Model:** a type of quantitative modelling that involves a specified set of mutually exclusive and exhaustive states (for example, of a given health status), and for which there are transition probabilities of moving from one state to another (including of remaining in the same state). Typically, states have a uniform time period, and transition probabilities remain constant over time.

**Meta-analysis:** systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. This combination may produce a stronger conclusion than can be provided by any individual study. (Also known as data synthesis or quantitative overview.)

**Micro-costing:** costing approach based on detailed resources used by patient on item-by-item basis; compare with **gross costing**.

**Non-randomised controlled trial (non-RCT):** a controlled clinical trial that assigns patients to intervention and control groups using a method that does not involve randomisation (such as at the convenience of the investigators or some other technique such as alternate assignment).

**Observational study:** a study in which the investigators do not manipulate the use of, or deliver, a technology (for example, do not assign patients to treatment and control groups), but only observe patients who are (and sometimes patients who are not as a basis of comparison) exposed to the intervention, and interpret the

outcomes. These studies are more subject to selection bias than experimental studies such as randomised controlled trials.

**Opportunity cost:** the value of the forgone benefits because the resource is not available for its best alternative use.

**Outcome:** consequence of condition or intervention; in economic guidelines, outcomes most often refer to health outcomes, such as surrogate outcomes or patient outcomes.

**Peer review:** the process by which manuscripts submitted to health, biomedical, and other scientifically oriented journals and other publications are evaluated by experts in appropriate fields (usually anonymous to the authors) to determine if the manuscripts are of adequate quality for publication.

**Perspective:** this is the viewpoint from which an economic evaluation is conducted. Viewpoints that may be adopted include that of the patient, the public healthcare payer or society.

**Purchasing power parity:** this theory states that in an efficient market, the exchange rate of two currencies results in equal purchasing power. The purchasing power indices are currency conversion rates that both convert to a common currency and equalise the purchasing power of different currencies. In other words, they eliminate the differences in price levels between countries in the process of conversion.

**Prevalence:** the number of people in a population with a specific disease or condition at a given time and is usually expressed as a ratio of the number of affected people to the total population.

**Primary study:** an investigation that collects original (primary) data from patients (e.g. randomised controlled trials, observational studies, series of cases, etc).

**Probability:** expression of degree of certainty that an event will occur, on scale from zero (certainty that event will not occur) to one (certainty that event will occur).

**Probability distribution:** portrays the relative likelihood that a range of values is the true value of a treatment effect. This distribution often appears in the form of a bell-shaped curve. An estimate of the most likely true value of the treatment effect is the value at the highest point of the distribution. The area under the curve between any two points along the range gives the probability that the true value of the treatment effect lies between those two points. Thus, a probability distribution can

be used to determine an interval that has a designated probability (e.g. 95%) of including the true value of the treatment effect.

**Probabilistic sensitivity analysis (PSA):** a type of sensitivity analysis where probability distributions are applied to a plausible range of values for key parameters to capture uncertainty in the results. A Monte Carlo simulation is performed and a probability distribution of expected outcomes and costs is generated. (Contrast with Deterministic sensitivity analysis).

**Productivity costs:** the costs associated with lost or impaired ability to work because of morbidity or death.

**Publication bias:** unrepresentative publication of research reports that is not due to the quality of the research but to other characteristics, e.g. tendencies of investigators to submit, and publishers to accept, positive research reports (i.e., ones with results showing a beneficial treatment effect of a new intervention).

**Quality-adjusted life year (QALY):** a unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years. QALYs can provide a common unit for comparing cost-utility across different technologies and health problems. Analogous units include Disability-Adjusted Life Years (DALYs) and Healthy-Years Equivalents (HYEs).

**Reliability:** the extent to which repeated measures of the same endpoint return the same value (See also **Validity**).

**Sensitivity analysis:** a means to determine the robustness of a mathematical model or analysis by examining the extent to which results are affected by changes in methods, parameters or assumptions.

**SF-36:** the SF-36 is a standardised instrument (questionnaire) used to measure health outcomes. It is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. For further information on SF-36, see: [www.sf-36.org](http://www.sf-36.org).

**Standard gamble:** a method of preference assessment used to measure utilities, that is, to ascertain an individual's preference for different health states that differ in quantity or quality of life. Preference is ascertained by choosing between a given

health state, or gambling between perfect health and immediate death. The probability of perfect health or immediate death is changed until the individual is indifferent between the health state and the gamble.

**Systematic review:** a form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from evidence base to formulate findings.

**Target population:** in the context of a budget impact analysis the individuals with a given condition or disease who might avail of the technology being assessed within the defined time horizon.

**Technology:** the application of scientific or other organised knowledge – including any tool, technique, product, process, method, organisation or system – to practical tasks. In healthcare, technology includes drugs, diagnostics, indicators and reagents, devices, equipment and supplies, medical and surgical procedures, support systems, and organisational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation.

**Time horizon:** in the context of a clinical trial it is the time span over which patients are monitored for treatment effect.

**Time trade-off:** a method of preference assessment used to measure utility. The utility value is measured by finding the point at which an individual is indifferent between two scenarios. That is, choices are provided to determine the length of time in an ideal health state that they would consider equivalent to a longer length of time with a specific condition. (Compare with standard gamble)

**Transferability:** a trial, study or model has transportability if it can produce unbiased inferences to another specified healthcare system (e.g. from overseas to Ireland).

**Transfer (or income transfer) payment:** payment made to individual (usually by government body) that does not perform any service in return; examples are social security payments and employment insurance benefits.

**Uncertainty:** where the true value of a parameter or the structure of a process is unknown.

**Usual care:** this is the most common or most widely used alternative in clinical practice for a specific condition. This is also referred to as “routine care” or “current practice” or “typical care.”

**Utility:** a measure of the relative desirability or preference (usually from the perspective of a patient) for a specific health outcome or level of health status compared to alternative health states. A numerical value is assigned on a cardinal scale of 0 (death) to 1 (optimal or ‘perfect’ health). Health states considered to be worse than death may be assigned a negative value.

**Validity:** the extent to which an endpoint measures what it is intended to measure (See also **Reliability**).

**Valuation:** the process of quantifying desirability of outcome in utility or monetary terms or of quantifying cost of resource or individual’s productivity in monetary terms.

**Variability:** this reflects known differences in parameter values arising out of inherent differences in circumstances or conditions. It may arise due to differences in patient population (e.g. patient heterogeneity – baseline risk, age, gender), differences in clinical practice by treatment setting or geographical location.

## **APPENDICES**

### **Appendix 1 – Types of economic evaluation**

The purpose of this appendix is to provide a brief overview of the different types of economic evaluation used in healthcare. A detailed discussion is beyond the scope of this document. Instead, readers are referred to the reference sources that are available.<sup>(2;36)</sup>

Economic evaluations fall into two major categories:

- cost-effectiveness analysis
- cost-benefit analysis.

Although they employ similar methods to define and evaluate costs, the methods differ in how the consequences are assessed and, therefore, in the conclusions drawn. These evaluation types are briefly described and their limitations noted. Also described is cost-minimisation analysis and the particular circumstances for its use.

#### **Cost-effectiveness Analysis**

In a cost-effectiveness analysis (CEA), outcomes are reported in a single unit of measurement and are given in natural units.<sup>(37)</sup> The outcome is common to all of the technologies, but may be achieved to various degrees. For programmes whose main effect is to extend life, the usual measure is life years gained. Sometimes the benefit measure may be an intermediate marker rather than a final outcome.<sup>(11)</sup> Where an intermediate (surrogate) marker is chosen it must have a validated, well established link with an important patient outcome.<sup>(38)</sup> The extent to which a clinically relevant effect can be precisely predicted based on changes in the surrogate marker should be stated.

#### Limitations

Cost-effectiveness analysis is limited in that only a single measure can be used in the calculation of the cost-effectiveness ratio. It does not reflect the effects of a technology on both the quality and quantity of life, nor can it reflect the situation where a technology is superior in some measures of outcome and inferior in others when compared to another intervention. As the measure of primary effectiveness may differ from programme to programme, cost-effectiveness analysis cannot be used to make comparisons across a broad set of technologies. The concept of cost-utility analysis was developed to address these problems.<sup>(36)</sup>

## **Cost-utility Analysis**

The cost-utility analysis (CUA) enables a broad range of relevant outcomes to be included by providing a method through which several outcomes can be combined into a single composite summary outcome, such as the QALY.<sup>(36)</sup> This analysis presents the consequences produced by the technologies in terms of the life-years gained, with each life-year adjusted by a utility value. Utility values are preference-based values that attach to the health state produced by a technology. They are measured on a cardinal scale, so that a year of life in perfect health has a score of one and death a score of zero.<sup>(39)</sup> There are several methods for obtaining utility values for health states, with the choice depending on the study setting and on whose values are considered to be the most relevant.<sup>(40)</sup> Values can be attached to the health state using a direct method such as the standard gamble or time trade off methods or a rating scale.<sup>(2)</sup> These values should ideally be attached by patients or the general population. The health state valuations should ideally be relevant to the population(s) under study<sup>(41)</sup> since valuation is believed to be influenced by culture and income.<sup>(42)</sup>

The most widely used outcome measure in cost-utility analysis is the quality-adjusted life year (QALY). QALYs combine survival and health-related quality of life into a single measurement. By converting the effectiveness data to a common unit of measure, such as QALYs gained, a cost-utility analysis is able to incorporate simultaneously both the changes in the quantity of life and in the quality of life. The superiority of one technology over another can be expressed in terms of the QALYs gained. The QALY is useful when changes in quality of life are being traded with changes in survival.<sup>(37)</sup> The use of such a generic measure of outcome makes it possible to compare outcomes from different technologies across different activities in the healthcare sector.<sup>(39)</sup> It is considered the gold standard method for conducting economic evaluations and is recommended by many expert and consensus groups.<sup>(43)</sup>

### Limitations

There are a number of limitations associated with cost-utility analysis. It has been argued that QALYs may suffer from a lack of sensitivity when comparing the efficacy of two competing yet similar technologies and in the treatment of less severe health problems. Chronic diseases, where quality of life is a major issue and survival less of an issue may also be difficult to accommodate in the context of the QALY. It has also been argued that preventive measures, where the impact on health outcomes may not occur for many years, may be difficult to quantify using QALYs.<sup>(15)</sup> Similarly, there is dispute regarding the capacity of QALYs to measure short-term outcomes

(e.g. acute pain relief) that do not affect the quantity of life and regarding the availability of good quality utility values available for certain populations.

### **Cost-benefit Analysis**

A cost-benefit analysis (CBA) is the broadest type of analysis; both costs and consequences are presented in monetary terms with the net present value determined as the difference in value between the discounted future streams of incremental benefits and the incremental costs.<sup>(2)</sup> This method provides an overall view as to whether a technology is economically desirable, i.e., whether the benefits of employing a technology outweigh the costs, simplifying decisions in the absence of budget constraints.

Money values may be assigned to the health outcomes in a number of ways. The value of the consequences may be provided by patients, health professionals or by the general population.<sup>(2)</sup> Two common approaches to the conversion of health outcomes to monetary terms are the 'Willingness to Pay' and the 'Human Capital' approach. The former ascertains the maximum amount an individual is willing to pay to achieve (or avoid) a particular health outcome, or to increase (or decrease) its probability of occurrence. In the latter, the value of the healthy time gained from a technology is determined by the present value of future earnings.<sup>(44)</sup>

#### Limitations

The use of cost-benefit analysis is limited by the methods used to translate benefits to monetary values.<sup>(44)</sup> In practice, cost-benefit analysis is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms.<sup>(45;46)</sup>

### **Cost-minimisation Analysis**

In a cost-minimisation analysis (CMA), alternative technologies are compared only in terms of their costs because their outcomes (effectiveness and safety) are found to be, or are expected to be, identical. Empirical justification using robust scientific evidence must be provided to support the claim that there is no meaningful difference in terms of important patient outcomes between the technologies being compared.

#### Limitations

The practical application of cost-minimisation analysis is limited by the requirement of equivalent outcomes. With the exception of generic drugs, there are a limited number of technologies for which the outcomes are expected to be identical. Cost-

minimisation analysis may be extended to comparisons of drugs with the same mechanism of action that produce outcomes that would not be judged to be clinically different ('me-too' drugs). However, it must be determined that the trial evidence to support equivalence was sufficiently powered to detect clinical differences.

## **Appendix 2 – Economic Search filter- Example**

The economic studies filter used by Scottish Intercollegiate Guidelines Network (SIGN) is an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination (CRD) at the University of York.

### **CINAHL**

- 1 Exp economics/
- 2 Exp "financial management"/
- 3 Exp "financial support"/
- 4 Exp "financing organized"/
- 5 Exp "business"/
- 6 Or/2-5
- 7 1 not 6
- 8 Health resource allocation.sh.
- 9 Health resource utilization.sh.
- 10 8 or 9
- 11 7 or 10
- 12 (cost or costs or economic\$ or pharmacoeconomic\$ or price\$ or pricing\$).tw.
- 13 11 or 12
- 14 Editorial.pt.
- 15 Letter.pt.
- 16 News.pt.
- 17 Or/14-16
- 18 13 not 17
- 19 "Animal studies"/
- 20 18 not 19
- 21 Cochrane library.so.
- 22 Anonymous.au.
- 23 20 not (21 or 22)

### **Appendix 3 – Example of a data extraction table**

<b>Study</b>	<b>Intervention</b>	<b>Analysis Details</b>	<b>Clinical &amp; QALY Outcomes</b>	<b>Costs</b>	<b>Results</b>
		Country: Discount rate: Perspective: Time Horizon: Model Type:			

## Appendix 4 – Quality tools

### Consensus on Health Economic Criteria (CHEC)-List<sup>2</sup>

	Item	Yes	No	Extract
1.	Is the study population clearly described?	▪	▪	
2.	Are competing alternatives clearly described?	▪	▪	
3.	Is a well-defined research question posed in answerable form?	▪	▪	
4.	Is the economic study design appropriate to the stated objective?	▪	▪	
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	▪	▪	
6.	Is the actual perspective chosen appropriate?	▪	▪	
7.	Are all important and relevant costs for each alternative identified?	▪	▪	
8.	Are all costs measured appropriately in physical units?	▪	▪	
9.	Are costs valued appropriately?	▪	▪	
10.	Are all important and relevant outcomes for each alternative identified?	▪	▪	
11.	Are all outcomes measured appropriately?	▪	▪	
12.	Are outcomes valued appropriately?	▪	▪	
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	▪	▪	
14.	Are all future costs and outcomes discounted appropriately?	▪	▪	
15.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	▪	▪	
16.	Do the conclusions follow from the data reported?	▪	▪	
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	▪	▪	
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	▪	▪	
19.	Are ethical and distributional issues discussed appropriately?	▪	▪	

<sup>2</sup> Reproduced from Evers S et al, Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care. 2005; 21(2): pp.240-5, with permission from Cambridge University Press

## British Medical Journal (BMJ) Checklist<sup>3</sup>

Item	Yes	No	N/C	N/A	Extract
<b>Study design.</b>					
1. The research question is stated.	*	*	*		
2. The economic importance of the research question is stated.	*	*	*		
3. The viewpoint(s) of the analysis are clearly stated and justified.	*	*	*		
4. The rationale for choosing alternative programmes or interventions compared is stated.	*	*	*		
5. The alternatives being compared are clearly described.	*	*	*		
6. The form of economic evaluation used is stated.	*	*	*		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	*	*	*		
<b>Data collection.</b>					
8. The source(s) of effectiveness estimates used are stated.	*	*	*		
9. Details of the design and results of effectiveness study are given (if based on a single study).	*	*	*	*	
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	*	*	*	*	
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	*	*	*		
12. Methods to value benefits are stated.	*	*	*	*	
13. Details of the subjects from whom valuations were obtained were given.	*	*	*	*	
14. Productivity changes (if included) are reported separately.	*	*	*	*	
15. The relevance of productivity changes to the study question is discussed.	*	*	*	*	
16. Quantities of resource use are reported separately from their unit costs.	*	*	*		
17. Methods for the estimation of quantities and unit costs are described.	*	*	*		
18. Currency and price data are recorded.	*	*	*		
19. Details of currency of price adjustments for inflation or currency conversion are given.	*	*	*		
20. Details of any model used are given.	*	*	*	*	
21. The choice of model used and the key parameters on which it is based are justified.	*	*	*	*	
<b>Analysis and interpretation of results</b>					
22. Time horizon of costs and benefits is stated.	*	*	*		
23. The discount rate(s) is stated.	*	*	*	*	
24. The choice of discount rate(s) is justified.	*	*	*	*	
25. An explanation is given if costs and benefits are not discounted.	*	*	*	*	
26. Details of statistical tests and confidence intervals are given for stochastic data.	*	*	*	*	
27. The approach to sensitivity analysis is given.	*	*	*	*	
28. The choice of variables for sensitivity analysis is justified.	*	*	*	*	
29. The ranges over which the variables are varied are justified.	*	*	*	*	
30. Relevant alternatives are compared.	*	*	*	*	
31. Incremental analysis is reported.	*	*	*	*	
32. Major outcomes are presented in a disaggregated as well as aggregated form.	*	*	*		
33. The answer to the study question is given.	*	*	*		
34. Conclusions follow from the data reported.	*	*	*		
35. Conclusions are accompanied by the appropriate caveats.	*	*	*		

<sup>3</sup> Reproduced from the BMJ, Guidelines for authors and peer reviewers of economic submissions to the BMJ, M F Drummond, T O Jefferson, 313:275, 1995 with permission from BMJ Publishing Group Ltd

## Philips Checklist<sup>(15)</sup>

Dimension of Quality	Questions for critical appraisal
<b>Structure</b>	
S1 Statement of decision problem/objective	Is there a clear statement of the decision problem? Is the objective of the evaluation and model specified and consistent with the stated decision problem? Is the primary decision-maker specified
S2 Statement of scope/perspective	Is the perspective of the model stated clearly? Are the model inputs consistent with the stated perspective? Has the scope of the model been stated and justified? Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?
S3 Rationale for structure	Is the structure of the model consistent with a coherent theory of the health condition under evaluation? Are the sources of data used to develop the structure of the model specified? Are the causal relationships described by the model structure justified appropriately?
S4 Structural assumptions	Are the structural assumptions transparent and justified? Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?
S5 Strategies/comparators	Is there a clear definition of the options under evaluation? Have all feasible and practical options been evaluated? Is there justification for the exclusion of feasible options?
S6 Model type	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?
S7 Time horizon	Is the time horizon of the model sufficient to reflect all important differences between options? Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?
S8 Disease states/pathways	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?
S9 Cycle length	Is the cycle length defined and justified in terms of the natural history of disease?
<b>Data</b>	
D1 Data identification	Are the data identification methods transparent and appropriate given the objectives of the model? Where choices have been made between data sources, are these justified appropriately? Has particular attention been paid to identifying data for the important parameters in the model? Has the quality of the data been assessed appropriately? Where expert opinion has been used, are the methods described and justified?
D2 Data modelling	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?
D2a Baseline data	Is the choice of baseline data described and justified? Are transition probabilities calculated appropriately? Has a half-cycle correction been applied to both cost and outcome? If not, has this omission been justified?
D2b Treatment effects	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques? Have the methods and assumptions used to extrapolate short-term

	<p>results to final outcomes been documented and justified? Have alternative assumptions been explored through sensitivity analysis? Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified? Have alternative assumptions been explored through sensitivity analysis?</p>
D2c Costs	<p>Are the costs incorporated into the model justified? Has the source for all costs been described? Have discount rates been described and justified given the target decision-maker?</p>
D2d Quality of life weights (utilities)	<p>Are the utilities incorporated into the model appropriate? Is the source for the utility weights referenced? Are the methods of derivation for the utility weights justified?</p>
D3 Data incorporation	<p>Have all data incorporated into the model been described and referenced in sufficient detail? Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)? Is the process of data incorporation transparent? If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified? If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?</p>
D4 Assessment of uncertainty	<p>Have the four principal types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been Justified?</p>
D4a Methodological	<p>Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?</p>
D4b Structural	<p>Is there evidence that structural uncertainties have been addressed via sensitivity analysis?</p>
D4c Heterogeneity	<p>Has heterogeneity been dealt with by running the model separately for different subgroups?</p>
D4d Parameter	<p>Are the methods of assessment of parameter uncertainty appropriate? If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?</p>
<b>Consistency</b>	
C1 Internal consistency	<p>Is there evidence that the mathematical logic of the model has been tested thoroughly before use?</p>
C2 External consistency	<p>Are any counterintuitive results from the model explained and justified? If the model has been calibrated against independent data, have any differences been explained and justified? Have the results of the model been compared with those of previous models and any differences in results explained?</p>

## Appendix 5 – Transferability tools

### EUnetHTA, economic evaluation domain<sup>(1)</sup>

#### Question Box 10: Economic evaluation questions

To assess relevance and reliability<sup>7</sup>

1. Was a well-defined economic question posed in an answerable form?
2.
  - a) What is the question being asked in the report?
  - b) Is the economic question relevant?
  - c) What type of economic analysis is being performed to answer the question (i.e. cost-minimisation, cost consequences analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis)?
3.
  - a) Has the viewpoint or perspective for the analysis been stated clearly, along with the reasons for this choice?
  - b) Is it a societal perspective, third-party payer perspective, or patient perspective?
  - c) Is the analysis presented in a disaggregated fashion showing these perspectives separately?
4. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?
5. Has the study included a comparison of alternative treatments for patients with the same clinical condition? Are those alternatives explicitly stated? Are the alternatives chosen valid and reasonable?
6.
  - a) Has the evidence of the product's efficacy been established through randomised trials?
  - b) Has the evidence of efficacy been supplemented by evidence of effectiveness applicable to the patient population or subgroups considered in the study?
  - c) Has the latter evidence been derived from studies documenting routine use in clinical practice?
  - d) Have all the relevant and significant variations in effectiveness for different subgroups been identified and reported?
7. Was the effectiveness of the programmes or services established?
8.
  - a) Are the methods and analysis displayed in a clear and transparent manner?
  - b) Are the components of the numerator (cost of each alternative) and denominator (clinical outcomes of each alternative) displayed?
  - c) Are clinical outcomes expressed first in natural units and then translated into alternative units, such as benefits or utility?
9. Are all important and relevant costs and consequences (outcomes), including adverse effects for each alternative identified?
10. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of clinician visits, lost work-days, gained life-years)?

11. How is Health Related Quality Of Life (HRQOL) measured?
12. a) Is HRQOL an important component of an economic analysis for this question?  
b) Based on the sensitivity analysis how sensitive is the estimate of cost-utility to variations in HRQOL?
13. Were costs and consequences valued credibly?
14. Were costs and consequences adjusted for differential timing?
15. Are costs and consequences modelled (as a decision trees) with information derived from a variety of sources or estimated directly from specific patient population(s)?
16. a) Are capital costs and overhead costs included as well as operating costs?  
b) How are they measured?
17. How have indirect costs (i.e. productivity costs, cost of lost time) been identified and estimated?
18. a) For variables which are difficult to measure, what method is used to handle this difficulty?  
b) Does this method slant the analysis all in favour of one intervention in order to bias the analysis against the expected result?
19. Was an incremental analysis of costs and consequences of alternatives performed?
20. Was allowance made for uncertainty in the estimates of costs and consequences?
21. Were adequate sensitivity analyses undertaken i.e. when parameters with high uncertainty were analysed, did the direction of the results change?
22. If a stochastic sensitivity analysis was applied, are the underlying distribution functions justified?
23. What equity assumptions have been made in the analysis? For example, are QALYs gained by any individual considered equal?
24. a) Is the incremental cost-effectiveness ratio estimated for a specific clinical indication that represents the majority of all of its expected use by those covered under the programs operated by the decision-makers to whom the report is addressed?  
b) Are there other indications which have not been considered which involve a large amount of utilization for which the ratio may be very different?
25. a) Is there an estimate of the aggregate incremental expenditure required for the decision-makers to whom the study is addressed, to provide this product to patients covered by their programs?  
b) What is the estimate of aggregate incremental costs?  
c) Does this estimate cover all of the major indications for use of the product?
26. Did the presentation and discussion of study results include all issues of concern to users?

**To assess transferability<sup>8</sup>**

27. How generalisable and relevant are the results, and validity of the data and model to the relevant jurisdictions and populations?
28. a) Are there any differences in the following parameters?
- I. Perspective
  - II. Preferences
  - III. Relative costs
  - IV. Indirect costs
  - V. Discount rate
  - VI. Technological context
  - VII. Personnel characteristics
  - VIII. Epidemiological context (including genetic variants)
  - IX. Factors which influence incidence and prevalence
  - X. Demographic context
  - XI. Life expectancy
  - XII. Reproduction
  - XIII. Pre- and post intervention care
  - XIV. Integration of technology in health care system
  - XV. Incentives
- b) If differences exist, how likely is it that each factor would impact the results? In which direction? Of what magnitude?
- c) Taken together, how would they impact the results and of what magnitude?
- d) Given these potential differences, how would the conclusions likely change in the target setting? Are you able to quantify this in any manner?
29. Does the economic evaluation violate your national/regional guidelines for health economic evaluation?

## ISPOR questionnaire<sup>(3)</sup>

Table 1 – Questionnaire* to assess the relevance and credibility of a modeling study.		
S. no.	Question	Helper questions to consider
<b>Relevance</b>		
1	Is the population relevant?	Are the demographics similar? Are risk factors similar? Are behaviors similar? Is the medical condition similar? Are comorbidities similar?
2	Are any critical interventions missing?	Does the intervention analyzed in the model match the intervention you are interested in? Have all relevant comparators been considered?
3	Are any relevant outcomes missing?	Does the background care in the model match yours? Are the health outcomes relevant to you considered? Are the economic end points relevant to you considered?
4	Is the context (settings and circumstances) applicable?	Is the geographic location similar? Is the health care system similar? Is the time horizon applicable to your decision? Is the analytic perspective appropriate to your decision problem?
<b>Credibility Validation</b>		
1	Is external validation of the model sufficient to make its results credible for your decision?	Has the model been shown to accurately reproduce what was observed in the data used to create the model? Has the model been shown to accurately estimate what actually happened in one or more separate studies? Has the model been shown to accurately forecast what eventually happens in reality?
2	Is internal verification of the model sufficient to make its results credible for your decision?	Have the process of internal verification and its results been documented in detail? Has the testing been performed systematically? Does the testing indicate that all the equations are consistent with their data sources? Does the testing indicate that the coding has been correctly implemented?
3	Does the model have sufficient face validity to make its results credible for your decision?	Does the model contain all the aspects considered relevant to the decision? Are all the relevant aspects represented and linked according to the best understanding of their characteristics? Have the best available data sources been used to inform the various aspects? Is the time horizon sufficiently long to account for all relevant aspects of the decision problem? Are the results plausible? If others have rated the face validity, did they have a stake in the results?
<b>Design</b>		
4	Is the design of the model adequate for your decision problem?	Was there a clear, written statement of the decision problem, modeling objective, and scope of the model? Was there a formal process for developing the model design (e.g. influence diagram, concept map)? Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context? Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem? Is the choice of model type appropriate? Were key uncertainties in model structure identified and their implications discussed?
<b>Data</b>		
5	Are the data used in populating the model suitable for your decision problem?	All things considered, do you agree with the values used for the inputs? Did the approaches to obtaining and processing the data inputs meet the criteria from their corresponding questionnaires?

<b>Table 1 – continued</b>		
<b>S. no.</b>	<b>Question</b>	<b>Helper questions to consider</b>
Analysis 6	Were the analyses performed using the model adequate to inform your decision problem?	
7	Was there an adequate assessment of the effects of uncertainty?	
Reporting 8	Was the reporting of the model adequate to inform your decision problem?	Did the report of the analyses provide the results needed for your decision problem? Was adequate nontechnical documentation freely accessible to any interested reader? Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?
Interpretation 9	Was the interpretation of results fair and balanced?	
Conflict of Interest 10	Were there any potential conflicts of interest?	
11	If there were potential conflicts of interest, were steps taken to address these?	

## **Appendix 6 – Inflating retrospective health costs using the Consumer Price Index**

The most up-to-date costs should be used where possible, however if inflating retrospective costs the CPI for health should be used. The CPI is the official measure of inflation in Ireland. It is designed to measure, in index form, the change in the average level of prices paid for consumer goods and services within Ireland. The overall CPI is broken down into the 12 divisions (of which health is one), and each of these divisions is constructed based on a weighted aggregation of subsections.

The health component is made up of three sections: medical products, appliances and equipment, outpatient services and hospital services. Each of these sub-sections is in turn broken down further. So for 'medical products, appliances and equipment' there are three further sub-groups: pharmaceutical products, therapeutic appliances and equipment, and other medical products. For each of these sub-groups, a small number of items are chosen and priced as a representative sample of goods.

If one of sub indices is used in place of the overall CPI for health the reasons why it is the more relevant index must be clearly justified, and the underlying items included in calculating the index should be checked.

Data on all 12 divisions, sub-sections, and the groups within them are produced monthly and available on the CSO website.

[http://www.cso.ie/px/pxeirestat/Database/eirestat/Consumer%20Prices%20Monthly%20Series/Consumer%20Prices%20Monthly%20Series\\_statbank.asp?SP=Consumer%20Prices%20Monthly%20Series&Planguage=0](http://www.cso.ie/px/pxeirestat/Database/eirestat/Consumer%20Prices%20Monthly%20Series/Consumer%20Prices%20Monthly%20Series_statbank.asp?SP=Consumer%20Prices%20Monthly%20Series&Planguage=0)

**Example:** Convert €50 (2010 to 2014) using the CPI for Health<sup>(34)</sup>

<b>Consumer Price Index by Commodity Group, Month and Statistic</b>		
<b>Month</b>	<b>2010</b>	<b>2014</b>
January	98.2	101.3
February	96.2	101.2
March	96.1	101.2
April	96.1	101.2
May	96.2	-
June	96.2	-
July	96.7	-
August	96.7	-
September	96.7	-
October	97.6	-
November	97.5	-
December	97.5	-
<b>Average</b>	<b>96.8</b>	<b>101.2</b>

Using the Formula:

$$\frac{[(\text{Latest Index Number}/\text{Earlier Index Number}) \times 100] - 100}{100}$$

$$\begin{aligned} \text{Price increase} &= [(101.2/96.8) \times 100] - 100 \\ &= 4.55\% \end{aligned}$$

Therefore, €50 in 2010 is equivalent to €52.27 in 2014.

When converting historical cost data from one country to another, costs should first be inflated to current costs using the CPI data from the origin country, before converting to local currency using the purchasing power parity index (see Appendix 7).

## Appendix 7 – Transferring costs to Ireland using the Purchasing Power Parity Index

The Organisation for Economic Co-operation and Development (OECD) details the number of specified monetary units needed in 30 different countries to buy the same representative basket of consumer goods and services. In each case the representative basket costs a hundred units in the country whose currency is specified.<sup>(47)</sup>

The purchasing power parities (PPPs) used to derive the table are obtained by extrapolating the 2011 PPPs for private final consumption expenditure using the relative rates of inflation between the countries as measured by their consumer price indices. Unless a country is a high inflation country, its PPP will tend to change slowly over time. Month-to-month changes in comparative price levels are more likely to be the result of exchange rate fluctuations. Of note:

- for European countries:
  - PPPs for **2006-2007, 2009-2010, 2012** are benchmark results calculated by Eurostat<sup>(48)</sup>
  - PPPs for 2009 are OECD estimates
- for non-European countries, all PPP are OECD estimates based on the triennial benchmark results for 2011.

More information is available on the internet site: <http://www.oecd.org/std/prices-ppp/>

### **Example:**

Convert £50 (year 2013) to (Irish costs in €) using the PPP

Using the Purchasing Power Parities for 2013,<sup>(47)</sup> the UK has a PPP of 0.694, and the value is 0.806 for Ireland.

Representative basket costs (U.K.)	0.694
Comparative price level for Irish basket	0.806
2013 value (£)	£50
Converted to Irish costs in €	€58.07

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