Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Draft Guidelines for the Economic Evaluation of Health Technologies in Ireland

2017

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent authority established to drive high-quality and safe care for people using our health and social care services in Ireland. HIQA's role is to develop standards, inspect and review health and social care services and support informed decisions on how services are delivered.

HIQA aims to safeguard people and improve the safety and quality of health and social care services across its full range of functions.

HIQA's mandate to date extends across a specified range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has statutory responsibility for:

- **Setting Standards for Health and Social Services —** Developing person-centred standards, based on evidence and best international practice, for health and social care services in Ireland.
- **Regulation —** Registering and inspecting designated centres
- **Monitoring Children's Services —** Monitoring and inspecting children's social services.
- **Monitoring Healthcare Safety and Quality —** Monitoring the safety and quality of health services and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health Technology Assessment —** Providing advice that enables the best outcome for people who use our health service and the best use of resources by evaluating the clinical effectiveness and cost-effectiveness of drugs, equipment, diagnostic techniques and health promotion and protection activities.
- **Health Information** — Advising on the efficient and secure collection and sharing of health information, setting standards, 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 (HIQA) 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 recognised that the findings of a HTA may have implications for other key stakeholders in the Irish healthcare system, such as patient groups, the general public, clinicians, other healthcare providers, academic groups, and the manufacturing industry.

The HTA guidelines provide an overview of the principles and methods used in assessing health technologies. They are intended as 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.

These guidelines are intended to inform economic evaluations conducted by, 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), to include health technology suppliers preparing applications for reimbursement. The guidelines are intended to be applicable to all healthcare technologies, including pharmaceuticals, procedures, medical devices, broader public health interventions and service delivery models.

This document, *Guidelines for the Economic Evaluation of Health Technologies in Ireland,* is part of the series of guidelines. This document is limited to methodological guidance on the conduct of economic assessments. The guidelines will be reviewed and revised as necessary. For ease of use, guideline statements that summarise key points are included prior to each section in italics.

The draft guidelines have been developed in consultation with the 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.

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Health Information and Quality Authority

Process and Acknowledgements

The economic guidelines have been developed by the Authority with technical input from the National Centre for Pharmacoeconomics and in consultation with its Scientific Advisory Group (SAG). Providing broad representation from key stakeholders in Irish healthcare, this group includes methodological experts from the field of health technology assessment (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 SAG meetings as appropriate
- be prepared to occasionally provide expert advice on relevant issues outside of SAG 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.

The Authority gratefully acknowledges all those who contributed to the development of these guidelines.

The methodology for the update of these guidelines included a review of guidelines published by other HTA agencies since 2014.

The membership of the Scientific Advisory Group is as follows:

Chairperson: Dr Michael Barry
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Contributors

Anthony Kelly undertook a review of guidelines published by international HTA agencies, and provided text to the current version.

Record of Updates

Date	Title / Version	Summary of Changes
2000	*Irish Healthcare Technology Assessment Guidelines*	• First national economic guidelines developed by the National Centre for Pharmacoeconomics in the context defined by the agreement between the Irish Pharmaceutical Healthcare Association and the Department of Health
November 2010	*Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.0*	• Major revision and reorganisation of text
January 2014	*Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.1*	• Minor revisions and reorganisation of text. • Updated VAT rate and pay-related costs calculation.
October 2017	*Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.2*	• Minor revisions and reorganisation of text. • Additional description of acceptable comparators (section 2.5). • Additional section on epidemiological parameters (section 2.10). • Inclusion of distinction between the 3L and 5L versions of EQ-5D (section 2.12.2). • Recommendation to report conflicts of interest (section 2.19).

Draft Guidelines for the Economic Evaluation of Health Technologies in Ireland
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This document is one of a set that describes the methods and processes for conducting health technology assessment in Ireland.

The document is available from the HIQA website (www.hiqa.ie).

List of Abbreviations

BIA	budget impact analysis
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CPI	Consumer Price Index
CUA	cost-utility analysis
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
DRG	diagnosis related groups
HIQA	Health Information and Quality Authority
HRQOL	health-related quality of life
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
LYG	life years gained
NNT	number needed to treat
PCRS	Primary Care Reimbursement Service
PPP	purchasing power parity
PRSI	Pay Related Social Insurance
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAG	Scientific Advisory Group
TTO	time trade-off
VAT	Value-Added Tax

1 Introduction

The health technology assessment (HTA) guidelines provide an overview of the principles and methods used in assessing health technologies. They are intended as a guide for those involved in the conduct or use of HTAs in Ireland.

The primary audience for HTAs 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 key stakeholders in the Irish healthcare system. These include patient groups, the general public, clinicians, other healthcare providers, academic groups and the manufacturing industry.

The purpose of the HTA guidelines is to promote the production of assessments that are timely, reliable, consistent and relevant to the needs of decision makers and key stakeholders.

The 'Economic Guidelines' represent one component of the overall HTA guidelines. They are limited to the methodological guidance on the conduct of economic assessments. These economic guidelines are an update to the 2010 and 2014 guidelines, which replaced the *Irish Healthcare Technology Assessment Guidelines, 2000*.[(1)] The guidelines are of relevance to all those conducting economic evaluations and as a reference source for those using economic evaluations to inform decision making in the publicly-funded health and social care system. They are intended to inform economic evaluations conducted by, 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), to include health technology suppliers preparing applications for reimbursement.

The guidelines are intended to be applicable to all healthcare interventions, including pharmaceuticals, procedures, medical devices, broader public health interventions, and service delivery models. They are relevant to the assessment of both new and existing technologies. Consequently, the guidelines are broad in scope and some aspects may be more relevant to particular interventions than others.

These guidelines have drawn on existing guidelines for economic evaluation and 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 Economic guidelines

The guidelines outline what are considered to be the appropriate methods for conducting economic assessments in HTA in Ireland. The goal of the guidelines is to inform decision making within the publicly-funded health and social care system in Ireland, so that the resources available to that system can be used 'in the most beneficial, effective and efficient manner to improve, promote and protect the health and welfare of the public'.[(2)]

1.1.1 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. These guideline statements are also included in italics at the beginning of each section for the individual elements of the assessment in Chapter 2.

1.1.2 Reference case

Key to any HTA is a high quality, robust economic analysis that is comprehensive, transparent and reproducible and includes all relevant evidence on health effects. While acknowledging the need for flexibility in reporting studies, a consistent methodological approach is required for assessments to facilitate comparisons between technologies and disease areas and over time.

These guidelines specify the preferred methods or 'reference case' that should be used in the primary analysis for HTAs. Use of a standard reference case approach increases transparency in the process and confidence that differences in study outcomes are representative of differences between technologies as opposed to differences in methodologies. A summary of the reference case is provided in Table 1.1 on the next page.

The use of a reference case does not preclude the inclusion of other analyses in the assessment. However, the rationale supporting the inclusion of additional non-reference case analyses should be outlined and the information presented separately from that of the reference case. It is also recognised that adoption of the reference case methods may not always be possible.

The use of any alternate methods in the primary analysis should be clearly documented and justified and an attempt should be made to quantify the likely consequences of such an approach.

Table 1.1 Summary of the reference case

Element of Technology Assessment	Reference Case	Guideline Section
Evaluation type	Cost-utility analysis	2.2
Perspective on costs	The publicly-funded health and social care system in Ireland (HSE)*	2.3
Perspective on outcomes	All health benefits accruing to individuals	2.3
Choice of comparator	Routine care in Ireland	2.5
Synthesis of effectiveness	Based on systematic review	2.8
Outcome measurement	QALYS^	2.12
Discount rate	Apply an annual rate of 5.0% on costs and outcomes occurring after the first year	2.13
Sensitivity analysis	Probabilistic and deterministic sensitivity analysis	2.16
Equity rating	Equal weighting should be applied to the outcome measure	2.17

** HSE: Health Service Executive*

^ QALYS: quality-adjusted life-years

1.2 Summary of Guideline Statements

Study Question (Section 2.1) The study question should be formulated to address the needs of the target audience by clearly establishing the context of the study. It should outline the purpose of the assessment and provide details of the study perspective, the proposed technology and its comparator(s), the target population and the impact on specific subgroups, where appropriate.

Types of Economic Evaluation (Section 2.2) The preferred evaluation type for the reference case is a cost-utility analysis (CUA) with the outcomes expressed in terms of quality-adjusted life-years (QALYs). In exceptional circumstances, a cost-effectiveness analysis (CEA) with the outcomes expressed in terms of life-years gained (or other relevant outcome if the technology does not add life-years) may be used as the reference case when a cost-utility analysis is an unsuitable choice. Clear, detailed empirical evidence must be provided to justify this position. A CEA can be presented as a secondary analysis when the use of an important patient outcome (other than a QALY) can be justified.

Study Perspective (Section 2.3) For the reference case, the perspective of the publicly-funded health and social care system in Ireland should be adopted when assessing costs. All health benefits accruing to individuals should be included in the assessment of outcomes.

Technology (Section 2.4) The technology should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.

Choice of Comparator(s) (Section 2.5) The preferred comparator for the reference case is 'routine care,' that is, the technology or technologies most widely used in clinical practice in Ireland in the context of the target population. Comparators are not limited to specific interventions, but may include alternative treatment sequences or alternative rules for starting and stopping therapy.

Target Population (Section 2.6) The target population should be clearly defined and the analysis conducted for this entire population using relevant efficacy and effectiveness data. Stratified analysis of subgroups (that have ideally been identified a priori) is appropriate when there is biological or clinical support for heterogeneity in the target population.

Time Horizon (Section 2.7) The time horizon should be of sufficient duration to capture any meaningful differences in the future costs and outcomes likely to accrue to the competing technologies. The time frame adopted should be clearly stated and its choice justified, with the same time horizon applied to both costs and outcomes.

Efficacy and Effectiveness (Section 2.8) Evidence to support the effectiveness of a technology should be derived by systematic review of all high-calibre, relevant data. Where available, evidence from randomised clinical trials (RCTs) should be used to quantify efficacy in the reference case analysis. Meta-analysis may be used to synthesise outcome data provided the homogeneity and quality of the studies included justifies this approach.

Safety (Section 2.9) All adverse effects that are of clinical or economic importance should be included in the analysis, with particular attention given to those that differ substantively between the technologies being compared. This evidence should be assembled in a clear, systematic, robust fashion with the limitations of the data and methods clearly described.

Epidemiologic Data (Section 2.10) A variety of epidemiologic data are typically incorporated into an economic model as parameters. Values should reflect the most unbiased estimate for the relevant target population. Imprecision in the parameter values should be appropriately estimated. The sources of data and details of values must be clearly described.

Measurement of Resource Use and Costs (Section 2.11) Only direct costs relevant to the publicly-funded health and social care system should be included in the reference case. Resource use in physical units and unit costs should be presented in addition to total costs. Costs for the most recent calendar year should be used with retrospective input costs inflated using the Consumer Price Index for health. Transfer payments (VAT) should be excluded. The method used to generate resource use and cost data should be systematic, clearly described and justified.

Valuing Outcomes (Section 2.12) For the reference case, health effects should be valued in QALYs. Changes in quantity and quality of life should be reported separately along with a clear explanation of how the measures were combined, the assumptions made and the methods used to estimate QALYs. The use of generic preference-based methods such as the EQ-5D or SF-6D is recommended to measure utilities. In the absence of Irish public preference data, the population from which preferences are derived should be clearly described along with its relevance to the Irish population.

Modelling (Section 2.13) Models used to synthesise and extrapolate available evidence should be developed in accordance with good modelling practice guidelines. The model should be clearly described, with the assumptions and inputs documented and justified. The methods for the quality assurance of the model should be detailed and the model validation results documented. The model and its key inputs should be subjected to comprehensive sensitivity analysis.

Discounting Costs and Benefits (Section 2.14) A standard rate of 5% per annum should be used to discount costs and outcomes in the reference case.

Subgroup analysis (Section 2.15) Stratified analysis of subgroups is appropriate to account for differences in cost-effectiveness that may arise due to important factors that impact on the target population or its management. Subgroups should ideally be identified a priori based on plausible biological, clinical or care-setting arguments.

Uncertainty (Section 2.16) The effects of model uncertainty (i.e., structure, methods and assumptions) and parameter uncertainty on the outcome of the economic evaluation must be systematically evaluated using sensitivity analysis and scenario analyses for the range of plausible scenarios. The range of values provided for each parameter must be clearly stated and justified. Justification for the omission of any model input from the sensitivity analysis should be included.

For the reference case, a one-way sensitivity analysis should be conducted to identify the key model inputs/assumptions contributing most to uncertainty. Multivariate analysis should be used for key model inputs. Probabilistic sensitivity analysis (PSA), in the form of a Monte Carlo simulation, should be used to assess parameter uncertainty. The expected value of perfect information (EVPI) should also be evaluated.

Equity Considerations (Section 2.17) For the purpose of the reference case, additional QALYs gained should be assumed to be of equal value, regardless of any considerations for specific characteristics of the population. However, an attempt should be made to meet the needs of decision makers by highlighting potential equity considerations in the report.

Generalisability (Section 2.18) The overall generalisability of the evaluation must be discussed in the context of the validity and relevance of the data used in addressing the needs of the target audience. Use of non-Irish data should be documented and its relevance to the Irish healthcare system established. Assumptions should be clearly stated, potential limitations identified and variability and uncertainty explored through sensitivity analysis.

Reporting (Section 2.19) A well structured report with information provided on each of the elements outlined in the guidelines should be provided. Data elements should be tabulated with details provided of their source and precision. The distributions used to characterise uncertainty in probabilistic analyses should be documented and justified. All results should be presented in both their disaggregated and aggregated forms. Expected mean costs, total costs and QALYs should be documented for the comparator technologies with Incremental Cost-Effectiveness Ratios (ICERs) calculated, as appropriate. Uncertainty should be presented graphically (tornado plot for one-way sensitivity analysis, scatter plot and cost-effectiveness acceptability curves for PSA) and in tabular form to facilitate interpretation. The probability that a technology is cost-effective at a range of threshold levels should also be presented.

Budget Impact Analysis (Section 2.20) A budget impact analysis should be submitted along with the economic evaluation of a technology to best inform the needs of the decision maker regarding its affordability and cost-effectiveness.

2 Economic Guidelines in Detail

2.1 Study Question

The study question should be formulated to address the needs of the target audience by clearly establishing the context of the study. It should outline the purpose of the assessment and provide details of the study perspective, the proposed technology and its comparator(s), the target population and the impact on specific subgroups where appropriate.

The primary purpose of HTA is to help inform decision making about the value of new and existing technologies. Implicit then is the requirement for HTAs to address the needs of decision makers.[3, 4] A clear, relevant study question should be included that establishes the context of the study. Ideally the study question is designed in conjunction with a scoping exercise to identify the pertinent issues that should be considered and the stakeholders relevant to the specific study question. Early identification of the stakeholders increases the opportunity for meaningful contribution to the process.[5]

The study question should outline the purpose of the assessment and detail what is included and omitted from the study. Aspects that should be addressed in defining the study question include the:

- study perspective (see also Section 2.3)
- proposed technology (see also Section 2.4)
- relevant comparator(s) (see also Section 2.5)
- target population and the impact of the technology on specific subgroups, where appropriate (see also Section 2.6).

Secondary questions that relate to the primary study question should be included and clearly specified if they are being addressed as part of the HTA. These may include issues such as the reporting of additional outcome measures or variations in treatment pathways that are being explored.

If the study question is too narrowly defined, then the assessment may fail to address issues that are relevant to the decision maker, or may provide inaccurate advice by the omission of important factors. If the study question is too broad, then the assessment may generate large quantities of information that are not relevant to the decision maker and fail to give adequate detail on the actual policy issue. As economic evaluation is a resource-intensive activity, it is important that an evaluation addresses the right question.

2.2 Types of Economic Evaluation

The preferred evaluation type for the reference case is a cost-utility analysis (CUA) with the outcomes expressed in terms of quality-adjusted life-years (QALYs). In exceptional circumstances, a cost-effectiveness analysis (CEA) with the outcomes expressed in terms of life-years gained (or other relevant outcome if the technology does not add life-years) may be used as the reference case when a cost-utility analysis is an unsuitable choice. Clear, detailed empirical evidence must be provided to justify this position. A CEA can be presented as a secondary analysis when the use of an important patient outcome (other than a QALY) can be justified.

The aim of health economic evaluations is to compare the costs and consequences of new or existing health technologies (e.g. drugs, diagnostics, devices, etc.) with one or more relevant alternatives.

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 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.

A cost-utility analysis is the preferred evaluation type for the reference case. It is considered the gold standard method for conducting economic evaluations and is recommended by many expert and consensus groups.[6] The preferred outcome measure to be used in the reference case is the quality-adjusted-life-year (QALY), (see also Section 2.12.1). The QALY is the most widely used outcome measure in cost-utility analysis. It is able to simultaneously incorporate changes in the quantity of life and in the quality of that life, with the superiority of one technology over another expressed in terms of the QALYs gained.[7] The use of a generic measure of outcome such as the QALY makes it possible to compare outcomes from different technologies across different activities in the healthcare sector.[8] Where there are concerns over the quality or suitability of the available utility data, then also reporting a cost-effectiveness analysis is advisable as supplementary information to the decision maker.

In a cost-effectiveness analysis (CEA), outcomes are reported in a single unit of measurement and are given in natural units (see Appendix 1).[7] For programmes whose main effect is to extend life, the usual measure is life years gained. The benefit measure may be an intermediate (surrogate)

marker rather than a final outcome. In exceptional circumstances, a CEA may be used as the reference case when a cost-utility analysis is considered an unsuitable choice. Clear, detailed, empirical evidence must be provided to justify this position that a cost-utility analysis is unsuitable. A CEA may be presented as a secondary analysis when the use of an important patient outcome (other than the QALY) can be justified. If the benefit measure in the CEA is a surrogate or intermediate outcome, there must be a well established, validated link between this marker and an important patient outcome.[9] Justification should be provided for the extrapolation of changes in surrogate markers to clinically relevant effects.

As a CEA presents effectiveness in terms of natural units, it may preclude comparison with other economic analyses if there are none using the same units of effect. For example, if the outcome is measured as cost per unit reduction in systolic blood pressure. Unlike a cost-utility analysis where there may be an accepted willingness-to-pay per QALY, there is no accepted threshold for CEAs. Use of outcomes other than QALYs may not therefore provide sufficient information to inform decision making. Where long-term outcomes are expressed in terms of an extrapolated increase in life years, the analysis may fail to adequately capture short-term benefits of improved health. An example is interventions that aim to reduce the risk of chronic disease.

As outlined in Appendix 1, in a cost-benefit analysis (CBA) both costs and consequences are presented in monetary terms with the net present value determined as the difference in value between costs and benefits.[10] In practice, cost-benefit analysis is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms.[11, 12]

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. The use of a cost-minimisation analysis may be considered for the reference case if empirical justification using robust scientific evidence is provided to support the claim that there is no meaningful difference in terms of important patient outcomes between the technologies being compared.[13]

2.3 Study Perspective

For the reference case, the perspective of the publicly-funded health and social care system in Ireland should be adopted when assessing costs. All health benefits accruing to individuals should be included in the assessment of outcomes.

The perspective of a study is the viewpoint from which the study is conducted (e.g. public payer, individual, society) and defines whose costs, resources and consequences should be examined. To ensure comparability of analyses, this perspective must be clearly stated so that the costs, resources and

consequences associated with the perspective adopted can be clearly identified for inclusion in the economic evaluation.

The costs perspective for the reference case should be 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 to the Health Service Executive (HSE).[13] Consistent with this outlook, all health effects accruing to individuals (QALYs, life-years gained, etc.) should be included in the outcomes for the reference case.

It is recognised that limiting the perspective to that of the primary stakeholders in the healthcare system may lead to healthcare policies that fail to optimise efficiency and social benefit. 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.[3] These may include direct and indirect costs, including productivity costs, as well as additional costs, savings or other benefits such as non-resource effects (e.g. improved education attainment) that may accrue to other public sector agencies, patients or their carers as a result of a technology.

In some circumstances, it may be appropriate to provide a secondary analysis that is not a full societal perspective but extends beyond the HSE and Department of Health to include other relevant government departments. For example, if there are significant costs or savings accruing to departments other than Health (e.g., the Department of Education). Inclusion of such an analysis must be clearly justified and supported by sufficient evidence.

If the inclusion of a wider societal perspective is expected to impact on the results of the analysis significantly, this may be presented as a secondary analysis in addition to the reference case analysis. Non-reference case costs should be presented separately, disaggregated from the reference case costs in any such additional analyses. These costs should also be subjected to sensitivity analysis (see also Section 2.16), and in the instance where quantification is difficult, an estimate of the magnitude of such costs and their impact on the results discussed.

2.4 Technology

The technology should be described in sufficient detail to differentiate it from its comparators and to provide context for the study.

In healthcare, technologies include 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. This includes pharmaceuticals, devices, medical equipment, medical and surgical procedures. It also includes the

organisational and supportive systems within which this healthcare is provided.

Adequate information should be provided about the technology under assessment. This should include detailed information about its technical characteristics (to differentiate it from its comparator technologies), regulatory status and the specific application (e.g. purpose, place and context) that is being explored as part of the assessment. For example, information on the licensed indication and dose, frequency and route of administration, and duration of use is required for pharmaceutical products. Details of associated diagnostic or prognostic tests should also be described.

Pertinent information on specific investments, tools required to use the technology, additional training and information requirements specific to the technology should be included as appropriate. The technology may form part of a treatment sequence, in which case the associated technologies in the sequence also need to be clearly defined and described. The treatment may be provided in a different setting to its comparators, or may require transport between healthcare providers, or may require additional healthcare supports in other areas, which may have important organisational and resource issues that need to be considered.

2.5 Choice of Comparator(s)

The preferred comparator for the reference case is 'routine care,' that is, the technology or technologies most widely used in clinical practice in Ireland in the context of the target population. Comparators are not limited to specific interventions, but may include alternative treatment sequences or alternative rules for starting and stopping therapy.

To achieve maximum generalisability and transparency, one would need to consider all available comparator technologies. The technical difficulty of doing this, as well as the additional time and resource implications required could make this hugely burdensome and inefficient. In practice, it is reasonable to limit the number of comparators to the recommended standard of care and those that are used in routine clinical practice in Ireland.

The comparator(s) should be clearly identified and justified with sufficient detail provided so that their relevance may be assessed. The choice of comparator will critically determine the relative cost-effectiveness of the technology and the relevance of the assessment to the decision makers. Where the technology and its comparator(s) form part of a treatment sequence, a comparison of different sequencing options and the impact of variations in the potential sequencing on the cost-effectiveness of various options should be considered. Technologies that do not have marketing authorisation (or CE mark for medical devices) for the indication defined may also be considered for the comparator if they are part of established clinical

practice for that indication. Where such an unlicensed technology is used as the comparator, the evidence of efficacy and safety included in the assessment must be relevant to the unlicensed use.

For the purpose of the reference case, the comparator should be 'routine care', that is, the technology or technologies that are most widely used in clinical practice in Ireland. It is feasible that there will be more than one appropriate comparator technology because of variations in routine practice within the Irish healthcare system, including where routine practice differs from what is considered best practice (as defined by evidence-based clinical practice guidelines) or the most appropriate care. 'Routine care' may be defined by a complex amalgam of treatments including first and second line treatments. In the absence of an active comparator, it is appropriate to have a comparator of 'no intervention.' In some circumstances it may be appropriate to include potential comparators that are not yet reimbursed, but may reasonably be expected to become the standard of care in the short- to medium-term. Inclusion of such comparators should be underpinned by appropriate assumptions regarding clinical effectiveness and cost.

In some situations, such as when current practice is not well defined or standardised, the use of a comparator of 'no intervention' in addition to 'routine care' can provide useful information on the relative benefits of the technologies.

2.6 Target Population

The target population should be clearly defined and the analysis conducted for this entire population using relevant efficacy and effectiveness data. Stratified analysis of subgroups (that have ideally been identified a priori) is appropriate when there is biological or clinical support for heterogeneity in the target population.

The population for which a technology is being appraised should be clearly defined. Parameters to define the population include baseline demographic characteristics (e.g. age, gender), disease characteristics (e.g. stage or severity, presence of co-morbidities, risk factors), treatment setting (e.g. primary care or hospital), or in the context of past treatment (e.g. non-responders, treatment relapse, non-adherence, poor tolerance). For certain technologies, notably medicines, the population will usually be defined by the licensed therapeutic indications for the product. Wherever possible, data on the target population should be specific to the population in Ireland.

The clinical and cost-effectiveness of a technology should be assessed for the entire population specified in the study question. The absolute size of the target population should be reported for contextual information.

Consideration should be given to modelling multiple cohorts where population or patient characteristics are expected to differ between current and future

incident cohorts, between incident and prevalent cohorts, or where there may be shared effects between cohorts. For example, effects may be shared where vaccination of the current cohort will have implications for disease transmission in future cohorts, thereby impacting on cost-effectiveness.

Specific subgroups may be identified for whom clinical and cost-effectiveness may be expected to differ to that of the overall population. These subgroups should be clearly defined and ideally identified based on an a priori expectation of differences in clinical or cost-effectiveness and supported by a plausible biological or clinical rationale for the subgroup effect. As part of the reference case analysis, differences in baseline parameters, treatment costs and effectiveness due to patient heterogeneity should be explored by conducting any relevant subgroup analyses (see also Section 2.15). However, subgroups should not be defined on the basis of treatment response. The issue of treatment response can be more appropriately explored within an economic model by incorporating information on response assessment and treatment stopping rules.

2.7 Time Horizon

The time horizon should be of sufficient duration to capture any meaningful differences in the future costs and outcomes likely to accrue to the competing technologies. The timeframe adopted should be clearly stated and its choice justified, with the same time horizon being applied to both costs and outcomes.

The study period should be clearly described and appropriate to the disease and its treatment. This time horizon should be of sufficient length to capture meaningful differences in costs and outcomes between the competing technologies. In the interest of consistency, the same time horizon should be applied to both costs and outcomes, and also to all technologies in the evaluation.

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 timeframe 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. A decision to use a shorter timeframe should be justified and an estimate provided of any possible bias introduced as a result of this decision.

Caution needs to be exercised in cases where only short- or medium-term follow-up data are available for an intervention with expected long-term effects. 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, inherent assumptions regarding future treatment effects and disease progression should be clearly outlined and tested as part of the sensitivity analysis (see also Section 2.16). In these cases it is advisable to present a sensitivity analysis with results for a time horizon that is equal to the duration of follow-up in the available data.

2.8 Efficacy and Effectiveness

For the reference case, evidence to support the effectiveness of a technology should be derived by systematic review of all high-calibre, relevant data. Where available, evidence from randomised clinical trials (RCTs) should be used to quantify efficacy in the reference case analysis. Meta-analysis may be used to synthesise outcome data provided the homogeneity and quality of the studies included justifies this approach.

The distinction between the efficacy and the effectiveness of a technology is recognised. In general, the efficacy of a health technology relates to its performance under ideal circumstances, often estimated through randomised controlled trials (RCTs). In contrast, effectiveness refers to the performance of a technology under normal circumstances, such as in routine clinical practice, often measured from observational studies, registry data or pragmatic RCTs.

Outside the arena of marketing authorisation, decision makers are primarily concerned with how technologies perform in the context of usual care. Economic assessments should be based on the effectiveness of the competing technologies and uncertainty surrounding these estimates assessed through sensitivity analyses and modelling techniques to enhance the robustness of the HTA findings. Detailed guidance with respect to estimating clinical effectiveness is provided in the Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland.[14]

In the reference case, evidence on outcomes should be obtained by means of a systematic review with all data sources clearly described.[15] It is recommended to systematically evaluate the body of evidence with the aid of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. The GRADE approach is a systematic, transparent, and explicit method of grading the quality of scientific evidence.[16] Evidence generated from this phase is necessary to inform decision making, but may also be used to populate economic decision-analytic models. These models can be used to project the potential health and economic consequences of using different technologies over an adequate time frame.

2.8.1 Locating and Selecting Studies

In assessing the evidence, the objective is to provide a comprehensive reproducible, transparent, unbiased estimate of the outcome parameters for the technologies being compared, including an estimate of their relative effectiveness.

A clear description of the systematic process used to obtain relevant information should be provided.[17] This should include a description of the search strategy, inclusion and exclusion criteria applied and restrictions used in locating studies (e.g. language, population, year). For best practice, two or more reviewers should be involved in the selection process using a pre-defined 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 search and selection processes. Individual studies selected based on the inclusion criteria should be critically assessed for their validity and relevance to the study question.[15]

All available evidence should be sought and considered as part of the review process. This may also include data that has been identified as commercial or academic in confidence. If the validity of a confidence claim is established, a clearly defined process should be used to facilitate the use of this data while maintaining confidentiality. It should be noted that data confidentiality is often for a limited time period. To maximise transparency, data used in the formation of HTA decisions should ideally be publicly available, even if it is limited to summary data.

To ensure robustness and to minimise publication bias, all attempts should be made to include unpublished and partially published studies. These studies should be assessed, where possible, using the same validity criteria applied to published data.[15]

Whenever available, data from randomised controlled trials (RCTs) should be presented in the reference case. A clear rationale for the identification and selection of trials should be provided. Inconsistencies between the evidence across different data sets and analytical methods should be reported and the imprecision or uncertainty regarding the available data explored as part of a sensitivity analysis (see Section 2.16).

Experimental, quasi-experimental and non-experimental or observational data may be submitted to supplement the available RCTs and to enhance the generalisability and transferability of the results. These data can be particularly valuable when estimating baseline event risks (with existing treatments) and for extrapolation of data. The validity of these studies should be assessed as part of the critical appraisal. Potential bias arising from the design of these studies should be assessed and documented.

Economic evaluations may be 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 from multiple trials or gathered in a systematic review. In such cases there are a number of risks of bias (e.g., protocol-driven costs, lack of longer-term follow-up data, inappropriate

outcomes) that can impact on the results. Adequate steps must be taken to show that the data are appropriate and generalisable to the relevant population in Ireland (e.g., it may be reasonable to make the trial data available for independent assessment).

Assessment of non-drug technologies including procedures and programmes may be more complicated as the evidence-base may be limited and trial designs complex. As such, assumptions and uncertainties arising from the use of this data should be clearly stated and explored as part of a comprehensive sensitivity analysis (see also Section 2.15). For medical devices, which can change substantially over time in terms of design, it must be clear that selected studies are based on the same device. Evidence of efficacy in a specific device 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.

2.8.2 Summarising the Evidence

The methods used to analyse or combine data should be clearly outlined and justified and the data provided in both aggregated and disaggregated form. Meta-analysis may be used to synthesise outcome data, provided there is sufficient, relevant and valid data to justify this approach. Particular attention should be paid to assessing heterogeneity between studies and testing for evidence of publication bias. In the event of limited head-to-head RCT data, mixed treatment comparisons can be used. Network meta-analyses combine direct and indirect evidence. Inconsistencies between the evidence across different data sets and analytical methods should be reported and the imprecision or uncertainty regarding the available data explored as part of a sensitivity analysis (see Section 2.16). The use of appropriate subgroup analyses may be considered where there is known clinical heterogeneity in the data (see also Sections 2.6 and 2.15). Detailed guidance with respect to evidence synthesis is provided in the Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland.[14]

The homogeneity and quality of the primary studies included in the meta-analysis should be discussed when developing the overall estimate of the treatment effect, with the justification for study inclusion clearly documented. A risk of bias assessment using a recognised method (e.g., Cochrane risk of bias tool) should be presented.[18]

The treatment effect may be reported in a number of different ways. Both absolute (absolute risk reduction, differences in number needed to treat [NNT]) and relative effect (odds ratio, risk ratio, relative risk reduction) should be presented for binary data. Mean values should be presented for continuous variables. The measures of precision of these estimates should also be detailed.

If the data limits the use of a quantitative summary, a qualitative summary may be provided. The characteristics and limitations of the study data included in the analysis should be clearly documented.

2.9 Safety

All adverse effects that are of clinical or economic importance should be included in the analysis, with particular attention given to those that differ substantively between the technologies being compared. This evidence should be assembled in a clear, systematic, robust fashion with the limitations of the data and methods clearly described.

Specific definitions have been derived for risks associated with the use of pharmaceutical products including definitions for adverse events, serious adverse events and adverse drug reactions.[13] International standards are also available for manufacturers of medical devices. These specify processes to identify the hazards (potential sources of harm) associated with medical device use and to estimate and evaluate the risks, to control the risks, and to monitor the effectiveness of the controls.[19] The amount and type of safety data available for a technology will depend on several factors most notably on the timing of the assessment within the lifecycle of the technology.

A structured and systematic approach should be adopted in assessing the safety of the product. Rare or infrequent adverse events as well as late-onset events are unlikely to be detected as part of RCTs, so the analyst must usually rely on case reports, cohort studies, patient registries and pharmacovigilance or post-marketing spontaneous reports. The sources of information examined should be clearly stated. Standard approaches should be taken for the extraction, synthesis and analysis of the evidence and the limitations of the data and methods used should be clearly stated when interpreting the data.[20]

All adverse events that are of clinical or economic importance should be included in the analysis. Particular attention should be paid to those instances where there are substantive differences between the technologies being compared. In addition to the impact of adverse events on quality of life and mortality, consideration should also be given to their impact on patients' ability to comply with therapy (adherence and persistence) as well as possible consequences for resource utilisation (e.g. prolongation of hospitalisation, use of additional medications, etc.).

2.10 Epidemiologic Data

A variety of epidemiologic data are typically incorporated into an economic model as parameters. Values should reflect the most unbiased estimate for the relevant target population. Imprecision in the parameter values should be appropriately estimated. The sources of data and details of values must be

clearly described.

Models will frequently require numerous additional parameters to define the target population and intervention, for example: baseline demographic characteristics (e.g., age and sex); disease characteristics (e.g., stage or severity, co-morbidities, risk factors); or the context of past treatment (e.g., relapse, poor tolerance, non-adherence). Some of these parameters may be reported as part of clinical trials, while many will not. As such, the values for these sorts of parameters will often be informed by local data on disease incidence and prevalence, service utilisation figures, and expert opinion.

As these parameters are not typically derived from systematic review, care must be taken to adequately address potential bias in the parameter estimates. Of particular importance is whether the data are applicable to the target population. Localised databases or international data may be collected for a population that is fundamentally different from the intended target population and hence any parameters derived from those sources are likely to be biased. For example, a life expectancy parameter may be estimated for a population with fewer co-morbidities than the target population, thereby overestimating life expectancy. It is also critical to adequately account for the uncertainty or lack of precision in the estimates, and to consider data quality. Parameter values should ideally be defined as distributions for inclusion in a probabilistic sensitivity analysis. As such, any sensitivity analyses should also include these parameters.

The sources of data for parameter estimates may be considered in terms of a hierarchy of evidence.[21] Preference should be given to data sources that provide the most unbiased estimate for the stated target population. Parameter data should be subject to a risk of bias assessment. Expert opinion is generally considered to be at the greatest risk of bias. Where parameter estimates are generated using expert opinion, it should be elicited in a manner that minimises bias and the process should be documented in sufficient detail to ensure transparency.[22] Any potential conflict of interest in relation to the experts should be documented. If possible, parameters derived using expert elicitation should be contrasted with other sources to test the consistency and plausibility of the estimates.

Unless a data source is identified that is directly applicable to the target population (e.g., a patient registry), attempts should be mode to identify multiple sources for parameter estimates. If parameters can be estimated from a number of sources, it may be appropriate to pool values to obtain a mean estimate. The method of pooling should be appropriate to the type of data and should take into account if the risk of bias is not uniform across sources. It may be more appropriate to use the estimate from the most applicable data source and then use all sources for deriving an estimate of imprecision. Adequate justification should be given to the choice of sources of data to inform a parameter value and the method of pooling, if used.

In some instances the data used to inform parameter values may be published as adjusted values, taking into account characteristics of the study population or setting. Caution must be applied in relation to adjusted values to ensure that the data used are applicable and fit for purpose.

Consideration should also be given to instances where parameters may be correlated with each other. For example, trial data may show that an increase in adverse events may be associated with an increase in patients ceasing treatment. The correlation should be estimated so that it can be accounted for in the economic model.

All parameters included in the model should be tabulated along with relevant information such as the source(s) of the data, details of the associated probability distribution, the mean value, and the 95% confidence bounds.

2.11 Measurement of Resource Use and Costs

Only direct costs relevant to the publicly-funded health and social care system should be included in the reference case. Resource use in physical units and unit costs should be presented in addition to total costs. Costs for the most recent calendar year should be used with retrospective input costs inflated using the Consumer Price Index for health. Transfer payments (VAT) should be excluded. The method used to generate resource use and cost data should be systematic, clearly described and justified.

Regardless of the perspective adopted in an evaluation, there is a requirement for resource use and costs to be identified, measured (in physical units) and valued (unit costs applied). These processes must be completed in a transparent and consistent manner.[4]

2.11.1 Resource Identification

The primary perspective for evaluations should be the publicly-funded health and social care system (HSE) in Ireland. Accordingly, for the reference case, the resources that should be considered are direct medical costs for the HSE. For example, this would include drugs, medical devices, medical services including procedures, hospital services and emergency visits, and primary care visits. Costs that are borne by patients, but are reimbursable from the HSE may also be included in the calculations. Other costs borne by patients including productivity costs should be excluded from the reference case. These may be included in any secondary analysis that is presented in addition to the reference case, where a societal perspective is adopted (see also Section 2.3).

Current and future costs arising as a consequence of a technology and that occur during the specified timeframe of the study should be included in the reference case analysis. Evidence should be presented to demonstrate that the data for resource use and costs has been identified systematically. A

variety of costs are likely to be relevant in the analysis, including capital, labour, technology and treatment costs. Capital costs should be appropriately depreciated (see Appendix 5). Relevant maintenance costs may apply over the lifetime of certain equipment (e.g., MRI scanner) and should be included in calculations.

In certain circumstances, cost and resource consumption that are common to all the technologies being compared may be excluded from the economic analysis. The cost and resource consumption must be equal in terms of quantity, timing, and duration. The process of omitting resources should be clearly described and justified. Where the comparator is 'no intervention', there will possibly still be treatment and labour costs and these must be included.

The introduction of a new technology may lead to reductions in resource use and costs elsewhere in the system. This may include reduction in use of another technology, savings from switching a drug from intravenous to oral, or a reduction in the use of concomitant therapies due to a reduction in adverse events. The inclusion of cost offsets must be clearly justified as they may not be achievable in practice. For example, a new technology could lead to a reduction in staff requirements which may be difficult for the budget holder to translate into savings (e.g., redeployment of staff).

It is recognised that some technologies have the capacity to impact significantly on costs (or savings) to other government departments. While these costs should not be included in the reference case, it may be appropriate to include them separately in the report. They should be accompanied by clear methods of their valuation.

2.11.2 Resource Measurement

Resource use data can be obtained from the literature or by primary data collection. Sources include RCTs, meta-analysis (synthesising data from several sources), clinical practice guidelines, local administration and accounting data, and expert opinion. The quality, validity, relevance and generalisability of this data to the publicly-funded Irish healthcare setting should be clearly described. This data should be subjected to comprehensive sensitivity analysis (Section 2.16) to determine the impact of the assumptions used in deriving the data. To maximise transparency, consumption of resources included in the economic evaluation should be reported in physical units of use.

2.11.3 Resource Valuation

Irish cost data should be used where possible. Currently, there are no agreed Irish cost models available. As a result, the generation of valid Irish cost data is challenging and time consuming. Until a valid Irish cost model is established, there is a need for flexibility regarding cost valuation. To maximise reproducibility and transferability, all assumptions and cost estimates must be clearly reported and subjected to one-way and probabilistic

sensitivity analysis (see also Section 2.16). In particular, where costs are applied from other countries, the assumptions necessary to transfer this data must be explicitly reported, with all costs converted to their Irish equivalent in euro using Purchasing Power Parity indices.[23] An example of how to transfer costs is included in Appendix 2.

There are two general approaches to determining costs: micro-costing and gross or macro-costing approaches. The former approach provides a direct assessment of unit costs for each input in the treatment of a particular patient type. While highly precise, this method is resource intensive and subject to bias and issues of generalisability depending on the source of the micro-costing data. Using aggregated costs such as in the macro-costing approach, national average levels for large units of input or output are applied. Macro-costing will typically involve the use of diagnosis-related group (DRG) or, in exceptional cases, average per diem costs.[24] The choice of DRG should be clearly justified. While less resource intensive and detailed, these data may be more generalisable nationally. The use of DRG costs may not always be appropriate (e.g. when the definition of the DRG is broad), or where it is unlikely that the mean cost reflects resource use in relation to the technology under appraisal. Sometimes the cost will have to be estimated as a weighted average of several DRGs, where weights are based on the expected number of cases with each DRG code. The precision of the estimates required and, therefore, the approach to be adopted will depend on the importance of each cost category to the evaluation. For example, a detailed micro-costing approach for the cost of drugs should be used in a comparison of different drug therapies, whereas costs for rare or infrequent hospitalisations for adverse effects attributed to the drugs may be assigned using a case-mix group cost if available or using a per diem rate.

Technology costs in the assessment should therefore reflect their cost to the HSE. The source of cost data must be reported with the details of what is included in the estimate. Data should be the most recently available, with the cost year specified. For the reference case, retrospective input costs should be inflated to the most recent calendar year using the Consumer Price Index for health or one of its sub-indices where reasonable justification is given for its use (see Appendix 2 for an example).[25] 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 indices (see Appendix 3 for an example).[26]

For non-drugs, the public list price should be used in the reference case analysis. To reflect the true cost of the technology to the HSE, additional discounts should also be accounted for, but only if these are consistently available within the HSE and are known to be guaranteed for the time specified. As noted, these costs should be varied as part of a comprehensive sensitivity analysis.

Pharmacy and wholesale margins and professional dispensing fees are set by the Department of Health and vary according to the product type, prescription volume and drug scheme through which the drug is supplied.[27, 28] Care should be taken to include and separately detail the prices, margins and fees relevant to the economic evaluation.

In general, the public list price paid for a drug should be used in the reference case analysis. Prices for drugs supplied through the community drugs schemes are listed in the reimbursement files of the Primary Care Reimbursement Service (PCRS) which are updated monthly.[28, 29] For new drugs, a system of external reference pricing is used by the government based on a currency-adjusted average price to the wholesaler in 14 EU Member States.[30] In the absence of a published list price, the price submitted by a manufacturer for a technology may be used, provided this price would apply throughout the HSE. The drug cost used in the reference case should reflect that of the product, formulation and pack size that gives the lowest cost, provided that this represents a realistic choice for use in clinical practice. Drug administration costs, the cost of drug wastage (e.g. from injection vials or from patient non-compliance), and the cost of therapeutic drug monitoring should be itemised and included where appropriate.

Drug cost estimates should reflect mandatory rebates from pharmaceutical manufacturers and importers. These costs may vary with changing pharmaceutical policy. A detailed guide for including drug costs in economic evaluations is available from the National Centre for Pharmacoeconomics.[29] So that the evaluation is relevant to decision making, in certain circumstances it may be appropriate to take into account discounted prices in order to reflect the true cost to the HSE. The use of price reductions for the HSE should only be used if these are consistently available throughout the HSE and are known to be guaranteed for the time specified.

Labour (pay) should be calculated using consolidated salary scales.[31] Associated non-pay costs should be estimated in accordance with the methods outlined in the Regulatory Impact Analysis guidelines issued by the Department of the Taoiseach,[32, 33] taking into account the most current information on the cost of superannuation for the public sector.[34, 35] If specialist equipment or consumables are also required, these should not be included as part of the general non-pay costs, but rather included as separate, specific cost items. An example of how to calculate labour (pay) and non-pay costs is included in Appendix 4. Due to the introduction of differential pay scales in 2011 for new entrants, care must be taken to ensure that estimated labour costs are reflective of the mix of salary scales in use. In most circumstances it may be pragmatic to use an unweighted average of the midpoint of the two scales and then use scenario analyses to separately test the impact of using only the existing or the new entrant pay scales.

Certain professional fees (such as the dispensing fees and patient care fees for pharmacists for drugs dispensed through the community drugs schemes and the High Tech Drugs Scheme) are set out in legislation and are available from the PCRS website.[28]

Value-added tax (VAT) is charged on goods and services provided within the state and is controlled by national and European law. VAT rates vary from 0% to 23% (correct as of October 2017) depending on the classification of the product. For example, the VAT rate for oral medicines is 0% whereas non-oral medicines (including topical preparations and injectables) attract VAT at a rate of 23% (correct as of October 2017). However, similar to other transfer costs, when assessed from the perspective of the government, VAT should be excluded from economic evaluations of cost-effectiveness.[26] However, VAT at the appropriate rate should be applied to the relevant resources when estimating budget impact.

In summary, while published drug cost data exist, the true cost to the HSE is impacted by a range of factors that must be considered when preparing the assessment. The methods of identifying other cost data are not well defined. The origin of the cost data should be clearly identified and justified. Where alternative sources are available, the cost chosen should be justified and where appropriate, the implications of using alternate data examined by sensitivity analysis (see also Section 2.16).

2.12 Valuing Outcomes

For the reference case, health effects should be valued in QALYs. Changes in quantity and quality of life should be reported separately along with a clear explanation of how the measures were combined, the assumptions made and the methods used to estimate QALYs. The use of generic preference-based methods such as the EQ-5D or SF-6D is recommended to measure utilities. In the absence of Irish public preference data, the population from which preferences are derived should be clearly described along with its relevance to the Irish population.

HTAs provide assessments of both the costs and benefits that accrue as a result of the use of alternative technologies. Typically, these benefits include a change in patients' health as a result of the technology. The data underpinning the measure of benefit must be appropriately appraised in terms of quality and quantity of evidence.

2.12.1 Quality-Adjusted Life Years

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.[36]

QALYs are calculated by assigning a value or weight (utility) to each possible health state experienced by the patient. Utilities are measured on an interval scale and range in value from 0 (death) to 1 (perfect health). Health states considered worse than death are permitted (score of less than zero). Summing the product of these values allows a quality adjustment to be made to the number of life years gained from a technology so that the relative desirability of the health state is reflected in the outcome, e.g.

> (Utility A x Years spent in health state A) + (Utility B x Years spent in health state B) = X QALYs

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. This increases its usefulness to decision makers who are charged with the allocation of finite resources between a diverse range of competing technologies and as such is recommended for the reference case.

Despite the apparent advantages of the QALY, its valuation may be inconsistent as utility weights used in its calculation are instrument-dependent. The utility measure used to capture health-related quality of life should be clearly stated and justified in order to maximise transparency and to facilitate comparisons between studies. Changes in the quantity and quality of life should be reported separately along with a clear explanation of how the measures were combined. Adopting QALYs as the preferred outcome measure facilitates comparisons with previous HTAs conducted in Ireland.

2.12.2 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.'[36]

As noted, weighted measures HRQoL of HRQoL (utilities) are used to calculate QALYs. This weighting of usually comprises two elements: a description of the health state and a valuation of that description.

Utility weights derived by different utility measurement techniques are known to give systematically different results.[37] One reason for differences in the utility value obtained for similar health states is due to differences in the valuation of the health state (e.g. whose preferences are measured and how these preferences are captured). 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[38] or SF-6D.[39] The commonly used EQ-5D is available in a three-level (EQ-5D-3L) version and, since 2009, a five-level (EQ-5D-5L) version. The

two measures value health states in different ways, although a mapping function based on UK data is available to convert between the two instruments.[40] The choice of instrument used in an evaluation should be justified. It is advisable to include a sensitivity analysis based on the alternative instrument (e.g., if the main analysis is based on EQ-5D-3L data, then include a sensitivity analysis based on the values mapped to EQ-5D-5L). 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.

For the reference case, information on the changes in the health state should be reported directly by the patient (or their carer, where relevant). A valuation of these changes in the health state should then be obtained using preferences elicited from a representative sample of the general population.

A transparent, systematic search (see also Section 2.8.1) should be used to gather health utility values from the literature. The choice of data should be clearly justified and the methods by which the data was generated clearly described. Where several data options are available, the uncertainty arising from this should be explored using a sensitivity analysis (see also Section 2.16).

Use of an generic preference-based measure, such as the EQ-5D or SF-6D, is recommended for the reference case as these measures have widespread availability, are easy to use and interpret and because they are based on preferences of the general public. The population from which these preferences are derived should be clearly described along with their relevance to the Irish population. Alternatively, direct HRQoL methods such as time trade-off or standard gamble may be used provided these have been gathered in a relevant population.

In the absence of relevant utility data from one of these generic techniques, alternative methods may be used including mapping data from other HRQoL measures to one of the generic instruments. Mapped utilities should be supported by a clear description of the regression model and study on which the mapping function is based and should be relevant to the population in question. The measure chosen must be fit for purpose, that is, it should accurately describe the health states arising in the illness. Details should be provided regarding the derivation, validation and relevance of any psychometric instrument used along with a description of its supporting published evidence.

2.12.3 Life years gained

Life years gained (LYG) expresses the additional years of life that a person lives as a result of receiving a treatment. For example, if a person is expected to live for five years with a given indication when untreated and ten years when treated, then five life years are gained by treatment. This outcome allows the effects of a treatment to be expressed in terms of the impact on

mortality. When applicable, LYG has the benefit of being easily understood. There is, however, no accepted willingness-to-pay threshold associated with LYG.

LYG is only a meaningful measure of effect if the treatment is expected to impact on mortality. The measure does not capture important health improvements that may not impact on mortality, such as improved physical ability, reduced neuropsychological stress, and reduced chronic pain.[41] If there is a long lead-in time to observed mortality effects, such as might occur with a vaccination programme, then LYG may be heavily discounted while lengthy periods of improved health status may not be captured in the analysis.

LYG is often extrapolated based on an intermediate outcome. For example, for an intervention that reduces blood pressure there may be anticipated benefits in terms of reduced mortality associated with reduced blood pressure. While trial data may provide evidence of a statistically significant effect on reducing blood pressure, the effect on mortality will have to be extrapolated from evidence regarding the impact of blood pressure on mortality. If LYG is used as the main outcome, then an evaluation will be heavily reliant on the accuracy of the extrapolation and assumptions regarding whether or not the treatment effect is sustained beyond what is captured in the supporting trials.

2.13 Modelling

Models used to synthesise and extrapolate available evidence should be developed in accordance with good modelling practice guidelines. The model should be clearly described, with the assumptions and inputs documented and justified. The methods for the quality assurance of the model should be detailed and the model validation results documented. The model and its key inputs should be subjected to comprehensive sensitivity analysis.

The use of modelling is typically required as part of an economic evaluation to make clinical and cost-effectiveness estimates relevant to the time frame under review. It may be necessary to extrapolate short-term outcome data or surrogate measures to long-term outcomes using modelling techniques. There are a variety of options to do this including superimposing the efficacy estimates from clinical trials on baseline probability estimates of survival from population-based sources.[42] Modelling techniques may also be used to generalise from clinical trial settings to routine practice, and to estimate the relative effectiveness of technologies where these have not been directly compared. There is no one optimal modelling technique, rather the choice of model should depend on the research question to be addressed.

Available modelling techniques include decision-tree analysis, state-transition or Markov models, discrete-event simulation (DES), system dynamic models, and partitioned survival models. Decision trees can be useful for relatively

simple models, or decision problems with special characteristics (e.g., 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.[43] System dynamic models are used to model the effects that may arise from a communicable disease programme.[44] Partitioned survival analysis is an approach similar to state transition modelling in which state membership is determined from a set of non-mutually exclusive survival curves. The major limitation of partitioned survival analysis is the underlying assumption that the survival endpoints are independent.[45]

The model should be transparent with all assumptions explicitly stated. Conclusions drawn from the model should be noted to be conditional on these assumptions.[3] Good modelling practice should be adhered to, so that the quality of the model and the analysis can be ensured.[3] To facilitate a critical appraisal of the outputs of a model, full documentation of the structure, data elements (identification, modelling and incorporation) and validation (internal, between-model and external) of the model should be addressed in a clear and transparent manner, with explicit justification provided for the options chosen. In the interests of transparency, an executable version of the model should ideally be available for scrutiny, having due regard for confidential commercial information and proprietary rights.

2.13.1 Model structure and validity

The model should be structured so that its inputs and outputs reflect the nature of the decision problem and should be sufficiently flexible so that it can be readily updated as data become available.

The structure of the model should reflect the true nature of the disease process being modelled as closely as possible. In the interest of simplicity, the model could be adapted to exclude clinical events not expected to differ between the comparator technologies in terms of severity, timing, and duration. In other words, if their exclusion has no impact on costs or effectiveness in terms of utilities, then they may be excluded. 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. Uncertainties in the parameters should be explored through sensitivity analysis (see also Section 2.16) and may include the use of alternate model structures. Heterogeneity in the modelled population (see also Section 2.15) should be accounted for where possible by disaggregating the population into

biologically or clinically plausible subgroups when there are differences in event probabilities, outputs and costs.

The internal validity of the model should be tested thoroughly prior to use to ensure that the mathematical logic of the model is robust. 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 and explaining differences if they exist. Calibration of the model using independent data may also be used, (although in practice such data may be hard to find) again with discrepancies in the findings explained. Counter-intuitive results generated by the model should be examined and explained. The validation, both internal and external, and calibration processes should be clearly documented.

Models may be deterministic or probabilistic. In a deterministic model, all parameters are set at an expected average value, and the outcome of interest is fully determined. In a probabilistic model, also called a stochastic model, parameter values can vary within plausible ranges so that each time the model is run a different answer is obtained. By running the model many times, referred to as Monte Carlo simulation, it is possible to determine a range of potential values for the outcome of interest. Probabilistic models are preferred as they allow for parameter uncertainty to be adequately incorporated into calculations. Outcomes of interest, such as the incremental costs or incremental benefits, should be calculated as the mean across simulations.

The Monte Carlo method provides an approximate estimate for an outcome of interest, such as the incremental costs between two technologies. The accuracy of the estimate depends on the number of simulations as Monte Carlo results are subject to sampling variability.[46] One approach to measuring whether sufficient simulations have been used is to examine the Monte Carlo error (MCE), which is the standard deviation of the Monte Carlo estimator. For large numbers of independent simulations, the MCE is approximately one over the square root of the number of simulations. The MCE for a given output (e.g., incremental costs) should preferably be less than five percent of the standard deviation of the outcome of interest.[47] It is also possible to monitor convergence on a stable estimate of the mean and upper and lower bounds for an outcome of interest. Justification should be provided for the choice of number of simulations along with evidence of convergence on a stable estimate for the outcome of interest.

Comprehensive sensitivity analyses (see also Section 2.16) of the key model parameters should be included using deterministic (one-way or multi-way) and probabilistic sensitivity analyses and an attempt made to quantify the uncertainty of the results.

It is important to note that a model is intended to be an accurate representation of what would happen if a technology was introduced. It

should be based on the best available information at the time of being reported. However, it must be acknowledged that for most technologies the evidence base and underlying parameters are not static. Even in the absence of further trials measuring treatment effect, the epidemiology of disease changes, as do the comparators, costs, and other factors influencing cost-effectiveness. An evaluation may therefore become out of date relatively quickly. Where there is a plausible expectation that parameters may change, scenario analyses can be used to test the impact of those anticipated changes.

2.14 Discounting Costs and Benefits

A standard rate of 5% per annum should be used to discount costs and outcomes in the reference case.

Costs and health outcomes that occur in the future should be discounted to present values to reflect society's rate of time preference. Accordingly, any costs or outcomes occurring beyond one year should be discounted using standard methods.

For comparability of results across evaluations, it is important that a common discount rate is used. For the reference case, a standard rate of 5.0% per annum for costs and outcomes should be used (see Appendix 6 for a sample calculation). This is rate is set by the Department of Finance and has been in effect since January 2014.[48] The discount rate should be varied in the univariate sensitivity analysis (see also Section 2.16). Limits of 0% and 10% are suggested. The lower limit allows the impact of discounting to be shown while the upper limit is reflective of a high rate of discounting. It can also be useful to investigate the impact of a ±1% in the discount rate.

2.15 Subgroup analysis

Stratified analysis of subgroups is appropriate to account for differences in cost-effectiveness that may arise due to important factors that impact on the target population or its management. Subgroups should ideally be identified a priori based on plausible biological, clinical or care-setting arguments.

The cost-effectiveness of a technology may be altered because of differences in costs, treatment outcomes or preferences arising from variations by treatment setting, by geographical location or because of patient heterogeneity (e.g. baseline risk, age, gender). Stratified analyses should be used to quantify the differences in cost-effectiveness that may exist in different subgroups. These subgroups should ideally be identified a priori with their choice clearly justified. The evidence supporting the biological or clinical plausibility of the subgroup effect should be fully documented, including

details of statistical analyses. Since the goal of the health system is to maximise the potential for health gain from its finite resources, a stratified analysis that allows cost-effectiveness to be modelled separately for each subgroup, may contribute important information to the final advice.

Clinical trials may be underpowered to detect differences in treatment effect in subgroups of patients. This applies to clinical effectiveness, safety, and other parameters of interest. Important parameters required for modelling, such as adherence, may not be available for the subgroups. Making assumptions that certain parameters may be applicable across subgroups may be incorrect and is likely to introduce bias. Consideration needs to be given to the quantity and quality of evidence supporting subgroups analysis, and appropriate justification provided for the data used to support such analyses.

2.16 Uncertainty

The effects of model uncertainty (i.e. structure, methods and assumptions) and parameter uncertainty on the outcome of the economic evaluation must be systematically evaluated using sensitivity analysis and scenario analyses for the range of plausible scenarios. The range of values provided for each parameter must be clearly stated and justified. Justification for the omission of any model input from the sensitivity analysis should be included. For the reference case, a one-way sensitivity analysis should be conducted to identify the key model inputs/assumptions contributing most to uncertainty. Multivariate analysis should be used for key model inputs. Probabilistic sensitivity analysis (PSA), in the form of a Monte Carlo simulation, should be used to assess parameter uncertainty. The expected value of perfect information (EVPI) should also be evaluated.

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.[49] 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. These ranges and the omission of any model input from the sensitivity analysis should be justified.

In economic evaluations it is very important to determine the impact of uncertain model inputs and assumptions on the study results. Potential bias and uncertainty may arise from a number of sources in the modelling process. These include:

- uncertainty arising out of possible bias in the structure of a model (e.g. how health states are categorised or the representation of care pathways). Assumptions about the model structure should be clearly

stated and justified and their impact on cost-effectiveness explored though a series of plausible scenario analyses.

- bias due to selective use of data sources to inform key parameters (e.g. estimates of relative efficacy, selection of cost data). These inputs must be fully justified and their impact on the uncertainty of the results explored by deterministic sensitivity analysis.
- uncertainty associated with the precision of the mean parameter values. These inputs should be clearly described and justified and their impact on cost-effectiveness explored through probabilistic sensitivity analysis.

To illustrate the impact of costs on the results, costs should be varied. Where no evidence of cost variation is available, it is pragmatic to vary costs by +/- 20% in one-way sensitivity analyses or using a log normal or gamma distribution in a probabilistic sensitivity analysis.

The bounds used in sensitivity analyses for some parameters may differ from those generated from the distribution used in the main analysis. The justification for parameter values used in the sensitivity analysis, whether represented as distributions or upper and lower bounds, should be provided. All parameters should be included in both deterministic and probabilistic sensitivity analyses, and the omission of any parameters from either analysis must be highlighted and justified.

2.16.1 Deterministic Sensitivity Analysis

Deterministic sensitivity analysis examines how parameter variables (included as point estimates) impact on model output. These include univariate and multivariate sensitivity analysis.

The simplest form of deterministic sensitivity analysis is the univariate or one-way sensitivity analysis. Here the impact of each variable in the study is examined by varying it across a plausible range of values while holding all other variables constant at their 'best estimate' or baseline value. The resulting difference provides some indication of how sensitive the results might be to plausible changes in that parameter.[(49)] Although useful, one-way sensitivity analyses do not capture the overall combined uncertainty that may be seen when parameters are varied simultaneously.[(49)]

In a multivariate analysis, two or more parameters are varied simultaneously in order to study the combined effect of these parameters on the results of the analysis. The greater the number of parameters in the model, the harder it becomes to present the results. To overcome this difficulty, the multivariate analyses may be presented in the form of scenario analyses, where a series of scenarios are constructed that represent a subset of the possible multivariate analyses. Examples include the use of extreme scenarios, corresponding to the best-case and worst-case situations, or the use of scenarios the analyst views to be probable. If a technology proves to be cost-effective under a worst-case scenario, then it is reasonable to predict that it will be cost-

effective if evaluated at the true values of the parameters. Where possible, the likelihood of particular scenarios arising should be assessed.

For the reference case, one-way and best/worst case sensitivity analysis are an important way of identifying parameters that are key drivers of the model and have a substantial impact on the cost-effectiveness. However, they do not represent the combined effects of multiple sources of uncertainty.

Sensitivity analysis in the form of threshold analysis may also be used when the baseline value of a parameter is unknown. Sensitivity analysis consists of estimating threshold values for parameters, above or below which the conclusions of the analysis change, e.g. by specifying the maximum incremental cost-effectiveness ratio that would be acceptable for a technology.

2.16.2 Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis (PSA) is the preferred approach for exploring uncertainty arising from parameter imprecision (e.g. uncertainty around the true mean values of cost and efficacy inputs) in decision-analytic modelling. With this approach, probability distributions are applied using specified plausible ranges for the key parameters rather than the use of varied point estimates for each parameter. Samples are then drawn at random from these distributions through a large number of simulations, as in the Monte Carlo simulation method. This enables the uncertainty associated with all parameters to be simultaneously reflected in the results of the model. In addition to reporting the number of Monte Carlo iterations, the range of values for each parameter as well as the distribution range used should be reported and justified. All uncertain parameters should be varied in the PSA. The amount that each parameter contributes to decision uncertainty should be quantified. Although computationally challenging, PSA produces a more realistic assessment of parameter uncertainty that the more simplistic deterministic analyses methods.[36] When selecting the model inputs, care should be taken to accurately reflect correlations that may exist between parameters.

Uncertainty can be characterised by estimating the probability that an option is cost-effective at different willingness-to-pay thresholds. The probabilities are plotted as a cost-effectiveness acceptability curve (CEAC). However, the option with the highest probability of being cost-effective at a given threshold will not necessarily have the highest expected net benefit. The cost-effectiveness acceptability frontier (CEAF) plots the option with the highest expected net benefit at different values of the cost-effectiveness threshold. As the consequences of failing to select the 'true' preferred alternative are ignored, the importance of uncertainty is not adequately reflected. A measure that does incorporate the magnitude of the difference between the true preferred and alternative options is the expected value of perfect information (EVPI).[50]

The EVPI can be determined directly from the results of the PSA. It estimates the value of simultaneously eliminating all the uncertainty of all uncertain parameters affecting the decision. Thus EVPI provides the decision maker with an indication of the expected costs of uncertainty and the value of collecting additional information to eliminate or reduce uncertainty. A higher EVPI indicates a larger opportunity cost associated with a wrong decision. If the EVPI exceeds the expected costs of further research to reduce parameter uncertainty, then it is potentially cost-effective to conduct additional research on the technology. EVPI should be computed for a range of ICER thresholds and presented graphically. Information on the parameters for which additional research is most useful can also be computed. Estimates of partial EVPI (EVPPI) can identify the parameters which uncertainties contribute most to the overall decision uncertainty.[51] Recent advances have greatly reduced the computational burden of estimating EVPPI making it feasible for models of typical complexity.[52-54]

2.17 Equity Considerations

For the purpose of the reference case, additional QALYs gained should be assumed to be of equal value, regardless of any considerations for specific characteristics of the population. However, an attempt should be made to meet the needs of decision makers by highlighting potential equity considerations in the report.

Achieving equity of health or healthcare is a key consideration of decision makers. There are many different ways in which this equity can be interpreted. For example, using a basis of equal need there may be a requirement for equal expenditure, equal utilisation or equal access to healthcare. Alternatively, regardless of need, equity could be defined as equal expenditure per capita or a simple criterion that all should enjoy equal health.

The incorporation of equity weights into QALY calculations has been proposed, so that societal concerns regarding the severity of health and the ability to realise benefits in health are considered. However, there are significant methodological issues concerning the derivation of equity weights and the circumstances and mechanisms by which these would apply to QALY calculations.

Research from the UK suggests that there is a societal preference for reducing inequalities in health, particularly those attributed to differences in socio-economic status.[55] There is also research to suggest that the public attributes a higher social value to improvements in health for those with worse lifetime health prospects and to those with dependents, but attributes a lower social value to improvements in health for the elderly and more controversially, to those perceived to have contributed to their own ill health.[56] It is possible that these findings may not be representative of societal preferences in Ireland.

The need to address inequalities in healthcare has been used as a criterion for prioritising HTA by decision makers. To meet the needs of the decision makers, an attempt should be made to include equity considerations in the report, such as highlighting unmet needs of certain disadvantaged groups. Consideration should also be given to describing the potential impact of a technology in addressing this concern.

For the purpose of the reference case, equity weights should not be applied to the outcome. Using QALYs as an example, an additional QALY should be assumed to be of equal value regardless of considerations of specific characteristics of the population.

2.18 Generalisability

The overall generalisability of the evaluation must be discussed in the context of the validity and relevance of the data used in addressing the needs of the target audience. Use of non-Irish data should be documented and its relevance to the Irish healthcare system established. Assumptions should be clearly stated, potential limitations identified and variability and uncertainty explored through sensitivity analysis.

Addressing the issues of generalisability and transferability of HTAs has been defined as a key principle for the improved conduct of HTA for resource allocation decisions. Transferability of economic evaluations across jurisdictions has been the subject of an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good research practices taskforce report. Working definitions employed by the task force were that evaluations were generalisable if they could be applied to other settings without adjustment. Evaluations were considered transferable if they could be adapted to apply to other settings.[57]

These issues are particularly pertinent to the use and transfer of evaluations between jurisdictions, e.g. the use of economic evaluations developed by manufacturers or sponsors to support pricing or reimbursement decisions at a local or national level.

The European Network of Health Technology Assessment (EUnetHTA) has developed a Core Model® for HTA that attempts to define and standardise elements of HTA. By reducing differences in content across reports, the Core Model® facilitates international adaptation and adoption 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.[58]

In the absence of national data, economic evaluation studies often rely on international data to develop their recommendations. Specific concerns for generalisability of clinical and economic data to HTAs in the Irish healthcare setting are:

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

The practice of generalising from efficacy to effectiveness and transferring clinical data between countries is usually accepted to be reasonable provided the criteria defining the population are clearly described, potential differences highlighted and the key parameters subjected to extensive sensitivity analysis. While epidemiological data may also be transferable, there is greater potential for variability. Any assumptions made should be clearly stated, potential limitations identified and variability and uncertainty explored through sensitivity analysis.

Economic data is generally not considered to be transferable between countries because of differences in the prices or tariffs of the resources used and differences in resource consumption due to differing healthcare management methods. The absence of an Irish cost database further complicates this issue. As outlined in Section 2.11, the quality, validity, relevance and generalisability of the cost and resource utilisation data to the publicly-funded Irish health and social care setting should be clearly described. To maximise transparency, resource use and unit costs should be detailed separately to the total costs. Undiscounted, disaggregated cost and outcome data should be presented in addition to providing the aggregated, discounted summaries.[59]

The overall generalisability of the evaluation must be discussed in the context of the validity and relevance of the data used in addressing the needs of the target audience. As noted, a primary concern is the extent to which regional differences (internal and external) in the costs and effectiveness of a technology may contribute to meaningful differences in the cost-effectiveness. These differences should be identified and discussed and the likely impact of the differences on the results and conclusions of the report highlighted.

2.19 Reporting

A well structured report with information provided on each of the elements outlined in the guidelines should be provided. Data elements should be tabulated with details provided of their source and precision. The distributions used to characterise uncertainty in probabilistic analyses should be documented and justified. All results should be presented in both their disaggregated and aggregated form. Expected mean costs, total costs and QALYs should be documented for the comparator technologies with ICERs

calculated, as appropriate. Uncertainty should be presented graphically (tornado plot for one-way sensitivity analysis, scatter plot and cost-effectiveness acceptability curves for PSA) and in tabular form to facilitate interpretation. The probability that a technology is cost effective at a range of threshold levels should also be presented.

The economic evaluation 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 report should be well structured with information provided on each of the elements outlined in these guidelines. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement has been developed to outline the elements that should be presented in an assessment.[60] Assessments should adhere to the CHEERS statement for reporting. In the interests of transparency, an assessment should include a conflict of interest statement in relation to all those involved in the assessment. A conflict of interest occurs when judgement might be influenced by a secondary interest such as financial gain.[61]

Detailed examples to illustrate how results should be presented are provided in Appendix 7.

2.19.1 Presenting Data

All parameters used in the estimation of clinical and cost-effectiveness should be itemised in tabular form with data sources and precision measurements for each parameter included. Individual cost components should be presented separately as well as being aggregated into total costs. In probabilistic sensitivity analysis, the distributions used to characterise the uncertainty surrounding each variable should be included. Sources of data should be clearly described. Where parameters have been synthesised using pooling, the method used should be stated.

2.19.2 Presenting Results

All results should be reported in detail in both their disaggregated and aggregated form. Final results should be tabulated for expected total and incremental costs, and expected total and incremental QALYs (or LYG, as appropriate) for each intervention. For QALYs, the life-year component should be reported separately. Where appropriate, the results for cost-utility analysis should be presented as incremental cost-effectiveness ratios (ICERs). ICERs present the cost per unit of outcome, e.g. the expected additional total cost to the expected additional QALYs (LYG) and are calculated as follows:

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

As the ICER becomes larger, the intervention is said to be less cost-effective.[10] Where more than two technologies are being compared, the

results should be reported in tabular form, presented in the order of increasing costs. Technologies that may be excluded on the basis of simple dominance (they are more costly and less effective than the alternatives) are eliminated from further calculations. The initial ICER should then be calculated by comparing each programme with the one above it, excluding those programmes that are dominated. The final ICER is then calculated after eliminating technologies that are subject to extended dominance (other alternatives available that are more effective and more costly, but provide better value for money as identified by the initial ICER). [36]

For deterministic models, the ICER is computed according to the base-case values. For a probabilistic model, the ICER may be computed as the mean incremental cost divided by the mean incremental benefit across simulations. It should be clearly reported which approach has been used. Where the latter approach is used, it is typically possible to also compute a 95% confidence interval for the ICER and this can also be reported to indicate the precision of the estimate. For probabilistic analyses it is also useful to present the probability of an ICER being below €20,000 and €45,000 per QALY, respectively. Where ICERs are presented from both deterministic and probabilistic analyses, any differences between the results of the two approaches should be explained. The preference is for ICERs calculated from a probabilistic analysis.

An ICER can be negative if either the incremental costs or incremental benefits are negative. In these cases it may be more appropriate to consider the results in terms of net monetary benefit (NMB).[62]

Uncertainty should also be presented in tabular form for ease of review. In addition to the expected mean results (costs, outcomes and ICERs), the probability that the intervention is cost-effective at a range of threshold values should be reported. For complex cost-effectiveness models fitted using simulation methods and where there is considerable uncertainty and instability around the estimates of ICERs between alternative technologies, the data should be displayed graphically to facilitate its interpretation. The choice of graphics depends on the nature of the analysis, but may include:

- cost-effectiveness plane to present the incremental costs and effects of two (or more) comparator technologies including the cost-effectiveness efficiency frontier
- tornado diagrams to display the results of subgroup effects and one-way sensitivity analysis
- scatter plots to present incremental effects and costs generated from probabilistic sensitivity analysis of comparator technologies on the cost-effectiveness plane
- cost-effectiveness acceptability curve to present the probability that a technology is more cost-effective than its comparator. In a study comparing more than two technologies, it should present the probability

that a technology is the most cost-effective as a function of the threshold willingness to pay for one additional unit of benefit.[36]

2.19.3 Interpreting Results

One of the implications of making comparisons regarding the cost-effectiveness of different technologies, is that a threshold ratio exists above which a technology is not considered to be cost-effective. Historically, the threshold 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. It is important to note that these thresholds have not been derived empirically. While consideration of the cost-effectiveness of a technology is necessary, it is not the sole basis for decision making.

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 healthcare settings. These may be briefly summarised into three main themes.

Opportunity cost: given a fixed budget, for the publicly funded health system, the true opportunity cost of a technology can be assessed in terms of what technologies must be foregone or displaced in order to fund new, potentially more costly technologies. In the absence of a fixed health budget, the true opportunity cost of a new technology must be examined in terms of what must be forgone in terms of other publicly-funded sectors (e.g. education, housing). In reality, the cost and benefits of all competing technologies within the healthcare and other sectors are unlikely to be known by the decision makers. It is also of note, that there may be a disconnect between the technologies that are displaced in practice to fund new technologies, and those that should be displaced based on efficiency grounds. The net impact of this may be that the decision to adopt a new technology may reduce, rather than increase overall population health.

Willingness-to-pay: the threshold ICER below which a technology would always be reimbursed could be informed by research that examines the value society attaches to health gain and how this value varies according to the population to be treated (equity considerations). In theory, however, a tacit value for health gain could be interpreted from the proportion of public expenditure allocated to health relative to other competing resources.

Past decisions: the ICER of a new technology could be compared to that of other technologies that are currently funded. Such comparisons may be helpful when an ICER is substantially lower than that of other technologies considered to be cost-effective that were recommended for reimbursement, or when an ICER is substantially higher than that of a

technology previously rejected as not cost-effective. Other factors such as equity issues, affordability, resource constraints and the uncertainty surrounding the advice have been considered in judging the cost-effectiveness of a technology for reimbursement.

In summary, there is no fixed cost-effectiveness threshold above or below which technologies are guaranteed to be rejected or accepted for reimbursement. Several factors may impact on a decision to reimburse a technology and any conclusions on cost-effectiveness should be supported by the strength of the evidence (e.g. clinical effectiveness, costs, plausibility of the inputs and assumptions in the model) and an estimate of the uncertainty surrounding the results (e.g. validity of the data, range and plausibility of the ICERs, likelihood of error).

2.20 Budget Impact Analysis

A budget impact analysis should be submitted along with the economic evaluation of a technology to best inform the needs of the decision maker regarding its affordability and cost-effectiveness.

In addition to assessment of cost-effectiveness, an assessment of the budget impact of technologies is increasingly being required by decision makers to enable financial planning and to address affordability issues. CEA and budget impact analysis (BIA) are viewed as distinct, but complementary approaches within a HTA, even though both analyses may share many of the same data. The purpose and distinguishing factor of a BIA is that it analyses the net financial impact, or affordability, of adopting a new technology relative to the current pattern of care.

Detailed guidelines in relation to the conduct of BIA from the perspective of the publicly-funded health and social care system in Ireland are also available.[63] The purpose of these guidelines is to standardise the method of performing and presenting BIA conducted in Ireland, so that decision makers can be provided with assessments that are reliable, consistent and relevant to their needs.

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.[10, 62]

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.[7] 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.[9] Where an intermediate (surrogate) marker is chosen it must have a validated, well established link with an important patient outcome.[64] 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.[62]

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.[62]

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.[8] 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.[59] 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.[10] 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[65] since valuation is believed to be influenced by culture and income.[66]

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.[7] 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.[8] It is considered the gold standard method for conducting economic evaluations and is recommended by many expert and consensus groups.[6]

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.[67] 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.[10] 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.[10] 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.[12]

Limitations

The use of cost-benefit analysis is limited by the methods used to translate benefits to monetary values.[12] In practice, cost-benefit analysis is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms.[11, 68]

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.[13]

Appendix 2 – How to inflate retrospective health costs using the Consumer Price Index for Health

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, outpatients 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

Example:

Convert €50 (2014 to 2017) using the CPI for Health[25]

Consumer Price Index by Commodity Group, Month and Statistic		
Month	**2014**	**2017**
January	101.3	102.4
February	101.2	103.9
March	101.2	103.8
April	101.2	104.0
May	101.0	104.1
June	101.0	-
July	101.2	-
August	101.1	-
September	101.1	-
October	101.4	-
November	101.4	-
December	101.5	-
Average	101.2	103.6

Using the Formula:

[(Latest Index Number/Earlier Index Number)x100] - 100

Price increase = [(103.8/101.2)x100] – 100

= 2.57%

Therefore, €50 in 2014 is equivalent to €51.29 in 2017.

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 3).

Appendix 3 – How to transfer 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.[23]

The monthly purchasing power parities (PPPs) used to derive the table are obtained by extrapolating the 2005 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, 2008 are annual benchmark results calculated by Eurostat[69]
  - PPPs for 2009 are OECD estimates
- for non-European countries, all PPP are OECD estimates based on the triennial benchmark results for 2005.

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

Example:

Convert £50 (year 2017) to (Irish costs in €) using the PPP

The representative basket costs a hundred units in the country whose currency is specified (U.K. representative costs = 100). Using the Purchasing Power Parities Comparative Price Levels for April 2017,[23] the comparative price level is 105 for Ireland.

Representative basket costs (U.K.)	100
Comparative price level for Irish basket	105
2017 value (£)	£50
Converted to Irish costs in €	€52.50

Appendix 4 – Adjusting for pay-related costs in Ireland

Labour (pay) should be calculated using consolidated salary scales available from the HSE.[31] An average salary cost should be used for the relevant grade by taking a cash value mid-way between the lowest and the highest points on the scale.[32, 33]

Associated non-pay costs should be estimated in accordance with the methods outlined in the Regulatory Impact Analysis (RIA) guidelines issued by the Department of the Taoiseach. This method includes adjustments for non-pay costs associated with hiring additional staff including employers' PRSI, superannuation, as well as general overheads such as rent, light and heat, office facilities, telephone, general supplies, etc.[32, 33] Where data are available on cost allocation within overhead departments, a more specific method for allocating overheads can be applied, however if data is not available a general rule of thumb of 25% of direct salary cost should be applied.[62] The net pension cost as a percentage of pensionable remuneration is an estimated 4% for healthcare workers in the public sector.[32]

The total staff cost is calculated as follows:

A	Pay	Mid-point of pay range
B	Direct Salary Cost	A + Employers PRSI
C	Total Salary Cost	B + (Imputed Pension Cost = 4% of A)
D	Total Staff Cost	C + Overheads (25% of A)

Example:

- a staff nurse has 13 points on a pay scale ranging from:€28,483 to €44,800 (as of 1st April 2017); the 7th point or mid-point of this scale is €37,137.
- direct salary cost is €37,137 + 10.75%(€37,137) = €41,129
- total salary cost is €41,129 + 4%(€37,137) = €42,614
- total staff cost is €42,614+ 25%(€37,137) = €51,898
- therefore, the total cost associated with employing an additional staff nurse includes the pay and non pay costs and is estimated at €51,898.

Notes:

- If specialist equipment or consumables are also required these should not be included under the general, non-pay costs, but rather as separate cost items.
- These are average costs and are applicable only on a general basis.
- Formulae for the calculation of daily and hourly rates are available in the RIA guidelines and should be consulted, where appropriate.

Appendix 5 – Depreciation of assets in accordance with Health Service Executive accounting practices

The accounting treatment to be used depends on the asset type.*

Asset Type	Accounting treatment
Land	Land is not depreciated
Buildings	Depreciated at 2.5% per annum, straight line basis
Modular buildings (i.e. prefabricated)	Depreciated at 10% per annum, straight line basis
Work in progress	No depreciation
Equipment – computers and ICT systems	Depreciated at 33.33% per annum, straight line basis
Equipment – other	Depreciated at 10% per annum, straight line basis
Motor vehicles	Depreciated at 20% per annum, straight line basis

Example: Depreciate a new office block valued at €5,000,000 completed 1 January 2010	
Year	**Depreciation Charge**
2010	€125,000
2011	€125,000
2012	€125,000
2013	€125,000
2014	€125,000
2015	€125,000
2016	€125,000
2017	€125,000
Continue charging for each year until the asset is disposed of or fully depreciated	

Of note, within the HSE, depreciation is not charged to the Income and Expenditure account, but is instead is charged to the Capitalisation Account in the Balance Sheet.

* Personal Communication, J Leech, General Manager, Vote, Treasury and Capital Finance Directorate, HSE

Appendix 6 – Application of discounting

Costs and benefits arising today are usually valued more highly than costs and benefits occurring at some point in the future. Discounting health benefits reflects society's preference for benefits to be experienced sooner rather than later. Discounting costs reflects society's preference for costs to be experienced in the future rather than the present. In Ireland, the same discount rate of 5% is specified for both costs and benefits. Some jurisdictions allow for differential discounting, whereby a (typically) lower rate of discounting is applied to benefits.

Costs and benefits are multiplied by the discount factor specific to the year in which they occur. The discount factor is computed as:

$$\text{discount}_t = \frac{1}{(1 + r)^t}$$

With: r = discount rate (0.05)
t = time point in years (=0,1,2,...,n)
n = time horizon

Costs and benefits are multiplied by the discount value specific to the year in which they occur. The following table shows an example application of discounting over 10 years where the annual cost of the intervention is €1,000 for two years with a further two years of follow-up care at €500 per annum. The annual QALYs are 0.70 during treatment, 0.8 during follow-up, and 0.9 thereafter.

Year (t)	Discount	Cost (€)		Benefit (QALYs)	
		Undiscounted	Discounted	Undiscounted	Discounted
0	1.0000	1,000.00	1,000.00	0.70	0.70
1	0.9524	1,000.00	952.38	0.70	0.66
2	0.9070	500.00	453.51	0.80	0.73
3	0.8638	500.00	431.92	0.80	0.69
4	0.8227	0.00	0.00	0.90	0.74
5	0.7835	0.00	0.00	0.90	0.71
6	0.7462	0.00	0.00	0.90	0.67
7	0.7107	0.00	0.00	0.90	0.64
8	0.6768	0.00	0.00	0.90	0.61
9	0.6446	0.00	0.00	0.90	0.58
Total		3,000.00	2,837.81	8.40	6.73

Appendix 7 – Presentation of results

The results of the base case and sensitivity analysis should be presented in tabular and graphical form to aid the understanding of the audience. A number of approaches may be used depending on the nature of the analysis. These include illustration on the cost-effectiveness plane, tornado diagrams, scatter plots and cost-effectiveness acceptability curves.

Comparison of Alternatives - ICERs and their Interpretation

Where appropriate, the results of the cost-effectiveness analysis (CEA) should be presented as incremental cost-effectiveness ratios (ICERs). The ICER describes the difference in costs and benefits of the two alternative technologies and illustrates the additional benefit achieved for the additional cost incurred. Note, one of these alternatives may be 'no treatment'.

The ICER for technology A compared to technology B is calculated as follows:

$$\text{ICER} = \frac{\text{(costs of A - costs of B)}}{\text{(effects of A - effects of B)}}$$

that is,

$$\text{ICER} = \frac{\text{incremental costs}}{\text{incremental effects (benefits)}}$$

An ICER therefore presents the incremental cost per additional unit of outcome. This could be the cost per case averted, cost per patient treated, cost per LYG or cost per QALY gained. The smaller the ICER, the more cost-effective technology A is relative to technology B. Where a technology is less costly and more effective, or more costly and less effective, an ICER that is less than zero will be generated.

Example: HTA of a population-based colorectal screening programme in Ireland

Table 5.1 shows the lifetime costs and benefits in terms of QALYs for six screening scenarios for colorectal cancer compared to a policy of no screening. The 'no screening' option was the least expensive policy. Once-only flexible sigmoidoscopy (FSIG) at age 60 was associated with the smallest increase in costs compared to no screening (€6.15 per person). All six screening scenarios were associated with small gains in QALYs compared to no screening. The maximum health gain was for faecal immunochemical test (FIT)-based screening (0.023 QALYs per person compared to no screening). Combining costs and benefits, and comparing each scenario with no screening, the incremental cost per QALY gained was smallest for FSIG at age 60 (€848), and highest guaiac-based faecal occult blood test (gFOBT) from ages 65 to 74 (€5,289).

Table 5.1: Costs and benefits for six screening scenarios for colorectal cancer compared to a policy of no-screening

Strategy	QALYs		Cost (€)		ACER[2]
	Mean	Incremental[1]	Mean	Incremental[1]	
No screening	10.957	-	1,064.63	-	-
FSIG age 60	10.965	0.007	1,070.79	6.15	848
FIT at 55-64 (biennial)	10.974	0.017	1,083.23	18.60	1,102
FIT at 55-74 (biennial)	10.980	0.023	1,103.02	38.39	1,662
gFOBT at 55-64 (biennial)	10.962	0.005	1,080.36	15.73	3,103
gFOBT at 55-74 (biennial)	10.965	0.008	1,094.07	29.44	3,885
gFOBT at 65-74 (biennial)	10.960	0.003	1,078.60	13.97	5,289

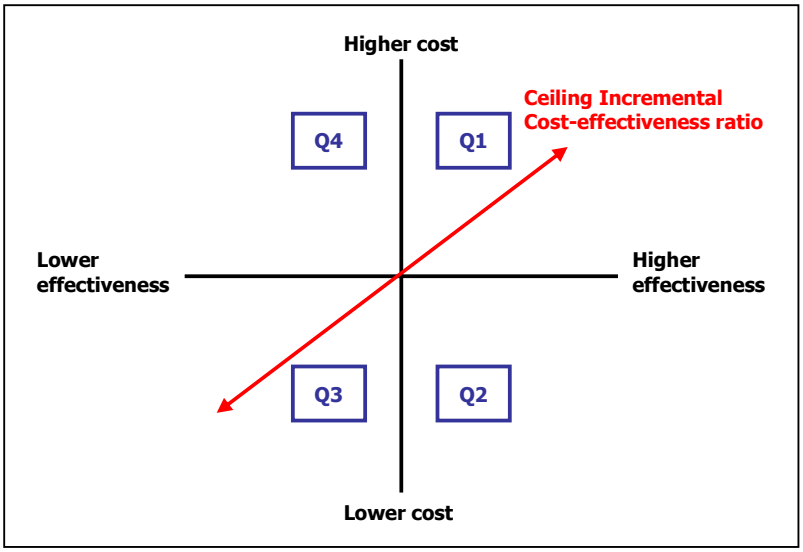
FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%
[1] Each incremental value compares value for that strategy to common baseline of no screening
[2] Average cost-effectiveness ratio (€/QALY), relative to strategy of no screening

Source: Adapted from Health Information and Quality Authority (2009*) Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

To aid interpretation, the point-estimates for costs and effects for the alternative technologies may be plotted on a cost-effectiveness plane (Figure 5.1). The incremental effects are shown on the horizontal axis (i.e., the difference in effects between technology A and technology B). The incremental costs are shown on the vertical axis (i.e., difference in costs between the two technologies). The cost-effectiveness plane can be considered in four quadrants: Q1 to Q4. A point-estimate in Q2 indicates that the new technology, B, is less costly and more effective than the alternative, that is, it is said to dominate the alternative and would be the preferred option. Conversely, a point estimate in Q4 would indicate that the new technology is more costly and less effective than its alternative, that is, the alterative would be considered the dominant strategy. A point estimate in Q3 indicates that the new technology is less costly, but also less effective than the alternative. A decision as to which is the preferred strategy would depend on whether the lower cost would make the lower effectiveness acceptable. A point estimate in Q1 indicates that the new technology is more costly and more effective than the comparator. If a line is drawn connecting the point-estimates for two technologies, the slope of this line represents the ICER between those technologies. In this scenario, the decision on which technology is preferable would depend on how a decision maker is willing to pay for the additional benefits associated with the new technology. For the data in table 5.1, each of the technologies considered would have a point estimate in Q1 when plotted on a cost-effectiveness plane, that is, each

technology was estimated to be more costly and more effective when compared against a policy of 'no screening'.

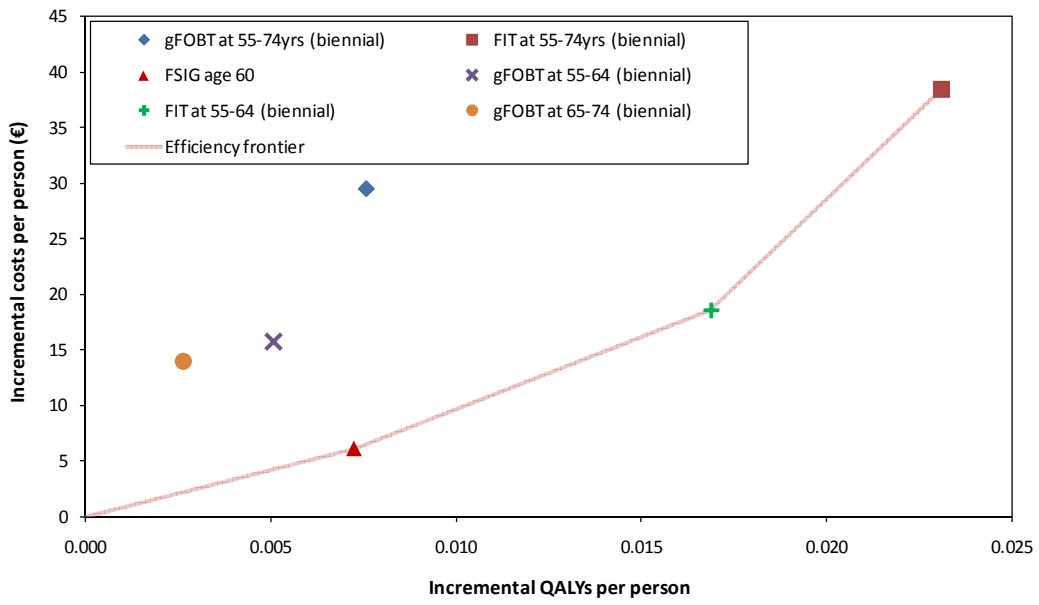
Figure 5.1: Cost-effectiveness Plane



Typically, when a series of technologies are being compared, an average cost effectiveness ratio (ACER) for each technology versus the alternative of usual care is calculated as a first step. The technologies may then be compared to one another by computing the ICERs of one alternative versus another. This estimates how much additional benefit is achieved for the additional cost incurred for each technology compared to the other. The information from Table 5.1 is further illustrated on an incremental cost-effectiveness plane in Figure 5.2. The ICERs for FSIG and the two FIT strategies can be connected with a line of lower slope than a line connecting any other two scenarios (indicating a lower cost-effectiveness ratio) – this line is the cost-effectiveness efficiency frontier.

An intervention is simply dominated when an alternative is at least as effective and is less costly, or if it is less effective and at least as costly. Extended dominance refers to the situation where an intervention is at less effective and at least as costly as a combination of two other interventions. In the example, biennial gFOBT from age 55 to 64 is subject to simple dominance by FSIG at age 60.

Figure 5.2 Incremental cost-effectiveness plane for screening scenarios, based on QALYs



FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%

Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

Once it has been determined which strategies are on the cost-effectiveness efficiency frontier, these may be compared on the basis of ICERs. From the current example, the FSIG and two FIT strategies formed the efficiency frontier. The ICERs for these strategies are given in Table 5.2 below. It can be seen that for FIT at ages 55 to 74, although the ACER was €1,662/QALY relative to no screening, it is €3,176/QALY relative to the next most cost-effective strategy – FIT from ages 55 to 64.

Table 5.2: Incremental cost-effectiveness of strategies on the cost-effectiveness efficiency frontier

Strategy	QALYs		Cost (€)		ICER[2]
	Mean	Incremental[1]	Mean	Incremental[1]	
No screening	10.957	-	1,064.63	-	-
FSIG age 60	10.965	0.007	1,070.79	6.15	848
FIT at 55-64 (biennial)	10.974	0.010	1,083.23	12.44	1,294
FIT at 55-74 (biennial)	10.980	0.006	1,103.02	19.79	3,177

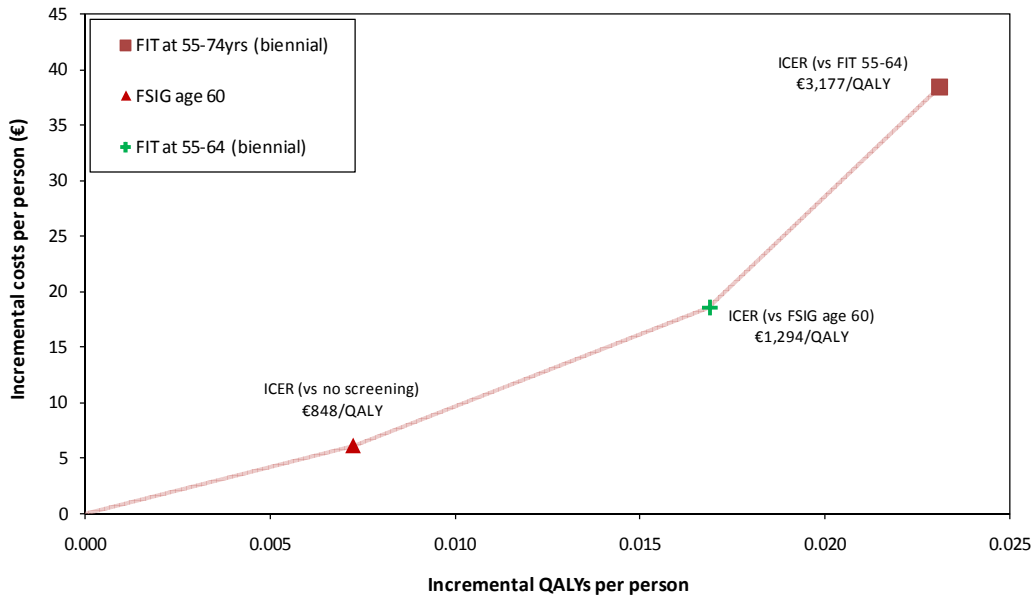
FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%
[1] Each incremental value compares value for that strategy relative to next most effective strategy
[2] Incremental cost-effectiveness ratio, relative to next most effective strategy

Source: Adapted from Health Information and Quality Authority (2009*) Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

For emphasis, it can be useful to plot the strategies on the cost-effectiveness efficiency frontier along with the appropriate ICERs (Figure 5.3).

The decision as to which strategy to adopt depends on the willingness-to-pay of the decision maker. Adopting FIT from age 55 to 74 rather than FIT from age 55 to 64, for example, would result in an increase in the total costs of €19.79 and in the QALYs of 0.006, yielding an ICER of €3,176.70 per QALY gained. This would be considered highly cost-effective.

Figure 5.3 Incremental cost-effectiveness plane for screening scenarios, based on QALYs



FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; QALY=quality-adjusted life year. Costs and outcomes discounted at 4%

Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

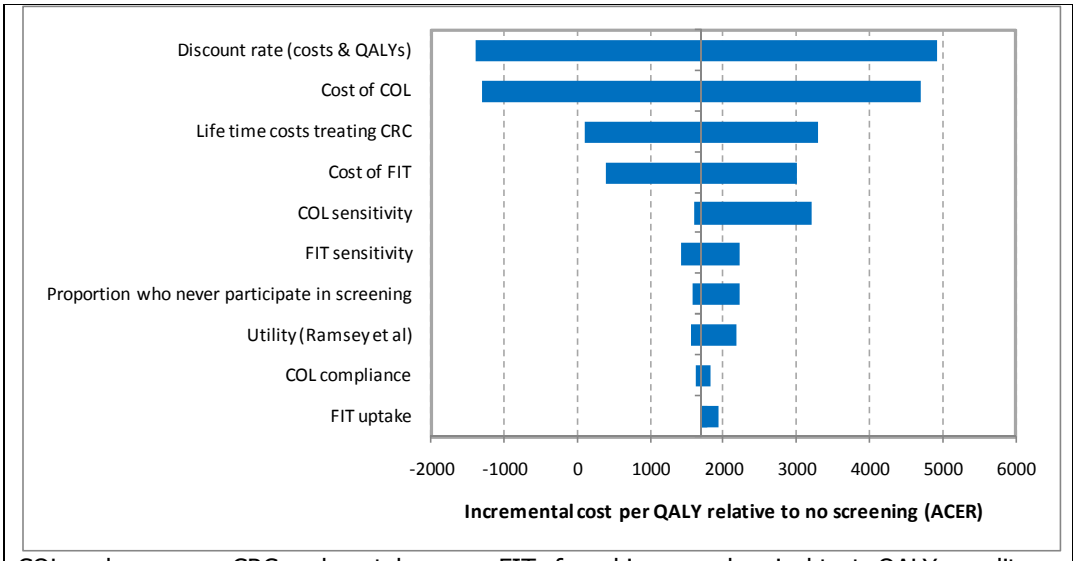
Comparison of Alternatives: Dealing with Uncertainty

Tornado diagram

A tornado diagram is a useful way to present the results of one-way and multi-way sensitivity analysis in a single graph. The ICER results are depicted on the horizontal axis, while the parameters analysed are depicted on the vertical axis. The dotted line represents the results for the Reference case, while the bars depict the results for the parameters when tested over the full range of values in the sensitivity analysis. Bars that extend beyond €0 indicate where the intervention is cost-saving.

Figure 5.4 provides an example of a tornado diagram. The ICER for the Reference (base) was less than €2,000 per QALY (€1,662), which would be considered highly cost-effective. Most of the parameters considered had relatively little impact on the estimates of cost-effectiveness, even when set at their most extreme values in the sensitivity analysis. In some instances, the intervention became cost-saving compared to no screening (i.e., an ICER less than €0 per QALY gained). The most influential parameters were the discount rate and costs of colonoscopy. However, even for these most influential parameters, the screening scenario remained highly cost-effective in all analyses (i.e., an ICER of less than €5,000 per QALY).

Figure 5.4 Tornado diagram of one-way and multi-way sensitivity analysis for FIT at 55-74 years



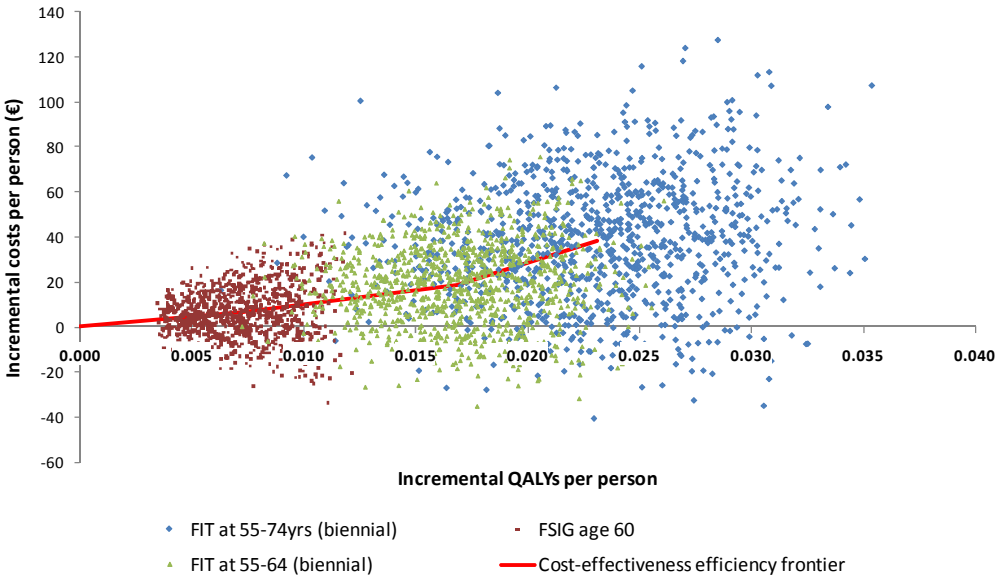
COL=colonoscopy; CRC=colorectal cancer; FIT=faecal immunochemical test; QALY=quality adjusted life year.

Source: Adapted from Health Information and Quality Authority (2009) *Health Technology Assessment (HTA) of a population-based colorectal screening programme in Ireland.*

Scatter Plot

For a probabilistic sensitivity analysis (PSA), the analyst is encouraged to present the results using the scatter plot on the cost-effectiveness plane, as depicted in Figure 5.5 below. Each symbol on the scatter plot represents one simulation of the parameter set. The level of uncertainty in the model is characterised by the spread of the point estimates.

Figure 5.5 Cost-effectiveness of the core scenarios: probabilistic sensitivity analysis



Note: Each symbol represents one simulation of the parameter set.

Source: Adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population-based colorectal screening programme in Ireland.*

In Figure 5.5, the spread of both the incremental costs and QALYs was wider for the FIT-based screening scenario than for the other options, indicating greater uncertainty for this option. Although considerable uncertainty is evident in the scatter plot, all three scenarios analysed remained cost-effective in all simulations compared to a policy of "no screening". In addition, there were instances where both FSIG and FIT-based screening appear to be cost-saving compared to "no screening". There is a clear distinction in terms of incremental QALYs between FIT screening and screening based on either gFOBT or FSIG, with almost all simulations of FIT-based screening associated with greater gains in QALYs than the other two options. For ease of reading, only the core strategies have been included in Figure 5.5. However, ideally all modelled strategies would be included in the above scatterplot.

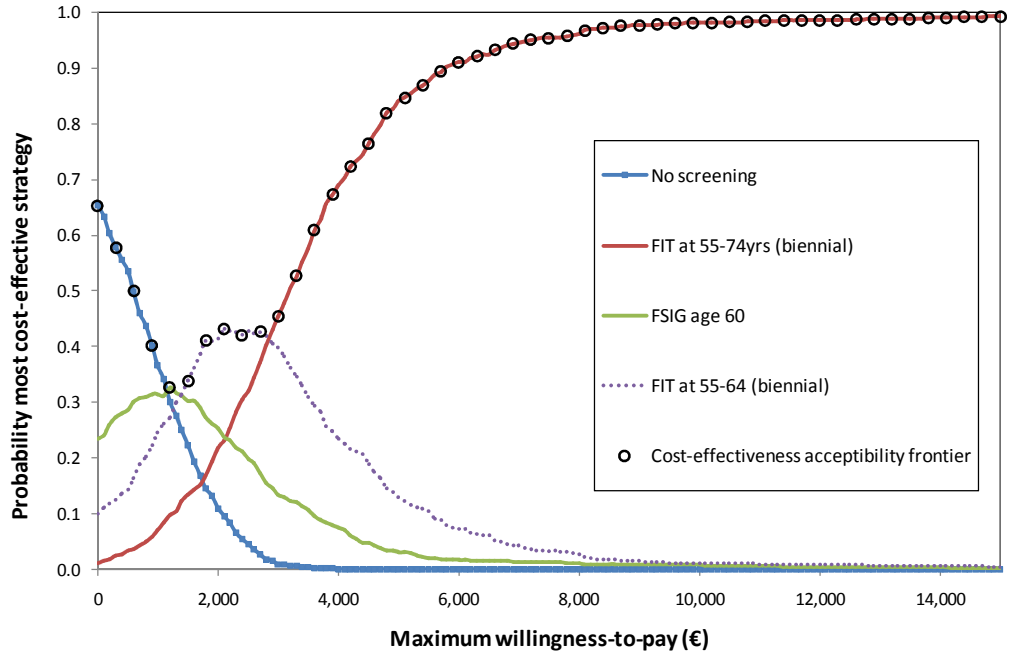
Cost-effectiveness Acceptability Curves

The results of a PSA can be summarised using cost-effectiveness acceptability curves (CEACs). The CEAC for a technology gives the probability that a technology is cost-effective across a range of willingness-to-pay thresholds. This allows the decision maker to set their own threshold ICER for how much they are willing to pay for an additional QALY and to see the probability that the technology would be cost-effective at this threshold. When a series of technologies are being considered, a cost-effectiveness acceptability frontier (CEAF) can be plotted. This shows the probability that the optimal option (the

one with the greatest expected net benefit) will be cost-effective at different willingness-to-pay thresholds.

Using the colorectal cancer screening example, Figure 5.6 graphs the CEACs for the three screening options compared to a policy of 'no screening' and includes the CEAF. Up to a willingness-to-pay threshold of €1,150 per QALY, no screening is the most cost-effective option. If the maximum decision makers are willing-to-pay is between €1,200 and €1,350 per additional QALY, the most cost-effective strategy would be expected to be FSIG once-only at age 60. If the willingness-to-pay threshold is increased to between approximately €1,400 and €2,800 per additional QALY, biennial FIT in the 55-64 age group would represent the screening option most likely to be cost-effective. At a threshold of €2,850 per additional QALY or more, the preferred option would be biennial FIT from age 55 to 74. The CEAF shows the probability that the 'optimal' option is cost-effective. At a threshold of €10,000 or more per additional QALY, there is a greater than 95% probability that screening would be cost-effective.

Figure 5.6 Example of cost-effectiveness acceptability curves and cost-effectiveness acceptability frontier for FSIG (once at age 60 years, FIT at ages 55-64 and FIT and ages 55-74)



FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy.

Strategies for gFOBT (guaiac-based faecal occult blood test) are excluded for readability. The maximum probability of gFOBT strategy being cost-effective at any willing-to-pay threshold was 0.008.

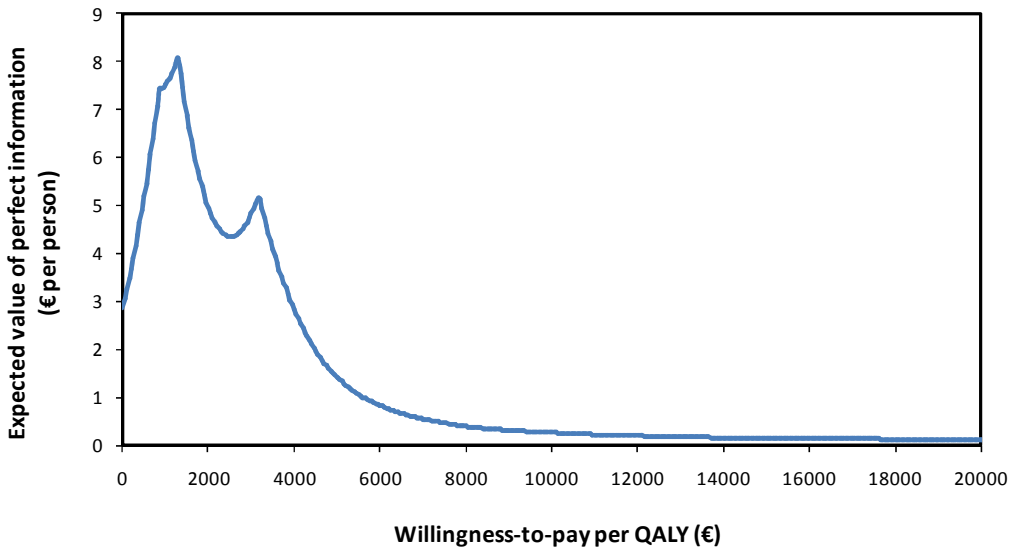
Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population based colorectal screening programme in Ireland.*

Expected value of perfect information (EVPI)

EVPI can be determined directly from the outputs of a probabilistic sensitivity analysis, where each simulation represents a possible future resolution of the existing uncertainty for which the optimal decision can be identified. EVPI combines both the probability of the wrong decision being made and the consequences of the wrong decision in terms of the net benefit forgone, and it can be expressed in health or monetary terms. EVPI can be reported for a range of specified ICER thresholds and is computed as part of a probabilistic sensitivity analysis or probabilistic model. For the following example, the EVPI has been computed at each specified willingness-to-pay threshold as the average maximum net monetary benefit across all simulations minus the maximum of the mean net monetary benefit across all strategies. In this example, the EVPI is expressed as cost per patient or individual (Figure 5.7).

The expression for EVPI refers to the maximum value that can be placed on additional information to inform treatment choice for an individual patient. [70] Information is a public good; as such, generation of perfect information for one instance of a decision ensures that the information is available for other instances of the decision. Hence, the overall value of perfect information surrounding a health care policy decision depends on the number of times that the decision is faced over the lifetime of the technology.[70] The population level estimates are determined by scaling up the individual estimates according to an assessment of the time horizon for the information, estimates of incidence over this period, and the discount rate.

Figure 5.7 Example of expected value of perfect information analysis



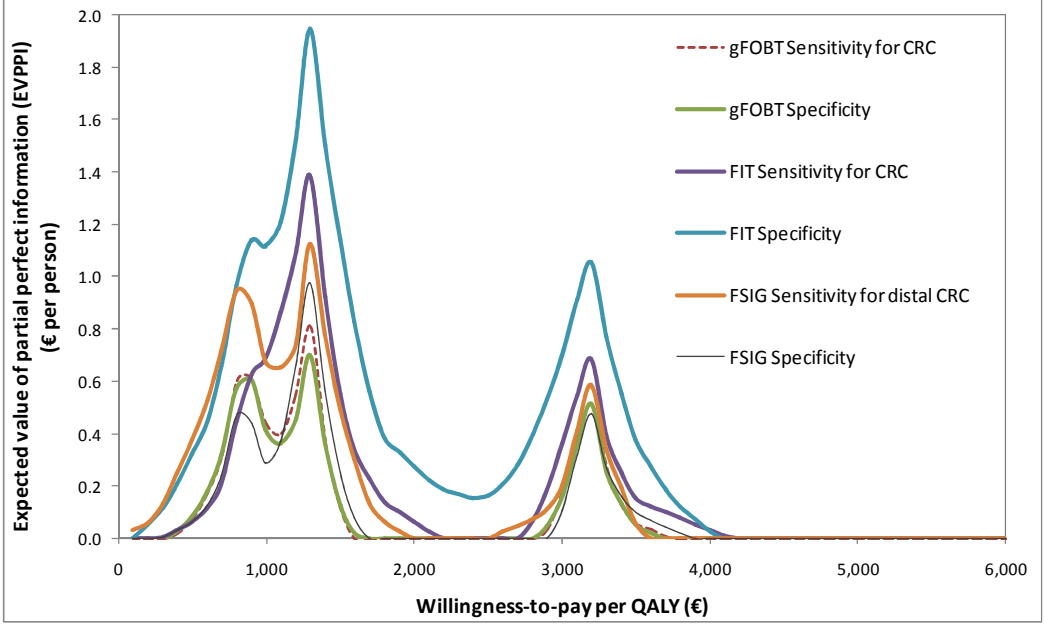
QALY=quality-adjusted life year.

Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population based colorectal screening programme in Ireland.*

In this example, the EVPI reaches a maximum of €8.07 per person at a willingness-to-pay threshold of €1,300/QALY. A second peak occurs at a threshold of €3,150/QALY when the EVPI is €5.15 per person. These two peaks occur at transitions between different strategies having the highest probability of being most cost-effective. For this reason, EVPI is sometimes presented in conjunction with the cost-effectiveness acceptability curves (shown in Figure 5.6).

It is also possible to estimate the EVPPI, or expected value of partial perfect information. This is computed for individual parameters or sets of parameters and can be used to identify for which parameters it may be most sensible to invest in further research to reduce uncertainty. For complex probabilistic models, the computation of EVPPI was immensely time consuming, but recent modelling advances have greatly reduced the computational burden.[71, 72] For illustrative purposes, the EVPPI has been calculated for the diagnostic test accuracy parameters of the three tests in the colorectal cancer screening example (Figure 5.8).

Figure 5.8 Example of expected value of partial perfect information analysis



gFOBT= guaiac faecal occult blood test; FIT=faecal immunochemical test; FSIG= flexible sigmoidoscopy; CRC=colorectal cancer; QALY=quality-adjusted life year.

Source: adapted from Health Information and Quality Authority (2009) *Health technology assessment (HTA) of a population based colorectal screening programme in Ireland.*

Appendix 6

HTA Glossary

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.

Absolute risk: the observed or calculated risk of an event in a defined population over a specified time period. (Compare with **Relative Risk**).

Absolute risk difference or reduction: a type of measure of treatment effect that shows the decrease in risk in the treatment group relative to the control group, i.e. P_c - P_t. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, then the absolute risk reduction would be 25% - 10% = 15%. It is the inverse of the number needed to treat. (See also **number needed to treat** and **odds ratio** and **relative risk reduction**.)

Accuracy: the extent to which a measurement, or an estimate based on measurements, represents the true value of the variable being measured. (See also **Validity**).

Adverse event: an undesirable effect of a health technology.

Attributable risk or attributable fraction: with a specified outcome, exposure factor, time period and population, the rate of an outcome that can be attributed to the factor in the population (i.e. net of background risk). The population should be specified as either the exposed or total population.

Base case: see **Reference case**.

Base case analysis: the results of the economic evaluation estimating how much it would cost to achieve additional health outcomes with the proposed technology compared with the main comparator, presented as an incremental cost-effectiveness ratio, and incorporating the costs associated with altered uses of drugs, medical and other related healthcare resources and all outcomes valued in terms of overall quality and length of life. (See also **Reference case analysis).**

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).

Baseline risk: at the time when a participant is enrolled in a study or when a patient is treated with a technology, baseline risk is the risk of future events of interest in the absence of that technology.

Bayesian Method: a branch of statistics that uses prior information on beliefs for estimation and inference.

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

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.

Budget impact analysis (BIA) or financial analysis: a procedure for comparing only the financial costs and cost offsets of competing options, rather than comparing their clinical and economic costs and benefits.

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

Case-control study: a retrospective observational study designed to determine the relationship between a particular outcome of interest (e.g. disease or condition) and a potential cause (e.g. a technology, risk factor, or exposure). For example, a group of people with lung cancer might be matched with a group of people the same age without lung cancer. The researcher could compare how often both groups had been exposed to tobacco smoke in their lives.

Cohort study: an observational study in which two or more sub-sets of defined populations are identified by the presence of a common factor or factors (e.g. non-randomly assigned to the proposed technology or to its main comparator(s)) and then followed in time to investigate the influence of the factors on the probability of occurrence of an outcome or outcomes.

Common reference: a drug or technology to which a proposed technology and its main comparator(s) have been compared in separate comparative randomised trials.

Comorbidity: the coexistence of a disease, or more than one disease, in a person in addition to the disease being studied or treated.

Composite outcome: a pre-specified outcome of a trial, which is recorded as occurring for a trial participant when any one of several component outcomes of the composite is experienced.

Comparator: the alternative against which the intervention is compared.

Confidence interval: the computed interval with a specified probability (by convention, 95%) that the true value of a variable such as mean, proportion, or rate is contained within the interval.

Conflict of interest: a conflict of interest arises when "a professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain)."[61]

Confounding: the distortion of a measure of the effect of an exposure (e.g. to therapy involving the proposed drug) on the risk of an outcome under investigation brought about by the association of the exposure with other factor(s) that can influence the outcome.

Consumer Price Index: this index measures the change in the average price levels (including all indirect taxes) paid for consumer goods and services

by all private households in the country and by foreign tourists holidaying in the country.

Control group: a group of participants who are observed but who do not receive treatment involving the proposed drug or technology. They may receive alternative treatment, no treatment or placebo. They provide data on the streams of outcomes (clinical and economic) for comparison with the streams of outcomes observed for participants who take therapy involving the proposed drug or technology.

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; range of costs (and benefits) included in a particular economic evaluation depends on perspective taken; average costs are average cost per unit of output (i.e., 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 acceptability curves (CEAC): a graph plotting a range of possible cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective on the vertical access. CEAC provide a visual representation of the uncertainty surrounding cost-effectiveness estimates.

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, e.g. reduced mortality or morbidity.

Cost-effectiveness acceptability frontier: a region on a plot that shows the probability that the technology with the highest expected net benefit is cost effective.

Cost-effectiveness efficiency frontier: linking the non-dominated strategies on the cost-effectiveness-plane produces a cost-effectiveness efficiency frontier.

Cost-effectiveness plane: a graph plotting difference in effect (between the technology of interest and the comparator) on the horizontal axis against the difference in costs on the vertical access, providing a visual representation of cost-effectiveness.

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, e.g. using quality-adjusted life years (QALYs).

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

Data synthesis: combining evidence from different sources.

Decision analysis: a technique that formally identifies the options in a decision making process, quantifies the probable outcomes (and costs) of each, determines the option that best meets the objectives of the decision maker and assesses the robustness of this conclusion.

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

Deterministic sensitivity analysis (DSA): a method of decision analysis that uses both one-way (variation of one variable at a time) and multi-way (two or more parameters varied at the same time) sensitivity analysis to capture the level of uncertainty in the results that may arise due to missing data, imprecise estimates or methodological issues. (Compare: **Probabilistic sensitivity analysis.**)

Dichotomous data: data that are classified into either one of two mutually exclusive values, for example, 'yes' and 'no' or 'cured' and 'not cured.'

Direct costs: the fixed and variable costs of all resources (goods, services, etc.) 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 (e.g. doctors' salaries).

Direct non-medical costs: the non-medical costs of treating a patient, e.g. 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, e.g. 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)**

Dominance: an intervention is subject to simple dominance if it has higher costs and worse outcomes than an alternative technology. An intervention is subject to extended dominance when it is more costly and more effective, and has lower incremental cost-effectiveness ratio, than a combination of alternatives.

Economic evaluation: application of analytical methods to identify, measure, value, and compare costs and consequences of alternatives being considered; 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 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**.)

Epidemiology: the study of the distribution and determinants of health-related conditions or events in defined populations.

Equity: as it relates to health, 'fairness' in allocation of resources, technologies, or outcomes among individuals or groups.

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.

Evidence-based medicine: the use of current best evidence from scientific and medical research to make decisions about the care of individual patients. It involves formulating questions relevant to the care of particular patients, searching the scientific and medical literature, identifying and evaluating relevant research results, and applying the findings to patients.

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 (e.g. 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, e.g. 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 problem of whether 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, e.g. 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**.

Hazard ratio: a measure of effect produced by a time-to-event survival analysis. This represents the increased instantaneous rate with which one group is likely to experience the outcome of interest.

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 well-being.

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, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient-focused and seek to achieve best value.

Heterogeneity: in the context of meta-analysis, clinical heterogeneity means dissimilarity between studies. It can be because of the use of different statistical methods (statistical heterogeneity), or evaluation of people with different characteristics, treatments or outcomes (clinical heterogeneity). Heterogeneity may render pooling of data in meta-analysis unreliable or inappropriate. Finding no significant evidence of heterogeneity is not the same as finding evidence of no heterogeneity. If there are a small number of studies, heterogeneity may affect results but not be statistically significant.

Homogeneity: used to describe when the results of studies included in a systematic review or meta-analysis are similar and there is no more variation than would occur by chance alone. Results are usually regarded as homogenous when any difference observed between studies could reasonably be expected to occur by chance alone.

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

Incremental cost-effectiveness ratio (ICER): the results of a cost-effectiveness analysis (CEA) are presented as an incremental cost-effectiveness ratio (ICER) and this describes how much additional benefit is achieved for the additional cost incurred. The ICER for two technologies A and B is calculated as follows:

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

Indication: a clinical symptom or circumstance indicating that the use of a particular intervention would be appropriate.

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 (e.g. 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.

Intention-to-treat analysis: a type of analysis of clinical trial data in which all patients are included in the analysis based on their original assignment to intervention or control groups, regardless of whether patients failed to fully participate in the trial for any reason, including whether they actually received their allocated treatment, dropped out of the trial, or crossed over to another group.

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.

Marginal benefit: the additional benefit (e.g. in units of health outcome) produced by an additional resource use (e.g. another healthcare intervention).

Marginal cost: the additional cost required to produce one additional unit of benefit (e.g. unit of health outcome).

Markov Model: a type of quantitative modelling that involves a specified set of mutually exclusive and exhaustive states (e.g. 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.

Monte Carlo simulation: a technique used in computer simulations that uses sampling from a random number sequence to simulate characteristics or events or outcomes with multiple possible values. For example, this can be used to represent or model many individual patients in a population with ranges of values for certain health characteristics or outcomes. In some cases, the random components are added to the values of a known input variable for the purpose of determining the effects of fluctuations of this variable on the values of the output variable.

Net benefit: refers to a method of reporting results of economic evaluations in terms of monetary units (called net monetary benefit) or units of outcome (called net health benefit).

$$\text{net monetary benefit (NMB)} = \lambda\Delta E - \Delta C$$

$$\text{net health benefit (NHB)} = \Delta E - (\Delta C/\lambda)$$

Where λ is the willingness-to-pay threshold, ΔE is the incremental effect, and ΔC is the incremental cost.

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, e.g. at the convenience of the investigators or some other technique such as alternate assignment.

Number needed to treat (NNT): a measure of treatment effect that provides the number of patients who need to be treated to prevent one outcome event. It is the inverse of absolute risk reduction (1 ÷ absolute risk reduction); i.e., $1.0 \div (P_c - P_t)$. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the number needed to treat would be $1.0 \div (0.25 - 0.10) = 6.7$ patients. (See also **Absolute risk reduction, Relative risk reduction,** and **Odds ratio**.)

Observational study: a study in which the investigators do not manipulate the use of, or deliver, a technology (e.g. 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.

Odds ratio: a measure of treatment effect that compares the probability of a type of outcome in the treatment group with the outcome of a control group, i.e., $[P_t \div (1 - P_t)]$ $[P_c \div (1 - P_c)]$. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the odds ratio of survival would be $[0.10 \div (1.0 - 0.10)] \div [(0.25 \div (1.0 - 0.25)] = 0.33$. (See also **Absolute risk reduction, Number needed to treat,** and **Relative risk**.)

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.

Partitioned survival analysis: a modelling approach in which membership to a set of mutually exclusive health states is determined from a set of non-mutually exclusive survival curves.

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 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 parameter. 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.

Prospective study: a study in which the investigators plan and manage the intervention of interest in selected groups of patients. As such, investigators do not know what the outcomes will be when they undertake the study. (Contrast with **Retrospective study**.)

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).

Randomised controlled trial (RCT): a trial in which participants are randomly assigned to one or more treatment groups and a control group.

Reference case or base case: this specifies the methodologies considered most appropriate to be used in the assessment of clinical and cost-effectiveness when conducting HTA in Ireland.

Relative risk difference or reduction: a type of measure of treatment effect that compares the probability of a type of outcome in the treatment group with that of a control group, i.e.: $(P_c - P_t) \div P_c$. For instance, if the results of a trial show that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the relative risk reduction would be: $(0.25 - 0.10) \div 0.25 = 0.6$. (See also **Absolute risk reduction, Number needed to treat,** and **Odds ratio**.)

Sample size: the number of patients studied in a trial, including the treatment and control groups, where applicable. In general, a larger sample size decreases the probability of making a false-positive error (α) and increases the power of a trial, i.e., decreases the probability of making a false-negative error (β). Large sample sizes decrease the effect of random variation on the estimate of a treatment effect.

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.

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 be 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.

Statistical significance: a conclusion that a technology has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test. Statistical significance indicates the probability that the observed difference was due to chance if the null hypothesis is true; it does not provide information about the magnitude of a treatment effect. (Statistical significance is necessary but not sufficient for clinical significance.)

Stratified analysis: a process of analysing smaller, more homogeneous subgroups according to specified criteria such as age groups, socioeconomic status, where there is variability (heterogeneity) in population.

Subgroup: a defined set of individuals in a population group or of participants in a study such as subgroups defined by sex or age categories.

Subgroup analysis: an analysis in which the intervention effect is evaluated in a subgroup of a trial, including the analysis of its complementary subgroup. Subgroup analyses can be pre-specified, in which case they are easier to interpret. If not pre-specified, they are difficult to interpret because they tend to uncover false positive results.

Surrogate endpoint: a measure that is used in place of a primary endpoint (outcome). Examples are decrease in blood pressure as a predictor of decrease in strokes and heart attacks in hypertensive patients, and increase in T-cell (a type of white blood cell) counts as an indicator of improved survival of patients with AIDS. Use of a surrogate endpoint assumes that it is a reliable predictor of the primary endpoint(s) of interest.

Systematic review: a form of structure 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.

System dynamic model: a model that can be used to model the direct and indirect effects that may arise from a communicable disease control program.

The approach involves the development of computer simulation models that portray processes of accumulation and feedback and that may be tested systematically to find effective solutions to persistent, dynamically complex problems.

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.

Threshold analysis: type of sensitivity analysis in which model input is varied over a range to determine value of input that would lead to major changes in conclusions.

Time horizon: the time span used in the assessment that captures the period over which meaningful differences between costs and outcomes between competing technologies would be expected to accrue.

Time-to-event data or survival data: data that incorporates a measure of the time lapse before an event occurs, for example, time to relapse, time to death or time to treatment cessation.

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)

Tornado diagram: diagrammatic display of the results of one-way sensitivity analysis; each bar represents the range of change in model results when the parameter is varied from its minimum to maximum values.

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 technique measures what it is intended to measure.

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.

Value Added Tax: this is a tax on consumer spending. It is collected by VAT-registered traders on their supplies of goods and services to customers. Each such trader in the chain of supply from manufacturer through to retailer charges VAT on his or her sales and is entitled to deduct from this amount the VAT paid on his or her purchases, that is, the tax is on the added value. For the final consumer, not being VAT-registered, VAT is simply part of the purchase price.

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.

Willingness-to-pay (WTP): evaluation method used to determine maximum amount of money individual is willing to pay for particular outcome or benefit (e.g. receive healthcare service); method is often used in cost-benefit analysis to quantify outcome in monetary terms.

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