



**Health
Information
and Quality
Authority**

An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

Draft National Guidelines for the Economic Evaluation of Health Technologies in Ireland

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory body established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector of Social Services within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children’s special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of permanent international protection accommodation service centres, health services and children’s social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children’s social services.
- **Health technology assessment** — Evaluating the clinical and cost effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland’s health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health and social care services, with the Department of Health and the HSE.

Foreword

The Health Information and Quality Authority (HIQA) has a statutory remit to evaluate the clinical and cost effectiveness of health technologies, and provide advice to the Minister for Health and to the Health Service Executive (HSE). It is recognised that the findings of a Health Technology Assessment (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.

HTA guideline documents provide an overview of the principles and methods used in assessing health technologies. These are intended as a guide for everyone who is 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 national guidelines relate specifically to the conduct of economic evaluation for HTA, one of a number of domains that inform health policy decision-making. They are intended to inform economic evaluations conducted by, or on behalf of HIQA, the National Centre for Pharmacoeconomics (NCPE), the Department of Health and the HSE, as well as health technology developers preparing applications for reimbursement. The guidelines are intended to be applicable to all healthcare technologies, including drugs, procedures, medical devices, broader public health interventions and service delivery models.

This document, *Draft National Guidelines for the Economic Evaluation of Health Technologies in Ireland*, is part of the [series of national HTA guidelines](#), and is limited to methodological guidance on the conduct of economic assessments. This guideline document has been updated to ensure that it reflects methodological advances and international best practice in the area of economic evaluation. For ease of use, guideline statements in italics that summarise key points are included prior to each section.

These updated draft national economic evaluation guidelines are now undergoing public consultation to gain feedback from a broad range of stakeholders. Guideline amendments and or additions will be finalised post consultation. Following HIQA Board approval, the final document will be published as *National Guidelines for the Economic Evaluation of Health Technologies in Ireland 2.0*.

HIQA would like to thank the members of its HTA Scientific Advisory Group and its Chairperson, Prof Michael Barry from the NCPE, and all who have contributed to the production of these guidelines.

A handwritten signature in black ink, appearing to read 'Máirín Ryan', written over a horizontal line.

Dr Máirín Ryan

Deputy Chief Executive & Director of Health Technology Assessment

Health Information and Quality Authority

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Process and Acknowledgements

These economic evaluation guidelines have been developed by HIQA with technical input from the the National Centre for Pharmacoeconomics (NCPE) and in consultation with its HTA Scientific Advisory Group (SAG). Providing broad representation from key stakeholders in Irish healthcare, this group includes methodological experts, patients, health technology developers, and decision-makers. The group provides ongoing advice and support to HIQA in its development of national HTA guidelines. The terms of reference for the SAG 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 HIQA in the generation of guidelines to establish quality standards for the conduct of HTA in Ireland
- support HIQA in the development of methodologies for effective HTA in Ireland
- advise HIQA on its proposed HTA Guidelines Work Plan and on priorities as required
- support HIQA in achieving its objectives outlined in the HTA Guidelines Work Plan
- review draft national guidelines and other HTA documents developed by HIQA and recommend amendments as appropriate
- contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process as required.

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

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Update process for the National Guidelines for the Economic Evaluation of Health Technologies in Ireland

The first national guidelines for the economic evaluation of health technologies in Ireland were developed in 2000 by the NCPE, in the context of the agreement between the Irish Pharmaceutical Healthcare Association and the Department of Health. Following this, between November 2010 and September 2020, five guideline updates were carried out by HIQA (see Record of updates, below).

In 2024, a further (sixth) update of the most recent national economic evaluation guidelines, *Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.4*, is being performed. A five-step process is being undertaken and documented to ensure the guideline update is performed in a robust and transparent manner:

- **Step one:** a comprehensive online search of websites of public agencies and or bodies responsible for HTA (such as the National Institute for Health and Care Excellence)⁽¹⁾ and HTA networks (such as the International Network of Agencies for Health Technology Assessment)⁽²⁾ was undertaken to identify HTA guidelines that have been published since the previous substantial update of these guidelines in January 2018. Using the current headings within these guidelines as a framework, information within identified relevant documents was extracted, where appropriate, and compared with *Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.4*.
- **Step two:** technical teams from HIQA and the NCPE were consulted to identify any additional updates required.
- **Step three:** potentially relevant updates were identified, and were presented to the SAG for expert feedback.
- **Step four:** a draft version of the updated national economic guidelines is undergoing public consultation to gain feedback from a broad range of stakeholders.
- **Step five:** guideline amendments and or additions will be finalised, Following HIQA Board approval, the final document will be published as *National Guidelines for the Economic Evaluation of Health Technologies in Ireland 2.0*.

Within the search for relevant documents, a 2023 review conducted by the Centre for Health Economics Research and Evaluation (University of Technology, Sydney) titled *Health Technology Assessment methods: Economic Evaluation*,⁽³⁾ was identified. This review was conducted as part of a broader HTA Policy and Methods Review commissioned by the Australian Government as an opportunity to support continuous improvement in Australia's HTA processes.⁽⁴⁾ The review compared the

methods used in economic evaluation as part of HTA processes in Australia, Belgium, Canada, England, France, Germany, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Scotland, Singapore, South Korea, Spain, Sweden, Taiwan, and Wales. Given the comprehensive number of countries, and the breadth of information included, this review provided the majority of data for comparison with the national economic evaluation guidelines in Ireland.

Following discussion with the SAG, a number of minor and major revisions will be included in the 2025 guideline update (see Record of updates, below).

Record of updates

Date	Title/Version	Summary of changes
2000	<i>Irish Healthcare Technology Assessment Guidelines</i>	<ul style="list-style-type: none"> ▪ First national economic guidelines developed by the NCPE in the context defined by the agreement between the Irish Pharmaceutical Healthcare Association and the Department of Health.
November 2010	<i>Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.0</i>	<ul style="list-style-type: none"> ▪ Major revision and reorganisation of text.
January 2014	<i>Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.1</i>	<ul style="list-style-type: none"> ▪ Minor revisions and reorganisation of text. ▪ Updated value-added tax (VAT) rate and pay-related costs calculation.
January 2018	<i>Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.2</i>	<ul style="list-style-type: none"> ▪ 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).

		<ul style="list-style-type: none"> ▪ Recommendation to report conflicts of interest (Section 2.19).
July 2019	<i>Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.3</i>	<ul style="list-style-type: none"> ▪ Revised test discount rate.
September 2020	<i>Guidelines for the Economic Evaluation of Health Technologies in Ireland 1.4</i>	<ul style="list-style-type: none"> ▪ Minor revisions to Appendix 3 (How to transfer costs to Ireland using the Purchasing Power Parity index) and Appendix 7 (Presentation of results).
October 2024	<i>Draft National Guidelines for the Economic Evaluation of Health Technologies in Ireland 2.0</i>	<ul style="list-style-type: none"> ▪ Major revisions to costing of pensions. ▪ Minor revisions throughout guidelines providing further clarifications and removal of out-of-date text and references. ▪ Updated Appendices 2-6, deletion of Appendix 7, HTA glossary, and list of abbreviations. ▪ Addition of a plain language summary and a section describing how these guidelines were updated.

Draft National Guidelines for the Economic Evaluation of Health Technologies in Ireland

Issued: October 2024

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

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

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Plain language summary

In Ireland, Health Technology Assessments (HTAs) are used to help decide what health technologies (such as drugs, medical tests, medical devices, surgeries, healthcare reorganisation) should be used and funded in our public healthcare system. A HTA looks at the effectiveness, safety and cost of different health technologies. An economic evaluation is often done as part of a HTA and it compares the costs and benefits of different choices to see which one is the best use of resources.

These national guidelines explain how economic evaluations in HTA should be done in Ireland. The guidelines were developed with the support of a HTA Scientific Advisory Group brought together by the Health Information and Quality Authority (HIQA). The group includes patients, researchers, policymakers, people from industry, doctors and other experts. Their input is important to make sure that the guidelines are fair and of high quality, and help inform healthcare decision-making and supporting safer, better healthcare.

These updated draft national guidelines for the economic evaluation of health technologies in Ireland are now undergoing public consultation to gain feedback from a broad range of stakeholders.

List of abbreviations

BIA	budget impact analysis
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CPI	Consumer Price Index
CUA	cost-utility analysis
DRG	diagnosis related groups
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
EVPI	expected value of perfect information
EVPPi	expected value of partial perfect information
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

ISPOR	The Professional Society for Health Economics and Outcomes Research
LYG	life years gained
NCPE	National Centre for Pharmacoeconomics
NMB	net monetary benefit
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 years
RCT	randomised controlled trial
SAG	Scientific Advisory Group
VAT	value-added tax

1 Introduction

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 patients, patient groups, the general public, clinicians, other healthcare providers, academic groups and health technology developers.

The purpose of 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 [series of national HTA guidelines](#), and are limited to the methodological guidance on the conduct of economic assessments. These economic guidelines are an update to the 2010, 2014, 2018, 2019 and 2020 guidelines, which replaced the *Irish Healthcare Technology Assessment Guidelines (2000)*.⁽⁵⁾ 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 (HIQA), the National Centre for Pharmacoeconomics (NCPE), the Department of Health and the Health Service Executive (HSE), as well as health technology developers preparing applications for reimbursement.

These guidelines are intended to be applicable to all healthcare interventions, including drugs, procedures, medical devices, broader public health interventions (for example immunisation and screening programmes) 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. For further guidance and information specifically on the HTA of drugs and related technologies and the associated submission process, please refer to the NCPE website (www.ncpe.ie).

As outlined in the preceding 'guideline update process' section, 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'.⁽⁶⁾

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 at the beginning of each section for the individual elements of the assessment in Chapter 2.

1.1.2 Reference case

A typical key component of 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 economic 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 economic analysis for HTAs. Use of a standard reference case approach increases transparency in the HTA 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 below.

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 adopting 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 (the 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	An annual rate of 4.0% on costs and outcomes occurring after the first year	2.14
Sensitivity analysis	Probabilistic and deterministic sensitivity analysis	2.16
Equity rating	Equal weighting should be applied to the outcome measure	2.17
* <i>HSE: Health Service Executive</i>		
[^] <i>QALYs: quality-adjusted life years</i>		

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 economic 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) or a cost-minimisation analysis (CMA) 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 controlled 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 (CPI) for health. Transfer payments (such as value-added tax (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 EuroQol-5 Dimension (EQ-5D) or Short Form-6 Dimension (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 4.0% 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 (that is to say, 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 and or 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) may 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) Whether an evaluation can be generalised to the Irish population 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 on each of the elements outlined in the guidelines should be provided. Data elements should be presented in tables 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 willingness-to-pay (WTP) 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 economic 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. It is therefore critical that HTAs address the needs of decision-makers.^(7, 8) A clear, relevant study question should be devised to establish the context of the economic assessment. Ideally the study question is designed in conjunction with a scoping exercise to identify the pertinent issues that should be considered and the stakeholders (including service providers, clinicians, patients and members of the public) relevant to the specific study question. Early identification of the stakeholders increases the opportunity for meaningful contribution to the process. For further guidance on involving stakeholders in the HTA process, please refer to the *Guidelines for Stakeholder Engagement in Health Technology Assessment in Ireland*.⁽⁹⁾

The study question should outline the purpose of the economic 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. These should clearly specify if the questions are being addressed as part of the HTA.

Secondary questions 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 economic 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) or a cost-minimisation analysis (CMA) 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 (for example, drugs, diagnostics, devices, and so on) 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:

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

Although both categories 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 (CUA) 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.⁽¹⁰⁾ 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 simultaneously incorporates 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.⁽¹¹⁾ 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.⁽¹²⁾ Where there are concerns over the quality or suitability of the available utility data, then also reporting a cost-effectiveness analysis (CEA) is advisable as supplementary information to the decision-maker.

In a CEA, outcomes are reported in a single unit of measurement and are given in natural units (see Appendix 1).⁽¹¹⁾ For programmes where the 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 CUA is considered an unsuitable choice. Clear, detailed, empirical evidence must be provided to justify the position that a CUA 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.⁽¹³⁾ 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 CUA where there may be an accepted willingness-to-pay (WTP) threshold 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, both costs and consequences are presented in monetary terms in a cost-benefit analysis (CBA), with the net present value determined as the difference in value between costs and benefits.⁽¹⁴⁾ In practice, CBA is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms.^(15, 16)

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, equivalent. This situation can arise where a statistically significant difference in treatment effect has not been demonstrated, or if a technology has been demonstrated to be no worse than the comparator in terms of effectiveness and adverse events (i.e., non-inferiority). The use of a CMA 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.⁽¹⁷⁾

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 (for example, public payer, individual, society). This 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 HSE.⁽¹⁷⁾ Consistent with this outlook, all health effects accruing to individuals (QALYs, life years gained, and so on) should be included in the outcomes for the reference case.

However, limiting the perspective of a study 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 of on whom these costs and consequences fall, is considered the most comprehensive approach that can be taken.⁽⁷⁾ These may include direct and indirect costs, including productivity costs, as well as additional costs, savings or other benefits such as non-resource effects (for example, 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 (for example, 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. The costs and outcomes added as part of a societal perspective should also be subjected to sensitivity analysis (see also Section 2.16), and where quantification is difficult, an estimate of the magnitude of such costs and outcomes and their impact on the results should be 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 drugs, 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 (for example, 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 drugs. Details of associated diagnostic or prognostic tests should also be described. In fields where there is rapid product development, such as emerging digital technologies, sufficient information should be given about the design and features to distinguish different generations of the technology. This is particularly relevant when considering the applicability of clinical effectiveness data incorporated into the economic evaluation.

Important 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; may require transport between healthcare providers; may have additional storage requirements; or may require additional healthcare supports in other areas, which could 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, a HTA needs 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 to allow their relevance to 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 the evaluation of public health interventions there may be scope to define a wide range of comparators that are different configurations of the same basic intervention. For example, a screening programme based on a particular diagnostic test may be specified for different age ranges and screening frequencies, potentially generating a very large number of comparators. Omission of potential comparators can impact on the estimated cost effectiveness of included interventions. In these cases, justification should be given for the included and excluded comparators, preferably with reference to their clinical plausibility and organisational feasibility.

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 (for example, age and or gender)
- disease characteristics (for example, stage or severity, presence of comorbidities and or risk factors)
- treatment setting (for example, primary care or hospital)
- or in the context of past treatment (for example, non-responders, treatment relapse, non-adherence and or poor tolerance).

For drugs, the population should be defined by the authorised therapeutic indication for the product, where applicable. For drugs which are part of established clinical

practice for off-label (unlicensed) indications, the off-label usage in the intended population should be clearly stated. For medical devices and diagnostics, the population should be defined according to their intended purpose. 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 time frame 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 for economic evaluation in HTAs, as the majority of technologies have costs and outcomes that impact over a patient's lifetime. This is particularly pertinent for chronic diseases such as diabetes. A shorter time frame may be considered when the costs and outcomes relate to a relatively short period of time, such as in an acute infection, and when mortality is not expected to differ between the competing technologies. A decision to use a shorter time frame 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). A sensitivity analysis in which the treatment effect only persists for the duration of follow up in the available data and is equal to standard care thereafter may be presented in specific situations, such as where the differences in treatment effects could plausibly diminish substantially beyond this period. A systematic approach to the selection of appropriate statistical methods for survival analysis must be followed and described.⁽¹⁸⁾

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 controlled 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.

Detailed guidance with respect to estimating clinical effectiveness is provided in the *Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland*.⁽¹⁹⁾ 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. 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. 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.

In the reference case, evidence on outcomes should be obtained by means of a systematic review with all data sources clearly described, and reported in accordance with current PRISMA guidelines.⁽²⁰⁾ It may be useful to systematically evaluate the body of evidence using a standardised methodology, for example 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 applicable to systematic reviews, clinical guidelines and health technology assessments.⁽²¹⁾ The reasons for the selected evidence grading should be clearly reported.

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.⁽²⁰⁾ This should include a description of the search strategy (the main bibliographic databases or other sources of scientific evidence searched); inclusion and exclusion criteria applied; and restrictions used in locating studies (for example, language (if appropriate), population, and year). For best practice, two or more reviewers should conduct study selection 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.⁽²⁰⁾

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 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.⁽²⁰⁾

Whenever available, data from 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 also 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. Where both RCT and observational data are available and incorporated into the analysis, the results of the two should be compared to determine consistency in findings, with any differences highlighted.

Economic evaluations may be conducted 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 (for example, 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 (for example, it may be reasonable to make the trial data available for independent assessment). For the purposes of HTA informing decision-making, notwithstanding the availability of cost and clinical evidence from a single trial, a *de novo* or appropriately critically appraised systematic review is required to identify the most appropriate clinical evidence for an economic evaluation.

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 these data should be

clearly stated and explored as part of a comprehensive sensitivity analysis (see also Section 2.16). 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 for 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 also 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 (including indirect treatment comparisons, handling heterogeneity and subgroup analyses) is provided in the *Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland*.⁽¹⁹⁾

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 (for example, the Cochrane risk of bias tool) should be presented.⁽²²⁾

The treatment effect may be reported in a number of different ways. Both absolute (for example, absolute risk reduction, differences in number needed to treat (NNT)) and relative effect (for example, 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 limit 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 drugs and other technologies, including definitions for adverse events, serious adverse events and adverse drug reactions.⁽¹⁷⁾ 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.⁽²³⁾ 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 usually relies 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.⁽²⁴⁾

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 (such as prolongation of hospitalisation, use of additional medications, and so on).

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 (age and sex); disease characteristics (stage or severity, comorbidities, risk factors); or the context of past treatment (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 comorbidities 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, as appropriate to the research question.⁽²⁵⁾ 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.⁽²⁶⁾ 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 (for example, a patient registry), attempts should be made 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 data sources 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 might 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 (CPI) for health. Transfer payments (for example, value-added tax (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 economic 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.⁽⁸⁾

2.11.1 Resource identification

The primary perspective for evaluations should be the publicly-funded health and social care system (the 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 time frame 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 have been identified systematically. A variety of costs are likely to be relevant in the analysis, including capital, labour, technology and treatment costs. Where relevant, capital costs should be appropriately depreciated (see Appendix 5). Relevant maintenance costs may apply over the lifetime of certain equipment (for example, 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 a reduction in the 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 (such as 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.

If there is a specific co-dependent or companion technology (for example, a test for the presence of a particular biomarker or gene expression which is required to assess suitability for a particular drug) that is used for some but not all interventions being assessed, then the cost of that technology should also be included in the model.⁽²⁷⁾

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 these data to the publicly-funded Irish healthcare setting should be clearly described. These data should be subjected to comprehensive sensitivity analysis (see also 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, generating 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 these data must be explicitly reported, with all costs converted to their Irish equivalent in euro using Purchasing Power Parity (PPP) indices.⁽²⁸⁾ 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. A micro-costing 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.⁽²⁹⁾ 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; for example, 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 the cost of the technology 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 (CPI) for health or one of its sub-indices, where reasonable justification is given for its use (see Appendix 2 for an example).⁽³⁰⁾ If transferring costs from another country, the inflation should be calculated using the CPI for the local currency prior to conversion to the Irish equivalent in euro using PPP indices (see Appendices 2 and 3 for examples).⁽³¹⁾

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.^(32, 33) 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.^(33, 34) 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.⁽³⁵⁾ 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 (for example, 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 drug manufacturers and importers. These costs may vary with changing drug policy. A detailed guide for

including drug costs in economic evaluations is available from the NCPE.⁽³⁴⁾ To ensure the evaluation is relevant to decision-making, in certain circumstances it may be appropriate to take into account discounted prices that 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.⁽³⁶⁾ 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,^(37, 38) taking into account the most current information on the cost of superannuation for the public sector.^(39, 40) 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. If the economic evaluation includes labour external to the HSE, the level of pay and decisions regarding included and excluded non-pay costs should be clearly justified with relevant data sources referenced.

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 Scheme) are set out in legislation and are available from the PCRS website.⁽³³⁾

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% (as of August 2024) depending on the classification of the product. For example, the VAT rate for oral drugs is 0% whereas non-oral medicines (including topical preparations and injectables) attract VAT at a rate of 23% (as of August 2024).⁽⁴¹⁾ However, similar to other transfer costs, when assessed from the perspective of the government, VAT should be excluded from economic evaluations of cost effectiveness.⁽³¹⁾ 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 quality-adjusted life years (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.

Economic evaluations in 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.⁽⁴²⁾

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. For example:

$$\begin{aligned} &(\text{Utility A} \times \text{Years spent in health state A}) + (\text{Utility B} \times \text{Years spent in health state B}) \\ &= \text{X QALYs} \end{aligned}$$

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 among 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.'⁽⁴²⁾

As noted, weighted measures of HRQoL (utilities) are used to calculate QALYs. This weighting 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.⁽⁴³⁾ One reason for differences in the utility value obtained for similar health states is due to differences in the valuation of the health state (for example, 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⁽⁴⁴⁾ or SF-6D.⁽⁴⁵⁾ 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. Of note, an Irish value set has been developed for the EQ-5D-5L.⁽⁴⁶⁾ In relation to submissions to the NCPE as part of the drug reimbursement process, the EQ-5D-3L is currently the preferred method for measuring HRQoL.⁽²⁷⁾ The two measures value health states in different ways. While a mapping function based on UK data is available to convert between the two instruments,⁽⁴⁷⁾ preference is to avoid mapping. The choice of instrument used in an evaluation should be justified. 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.

There are a wide range of general and disease-specific HRQoL instruments that have been applied to measure treatment effects in research. Although functions may be

available to map values to a preferred utility value instrument such as EQ-5D, the applicability and statistical rigour of these mapping functions may be limited.⁽⁴⁸⁾

It is important to note that there are methodological challenges in developing value sets for children and young people. Issues include the population (adults or children) from whom preferences are elicited, the perspective ('own' or 'other') required in the elicitation of preferences, the elicitation technique and mode of administration.⁽⁴⁹⁾ No specific measure of HRQoL in children and young people is recommended. However, there are paediatric HRQoL instruments available, such as the Child Health Utility 9D (CHU9D) index.⁽⁵⁰⁾ If data from a paediatric HRQoL instrument are used to generate utility values, this process needs to be clearly explained.⁽⁵¹⁾

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 were 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 are based on preferences of the general public. If Irish public preference data are not used, 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 some contexts, a generic measure may not be sufficiently sensitive to capture what may be considered a clinically meaningful change in health status. In these situations, a validated disease-specific quality of life measure may be acceptable. If both a generic and a validated disease-specific measure are available, both should be presented to facilitate comparison across economic evaluations.

In the absence of relevant utility data from one of the generic measures, it may be possible to map 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.

Of note, there are other health outcome measures (such as Healthy Year Equivalents (HYEs), Health Years in Total (HYTs), and Disability Adjusted Life Years (DALYs)) that may provide additional contextual information when considering the QALY data.

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 10 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.⁽⁵²⁾ If there is a long lead-in time to 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 produce 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.⁽⁵³⁾ 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, system dynamic models, and partitioned survival models. Decision trees can be useful for relatively simple models, or decision problems with special characteristics (for example, 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.⁽⁵⁴⁾ System dynamic models are used to model the effects that may arise from a communicable disease programme.⁽⁵⁵⁾ 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.⁽⁵⁶⁾

The model should be transparent with all assumptions explicitly stated. Conclusions drawn from the model should be noted to be conditional on these assumptions.⁽⁷⁾ Good modelling practice should be adhered to, so that the quality of the model and the analysis can be ensured.⁽⁷⁾ 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. If both deterministic and probabilistic model results are presented and they differ, then the reasons for those discrepancies should be explained, and the impact on any deterministic sensitivity analyses should be highlighted.

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.⁽⁵⁷⁾ One approach to measuring whether sufficient simulations have been used is to examine the Monte Carlo error, which is the standard deviation of the Monte Carlo estimator. For large numbers of independent simulations, the Monte Carlo error is approximately one over the square root of the number of simulations. The Monte Carlo error for a given output (for example, incremental costs) should preferably be less than 5% of the standard deviation of the outcome of interest.⁽⁵⁸⁾ 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 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 could 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 4.0% 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-day 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 4.0% per annum for costs and outcomes should be used (see Appendix 6 for a sample calculation). This rate is set out in the Public Spending Code published by the Department of Public Expenditure, NDP Delivery and Reform and has been in effect since July 2019.⁽⁵⁹⁾ 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 is also useful to investigate the impact of a $\pm 1\%$ change 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, geographical location or because of patient heterogeneity (such as 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. 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 (that is to say, 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 and or 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) may also be evaluated.

The primary purpose of a sensitivity analysis is to inform the decision-maker of the certainty and robustness of the results and conclusions of the economic analysis. This involves a systematic examination of the influence of the variables and assumptions used in an economic evaluation.⁽⁶⁰⁾ 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 (for example, 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 through a series of plausible scenario analyses.
- Bias due to selective use of data sources to inform key parameters (for example, 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.

Costs should be varied to illustrate the impact of costs on the results. 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. In this type of analysis, 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 value.⁽⁶⁰⁾ The results of the one-way sensitivity analysis may be presented on a tornado plot, displaying those parameters where the variation in parameter values has the biggest impact on the results of the analysis. The plot is usually arranged with the parameter for which variation has the biggest impact at the top.^(61, 62) Although useful, one-way sensitivity analyses do not capture the overall combined uncertainty that may be seen when parameters are varied simultaneously.⁽⁶⁰⁾

In a multivariate analysis, two or more parameter values 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. 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 an 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- or worst-case sensitivity analyses are an important way of identifying the parameters that are key drivers of the model and have a substantial impact on cost effectiveness. However, they do not represent the combined effects of multiple sources of uncertainty.

Sensitivity analysis in the form of a 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, for example by specifying the maximum incremental cost-effectiveness ratio (ICER) that would be acceptable for a technology.

A decision on the most appropriate deterministic sensitivity analysis to conduct should be guided by the identified parameter uncertainties and informed by discussions with the decision-maker as to the type of analysis that will suit their needs. Many reporting methods may be used to convey the impact of deterministic sensitivity analysis. Recommendations and good practice guidelines relating to reporting the results of uncertainty analysis (one-way, multi-way, scenario and threshold analyses) have been published elsewhere.^(61, 62)

2.16.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) is the preferred approach for exploring uncertainty arising from parameter imprecision (such as 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 than the more simplistic deterministic analyses methods.⁽⁴²⁾ 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 WTP 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).⁽⁶³⁾

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 may 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 the expected value of partial perfect information (EVPPI) can identify the parameters whose uncertainties contribute most to the overall decision uncertainty.⁽⁶¹⁾ Recent advances have greatly reduced the computational burden of estimating EVPPI, making it feasible for models of typical complexity.⁽⁶⁴⁻⁶⁶⁾

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.

Incorporating equity weights into QALY calculations is 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.⁽⁶⁷⁾ 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. However, it 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.⁽⁶⁸⁾ It is possible that these findings may not be representative of societal preferences in Ireland.

Decision-makers have used the need to address inequalities in healthcare as a key criteria for prioritising HTAs. To meet the needs of the decision-makers, an attempt should be made to include equity and inequality 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 is 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 ISPOR (The Professional Society for Health Economics and Outcomes Research) good research practices task force 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.⁽⁶⁹⁾

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

As part of the European Network of Health Technology Assessment (EUnetHTA), a Core Model® for HTA was developed that attempted 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.⁽⁷⁰⁾ While EUnetHTA is no longer operating, the Core Model® still provides a useful framework for HTA.

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 are representative of the likely effectiveness that can be achieved in Ireland
- the extent to which economic data are representative of the likely costs and resource utilisation incurred in Ireland
- the generalisability of the economic and clinical data across different patient populations (for example 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 are 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 are 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 system 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.⁽⁷¹⁾

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 sensitivity analyses (PSA) 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.⁽⁷²⁾ 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 judgment might be influenced by a secondary interest such as financial gain.⁽⁷³⁾

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 PSA, 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 CUA should be presented as ICERs. ICERs present the cost per unit of outcome, for example, the expected additional total cost to the expected additional QALYs (LYG) and are calculated as follows:

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

As the ICER becomes larger, the intervention is said to be less cost effective.⁽¹⁴⁾ 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 ICERs should then be calculated by comparing each programme with the one below it, excluding those programmes that are dominated. The final ICERs are 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).⁽⁴²⁾

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.

Where an intervention is less costly and more effective than the comparator, or less effective and more costly, calculation of the ICER generates a negative value. This creates challenges for consistent interpretation. In these cases it is appropriate to clearly identify into which quadrant of the cost-effectiveness plane the results fall, and to consider the results in terms of net monetary benefit (NMB)⁽⁶²⁾ and. NMB is calculated in terms of a specific WTP threshold. Due to the lack of stated WTP threshold in Ireland (see 2.19.3), presenting results as NMB should include a clear description of the WTP threshold values used.

Uncertainty should also be presented in the form of a table 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 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 PSA 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 WTP for one additional unit of benefit.⁽⁴²⁾

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, there has been no stated willingness-to-pay (WTP) threshold in Ireland below which funding was guaranteed. In relation to drugs, thresholds of €20,000 and €45,000 per QALY have been used previously in conjunction with budget impact thresholds to determine the level of authority

required within the HSE to make funding decisions. 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:

1. Opportunity cost: given a fixed budget, for the publicly-funded health and social care 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 (for example, 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.
2. 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.
3. Past decisions: the ICER of a new technology could be compared with those 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 and that were funded, 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 funding.

In addition to the estimated cost effectiveness of the interventions considered in the economic evaluation, an understanding of the decision uncertainty is critical for

interpretation. The sensitivity and scenario analyses conducted as part of the evaluation will highlight conditions under which the economic evaluation conclusions may change. The interpretation must acknowledge uncertainty in the results and provide guidance on the implications of that uncertainty for decision-making.

A number of countries are exploring the use of modifiers to adjust results to take into account factors such as disease severity or rarity, for example.⁽⁷⁴⁾ It is an evolving area of research and there is a lack of consensus about how and when such modifiers should be applied. No modifiers are currently accepted for use in economic evaluations in Ireland.

In summary, there is no fixed cost-effectiveness threshold above or below which technologies are guaranteed to be rejected or accepted for funding. 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 (such as clinical effectiveness, costs, plausibility of the inputs and assumptions in the model) and an estimate of the uncertainty surrounding the results (such as validity of the data, range and plausibility of the ICERs, and likelihood of error).

2.20 Budget impact analysis

A budget impact analysis (BIA) 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 assessing 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.⁽⁷⁵⁾ 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.

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.^(14, 62)

Economic evaluations fall into two major categories:

1. cost-effectiveness analysis
2. 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.⁽¹¹⁾ 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.⁽¹³⁾ Where an intermediate (surrogate) marker is chosen, it must have a validated, well-established link with an important patient outcome.⁽⁷⁶⁾ The extent to which a clinically relevant effect can be precisely predicted based on changes in the surrogate marker should be stated.

Limitations

CEA 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, CEA 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.⁽¹²⁾ 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.⁽⁷¹⁾ 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.⁽¹⁴⁾ 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⁽⁷⁷⁾ since valuation is believed to be influenced by culture and income.⁽⁷⁸⁾

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 CUA 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.⁽¹¹⁾ 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.⁽¹²⁾ It is considered the gold standard method for conducting economic evaluations and is recommended by many expert and consensus groups.⁽¹⁰⁾

Limitations

There are a number of limitations associated with CUA. 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.⁽⁷⁹⁾ Similarly, there is dispute regarding the capacity of QALYs to measure short-term outcomes (for example, acute pain relief) that do not affect the quantity of life, and regarding the availability of good quality utility values for certain populations.

Cost-benefit analysis

A cost-benefit analysis (CBA) is the broadest type of economic 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.⁽¹⁴⁾ This method provides an overall view as to whether a technology is economically desirable, that is to say, whether the benefits of employing a technology outweigh the costs which simplifies decisions in the absence of budget constraints.

Monetary values may be assigned to health outcomes in a number of ways. The value of the consequences may be provided by patients, health professionals or by the general population.⁽¹⁴⁾ 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.⁽¹⁶⁾

Limitations

The use of CBA is limited by the methods used to translate benefits to monetary values.⁽¹⁶⁾ In practice, CBA is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms.^(15, 80)

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 CMA 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. CMA 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.⁽¹⁷⁾

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 Consumer Price Index (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 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 indices: medical products, appliances and equipment; outpatient services; and hospital services. 'Medical products, appliances and equipment' has three further sub-indices: pharmaceuticals products (comprising prescribed drugs and other drugs), therapeutic appliances and equipment, and other medical products. 'Outpatient services' has two further sub-indices: medical and paramedical services (comprising doctors' fees and other medical and paramedical services), and dental services. For each of these indices, a small number of items are chosen and priced as a representative sample of goods.

If one of the indices or 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 Central Statistics Office (CSO) [website](#).

Example:

Convert €50 (2014 to 2024) using the CPI for health.⁽³⁰⁾

Consumer Price Index by commodity group, month and statistic		
Month	2014	2024
January	87.8	100.7
February	87.7	100.7
March	87.7	100.6
April	87.7	100.5
May	87.5	100.4
June	87.6	100.4
July	87.7	100.0
August	87.7	-
September	87.6	-
October	87.9	-
November	87.9	-
December	88.0	-
Average	87.7	100.5

Using the formula:

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

$$\text{Price increase} = [(100.5/87.7) \times 100] - 100 = 14.6\%$$

$$\text{Updated price} = \text{€}50 \times (100\% + 14.6\%)$$

$$= \text{€}57.30$$

Therefore, €50 in 2014 is equivalent to €57.30 in 2024.

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 (PPP) index (see Appendix 3).

Appendix 3 How to transfer costs to Ireland using the Purchasing Power Parity index

The purpose of the Eurostat-Organisation for Economic Co-operation and Development (OECD) Purchasing Power Parity (PPP) Programme is to compare on a regular and timely basis, the gross domestic products (GDPs) of three groups of countries: EU Member States, OECD Member Countries, and associate non-member countries (countries that have an association other than membership with the European Union or the OECD). Specifically, the programme's objective is to compare the price and volume levels of GDP and its component expenditures across the three groups of countries. To make these comparisons, the GDPs and the component expenditures — which are in national currencies and valued at national price levels — are expressed in a common currency at a uniform price level. PPPs are used to effect this double conversion. The PPPs are calculated by Eurostat and the OECD with the price and expenditure data that countries participating in the programme supply specifically for the calculation.⁽⁸¹⁾

More information is available on the OECD website:

- <https://www.oecd.org/en/data/indicators/purchasing-power-parities-ppp.html>
- [OECD Data Explorer](#)

Example:

Convert GBP £50 (year 2022) to Irish costs (in €) using the PPP for GDP (national currency per US\$).

Using the 2022 Purchasing Power Parities for GDP, the UK has a PPP of 0.651/US\$ and the value for Ireland is 0.738/US\$:

United Kingdom – currency/US\$	0.651
Ireland – currency/US\$	0.738
Ratio (Ireland : United Kingdom)	1.134
2022 value (GBP £)	£50.00
Converted to 2022 Irish costs in €	€56.70

Appendix 4 Adjusting for pay-related costs in Ireland

Labour (pay) should be calculated using consolidated salary scales available from the HSE.⁽³⁶⁾ For consultants (both clinical and academic), the relevant salary scale(s) under the 2023 contract should be used unless there is a valid reason for using an alternative scale, and this should be clearly justified. An average salary cost should be used for the relevant grade by taking a value midway between the lowest and the highest points on the current pay scale at the time of the evaluation.^(38, 82)

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.⁽³⁸⁾ 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, and so on as follows:^(38, 82)

- PRSI rates are subject to change under government policy and the Department of Employment and Social Protection guidelines should be consulted for the most recent rates that pertain to each employee category.⁽⁸³⁾
- In 2013, the Single Public Service Pension Scheme was introduced to replace existing pension schemes for new entrants to the public service in Ireland.⁽⁸⁴⁾ As such, notional employer pension contribution rates, calculated as a percentage of pensionable salary, have been estimated separately for employees first entering the public service before and after 2013.⁽⁸²⁾ Average notional employer contribution rates, for both the pre- and post-2013 cohorts, have been published for public service employees with broadly similar benefit structures and salary progression. However, hospital consultants were excluded in this calculation due to their faster-than-average salary progression, and separate employer contribution rates have been published for this group (Table A4.1). The average notional employer contribution rate for public service employees should be applied in estimating the imputed pension cost for all posts with the exception of hospital consultants. Given that estimates of the composition of public service employees in terms of the pre- and post-2013 cohorts are approaching a 50/50 split,⁽⁸⁵⁾ in the base-case scenario it should be assumed that a post in the public service is equally likely to be filled by someone who first entered the public service either pre- or post-2013. Therefore, the imputed pension cost should be estimated based on applying an average of the pre- and post-2013 employer contribution rates to pensionable remuneration (Table A 1). The composition of public service employees in terms of the pre- and post-2013 cohorts will continue to change

over time, with an increasing proportion of employees in the post-2013 entrant cohort. As such, a scenario analysis should also be conducted where it is assumed a post will be filled by a post-2013 entrant, thereby applying the lower employer contribution rate only.

- Where data are available on cost allocation within overhead departments, a more specific method for allocating overheads can be applied. However, if data are not available, an overhead rate of 25% of pay should be applied.⁽⁸²⁾

The total staff cost is calculated as follows:

A	Pay	Mid-point of pay range
B	Direct salary cost	A + Employers PRSI (as a % of A) (Employer's PRSI rate of 11.15% applied in example below)
C	Total salary cost	B + Imputed pension cost (as a % of A) (see Table A 1 below for employer contribution rates)
D	Total staff cost	C + Overheads (25% of A)

Table A 1 Estimated employer pension contribution rates (cost of pension less normal employee contributions)

	Estimated employer pension contribution rates⁽⁸²⁾		
	Pre-2013 cohort	Post-2013 cohort	Average rate
Public service employees (excluding hospital consultants)[†]	29%	9%	19%
Hospital consultant	46%	14%	30%

[†]An average notional employer contribution rate was calculated for public service employees with broadly similar benefit structures and salary progression i.e. civil servants, national school teachers, nurses and engineers. Hospital consultants were excluded from the average as their average employer contribution rate is higher due to their faster-than-average salary progression.⁽⁸²⁾

Example:

- A staff nurse has 13 points on a pay scale ranging from €35,419 to €53,318 (as of 1 June 2024); the seventh point or mid-point of this scale is €44,658.
- direct salary cost is €44,658 + 11.15% of €44,658 = €49,637
- total salary cost is €49,637 + (19% of €44,658) = €58,122
- total staff cost is €58,122 + 25% of €44,658 = €69,287
- therefore, the total cost associated with employing an additional staff nurse includes the pay and non-pay costs and is estimated at €69,287.

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. The average cost reflects that staff may be recruited at any point on the pay scale. Uncertainty in the average salary cost can be based on the pay scale or can be based on an arbitrary value, such as $\pm 20\%$.
- Formulae for the calculation of daily and hourly rates are available in the Regulatory Impact Analysis guidelines and should be consulted, where appropriate.⁽³⁸⁾

Appendix 5 Depreciation of assets in accordance with Health Service Executive (HSE) accounting practices⁽⁸⁶⁾

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 (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

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 4.0% is specified for both costs and benefits.⁽⁸⁷⁾

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

$$discount_t = \frac{1}{(1 + r)^t}$$

With: r = discount rate (0.04)

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 at 4% per annum over 10 years. 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	1.000	1,000.00	1,000.00	0.70	0.70
1	0.962	1,000.00	961.54	0.70	0.67
2	0.925	500.00	462.28	0.80	0.74
3	0.889	500.00	444.50	0.80	0.71
4	0.855	0	0	0.90	0.77
5	0.822	0	0	0.90	0.74
6	0.790	0	0	0.90	0.71
7	0.760	0	0	0.90	0.68
8	0.731	0	0	0.90	0.66
9	0.703	0	0	0.90	0.63
Total		3,000.00	2,868.32	8.40	7.01

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, that is to say, $P_c - P_t$. 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 (that is, 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 (for example, medical equipment) to provide a service (for example, healthcare).
Case-control study	A retrospective observational study designed to determine the relationship between a particular outcome of interest (for example, disease or condition) and a potential cause (for example, 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 (for example, 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)." ⁽⁷³⁾
Confounding	The distortion of a measure of the effect of an exposure (for example, 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 (that is, 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 or loss or benefit gain or loss.
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, for example, 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, for example 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 with 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, and so on) consumed in the provision of a technology as well as any consequences of the intervention such as adverse effects or goods or services induced by the intervention. These include direct medical costs and direct non-medical costs such as transportation or child care.

Direct medical costs	Medical costs that vary with the healthcare provided (for example, doctors' salaries).
Direct non-medical costs	The non-medical costs of treating a patient, such as transportation provided to and from a medical appointment.
Disability-adjusted life years (DALYs)	A unit of healthcare status that adjusts age-specific life expectancy by the loss of health and years of life due to disability from disease or injury. DALYs are often used to measure the global burden of disease.
Discounting	The process used in economic analyses to convert future costs or benefits to present values using a discount rate. Discounting costs reflects societal preference for costs to be experienced in the future rather than the present. Discounting benefits reflects a preference for benefits to be realised in the present rather than at a later date.
Discount rate	The interest rate used to discount or adjust future costs and benefits so as to arrive at their present values, for example 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 a higher 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-3L	The EQ-5D-3L 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-3L questionnaire describes five attributes (mobility, self-care, usual activity, pain and or discomfort, and anxiety and or depression) each of which has three levels (no problems, some problems, and major problems). This combination defines 243 possible health states. Each EQ-5D-3L health state (or profile) provides a set of observations about a person by way of a five-digit code number. This EQ-5D-3L 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 the EQ-5D-3L see: www.euroqol.org .
EQ-5D-5L	<p>Like the EQ-3D-3L, the EQ-5D-5L is a standardised instrument (questionnaire) used to measure health outcomes and it comprises the same five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It differs from the EQ-5D-3L on the following points:</p> <ul style="list-style-type: none"> ▪ The number of levels of perceived problems per dimension is five, compared with three in the EQ-5D-3L, increasing the sensitivity and reducing the ceiling effect. The EQ-5D-5L therefore allows a total of 3,125 possible health states. ▪ The most severe label for the mobility dimension is 'unable to walk about', compared with 'confined to bed' in the EQ-5D-3L, enhancing its applicability and increasing the sensitivity of the mobility dimension. <p>For further information on the EQ-5D-5L see: www.euroqol.org.</p>
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 a study.
Extrapolation	Prediction of value of model parameter outside measured range or inference of value of parameter of related outcome (for example, extrapolation of reduction in rate of progression to AIDS from improvement in HIV viral load).

Final outcome	A health outcome that is directly related to the length of life, for example, life years gained or quality-adjusted life years.
Follow up	The observation over a period of time of study or 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, for example 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 wellbeing.
Health technology	The application of scientific or other organised knowledge — including any tool, technique, product, process, method, organisation or system — in healthcare and prevention. In healthcare, technology includes drugs, diagnostics, indicators and reagents, devices, equipment and supplies, medical and surgical procedures, support systems and organisational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation.

Health technology assessment (HTA)	HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.
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: $ICER = \frac{\text{cost of A} - \text{cost of B}}{\text{outcome of A} - \text{outcome of B}}$
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 (for example, health utilities index (HUI) 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 (for example, in units of health outcome) produced by an additional resource use (for example, another healthcare intervention).
Marginal cost	The additional cost required to produce one additional unit of benefit (for example, unit of health outcome).
Markov Model	A type of quantitative modelling that involves a specified set of mutually exclusive and exhaustive states (for example, of a given health status), and for which there are transition probabilities of moving from one state to another (including of remaining in the same state). Typically, states have a uniform time period, and transition probabilities remain constant over time.
Meta-analysis	Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. This combination may produce a stronger conclusion than can be

	provided by any individual study. Also known as data synthesis or quantitative overview.
Micro-costing	Costing approach based on detailed resources used by patient on item by item basis; compare with gross costing.
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): $\text{net monetary benefit (NMB)} = \lambda \Delta E - \Delta C$ $\text{net health benefit (NHB)} = \Delta E - \left(\frac{\Delta C}{\lambda}\right)$ 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 — for example, 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 ($1 \div$ 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 (for example do not assign patients to treatment and control groups), but only observe patients who are (and sometimes patients who are not as a basis of comparison) exposed to the intervention, and interpret the outcomes. These studies are more subject to selection bias than experimental studies such as randomised controlled trials.
Odds ratio	An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.
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 — for example, randomised controlled trials, observational studies, series of cases, and so on.
Probability	Expression of degree of certainty that event will occur, on a 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 (such as 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 (that is, 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 or 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, that is, 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 wellbeing scores as well as psychometrically-based physical and mental health summary

	<p>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.</p> <p>For further information on SF-36 see: 36-Item Short Form Survey (SF-36).</p>
Standard gamble	<p>A method of preference assessment used to measure utilities, that is, to ascertain an individual's preference for different health states that differ in quantity or quality of life. Preference is ascertained by choosing between a given health state, or gambling between perfect health and immediate death. The probability of perfect health or immediate death is changed until the individual is indifferent between the health state and the gamble.</p>
Statistical significance	<p>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.)</p>
Stratified analysis	<p>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.</p>
Subgroup	<p>A defined set of individuals in a population group or of participants in a study such as subgroups defined by sex or age categories.</p>
Subgroup analysis	<p>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</p>

	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 structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from the 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 incorporate 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 an individual 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 transferability if it can produce unbiased inferences to another specified healthcare system (for example, 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 a 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 (VAT)	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 (for example, 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 the maximum amount of money an individual is willing to pay for a particular outcome or benefit (for example, receive healthcare service); method is often used in cost-benefit analysis to quantify outcome in monetary terms.

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