

Guide to the methods of technology appraisal 2013

Process and methods

Published: 4 April 2013

[nice.org.uk/process/pmg9](https://www.nice.org.uk/process/pmg9)

Contents

Foreword	8
Acknowledgements	9
1 Introduction.....	10
1.1 The methods of technology appraisal.....	10
1.2 Health technologies and their selection	11
1.3 What is technology appraisal?.....	12
1.4 Fundamental principles.....	13
1.5 Implementation of NICE guidance.....	14
2 Developing the scope.....	16
2.1 Introduction.....	16
2.2 Components of the scope.....	17
3 Evidence	20
3.1 Introduction.....	20
3.2 Guiding principles for evidence	20
3.3 Types of evidence.....	21
4 Involvement and participation	24
4.1 Independent academic groups	24
4.2 Manufacturers and sponsors	25
4.3 Patient and carer groups.....	26
4.4 Healthcare providers and commissioners of health services	27
4.5 Clinical specialists, commissioning experts and patient experts	28
5 The reference case	31
5.1 Framework for estimating clinical and cost effectiveness	31
5.2 Synthesis of evidence on health effects.....	36
5.3 Measuring and valuing health effects.....	40
5.4 Equity considerations in cost-effectiveness analysis	43
5.5 Evidence on resource use and costs.....	43

5.6 Discounting	46
5.7 Modelling methods	46
5.8 Exploring uncertainty	49
5.9 Companion diagnostics	51
5.10 Analysis of data for patient subgroups.....	52
5.11 Presentation of data and results.....	55
5.12 Impact on the NHS	56
6 The appraisal of the evidence and structured decision-making	58
6.1 Introduction.....	58
6.2 Appraisal of the evidence	61
6.3 Decision-making	68
6.4 Research recommendations.....	69
7 Further information.....	71
7.1 NICE project team and Steering Group.....	71
7.2 NICE Methodology Working Party	71
7.3 Bibliography.....	76
Glossary	77
Absolute risk reduction (or increase)	77
Abstract	77
Adherence	77
Adverse effect	77
Appraisal Committee	77
Assessment Group	77
Assessment report	77
Baseline	78
Bias	78
Blinding	78
Carer	78

Case-control study	78
CE mark	78
Citizens Council	78
Class (of drugs in a NICE technology appraisal)	79
Clinical audit	79
Clinical effectiveness	79
Clinical specialist	79
Cohort study	79
Commentator	79
Comorbidity	80
Comparator	80
Confidence interval (CI)	80
Confounding	80
Constant proportional trade-off	80
Construct validity	80
Consultation	81
Consultee	81
Control	81
Cost-benefit analysis	81
Cost-effectiveness acceptability curves	81
Cost-effectiveness analysis	81
Cost-effectiveness frontier	82
Cost-effectiveness model	82
Cost-effectiveness plane	82
Decision problem	82
Director of the Centre for Health Technology Evaluation	82
Discounting	82
Dominance	83

Effectiveness	83
Efficacy	83
End point	83
Epidemiological study	83
Equity	83
European Medicines Agency	83
Evidence	83
Evidence Review Group	84
Evidence Review Group report	84
Extended dominance	84
External validity	84
Extrapolation	84
Forest plot	84
Generalisability	85
Health-related quality of life	85
Health technology	85
Healthcare Resource Groups (HRGs)	85
Heterogeneity	85
Inclusion criteria (literature review)	85
Incremental cost-effectiveness ratio (ICER)	85
Indication (specific)	86
Indirect comparison	86
Intention-to-treat (ITT) analysis	86
Intermediate outcome	86
Internal validity	86
Life-years gained	86
Marketing authorisation	86
Medicines and Healthcare products Regulatory Agency (MHRA)	87

Meta-analysis	87
Mixed treatment comparison	87
Multiple technology appraisal (MTA)	87
National Institute for Health Research (NIHR)	87
Natural history of a disease	87
Net benefit	87
NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)	88
Non-reference-case analysis	88
Observational study	88
Opportunity cost	88
Outcome	88
Pairwise comparisons	88
Parameter	89
Parameter uncertainty	89
Patient expert	89
Perspective (in economic evaluation)	89
Primary research	89
Quality-adjusted life year (QALY)	89
Quality of life	89
Random effects model	90
Randomisation	90
Randomised controlled trial (RCT)	90
Reference case	90
Relative risk (RR)	90
Relative treatment effect	90
Remit	91
Sensitivity analysis	91
One-way simple sensitivity analysis (univariate analysis)	91

Multi-way simple sensitivity analysis (scenario analysis)	91
Threshold sensitivity analysis	91
Probabilistic sensitivity analysis	91
Single technology appraisal (STA)	91
Structural uncertainty	92
Synthesis of evidence	92
Systematic review	92
Technology	92
Technology assessment	92
Time horizon	92
Time trade-off	92
Treatment options	93
Treatment sequence	93
Utility	93
Variable	93

Foreword

The National Institute for Health and Care Excellence (NICE, or the Institute) provides guidance to the NHS in England on the clinical and cost effectiveness of selected new and established technologies. The Institute undertakes appraisals of [health technologies](#) at the request of the Department of Health. Guidance produced by the Institute on health technologies is also applied selectively in Northern Ireland, Scotland and Wales.

The purpose of this document is to provide an overview of the principles and methods of [health technology assessment](#) and appraisal within the context of the NICE appraisal process. It describes key principles of appraisal methodology and is a guide for all organisations considering submitting [evidence](#) to the technology appraisal programme of the Institute.

The Institute regularly reviews its processes and methodology. This document updates the 'Guide to the methods of technology appraisal' published in 2008. This document does not provide a detailed description of the processes used to develop guidance. Information on the process of conducting a technology appraisal is available in 2 companion documents to this guide: [Guide to the multiple technology appraisal process](#) and [Guide to the single technology appraisal process](#). A review of these documents is currently underway; further information will be available on the [NICE website](#).

Because the methodology of technology appraisal continues to develop, there remain areas of controversy and uncertainty, particularly in relation to the methods of [cost-effectiveness analysis](#). However, it is important that the methods used to inform the [Appraisal Committee's](#) decision-making are consistent. For this reason, the Institute has adopted the approach of using a '[reference case](#)' for cost-effectiveness analysis; this was chosen as most appropriate for the Appraisal Committee's purpose.

The Institute sponsors research into the methods of technology appraisal and welcomes suggestions to the [Director of the Centre for Health Technology Evaluation](#) for both [primary](#) and secondary research that might lead to improvements in methods and make subsequent editions of this document more helpful.

In August 2017, NICE issued a [position statement](#) on the use of the EQ-5D-5L valuation set. Companies and academic groups should refer to this statement.

Acknowledgements

The Institute is grateful to the members of the Steering Group and Working Party and its specialist advisers for their contribution to the development of this document. It is also grateful to the people who attended the workshops held by the Institute on specific methodological issues relating to this update.

1 Introduction

1.1 *The methods of technology appraisal*

- 1.1.1 This document provides an overview of the principles and methods of health technology assessment and appraisal within the NICE technology appraisal process. It introduces the general methodological concepts underlying each stage of the appraisal process and describes what is required of participants submitting evidence to NICE. Earlier versions of this guide were published in 2004 and 2008.
- 1.1.2 The Institute has 2 appraisal processes: the [multiple technology appraisal \(MTA\)](#) process and the [single technology appraisal \(STA\)](#) process. Although there are differences between the 2 processes, the principles relating to decision-making, the methods of assessment and the decision [outcomes](#) are consistent.
- 1.1.3 Two other documents describe the Institute's appraisal processes.
- [Guide to the multiple technology appraisal process.](#)
 - [Guide to the single technology appraisal process.](#)
- 1.1.4 The Institute's appraisal processes rely on information from a number of sources, including independent academic groups, manufacturers and sponsors (see sections [4.1](#) and [4.2](#)), healthcare professionals, commissioners of health services and patient or [carer](#) representatives. These groups are also consulted on the draft scope of the technology appraisal and, when appropriate and in line with the technology appraisal process, on the decisions made by the Appraisal Committee.
- 1.1.5 Documents describing the Institute's current methods and processes are available on the [NICE website](#).
- 1.1.6 The Institute supports the development of methods through its Research and Development programme, its links with the [National Institute for Health Research](#), the Medical Research Council, and its liaison with academic groups.
- 1.1.7 This document includes a glossary of terms (see [section 7](#)).

1.2 *Health technologies and their selection*

1.2.1 The Institute undertakes appraisals of new and established technologies, as formally requested by the Department of Health. Health technologies referred to the NICE technology appraisals programme include:

- medicinal products
- medical devices
- diagnostic techniques
- surgical procedures
- therapeutic technologies other than medicinal products
- systems of care
- screening tools.

Some of these technologies will be considered by other programmes within NICE such as the clinical guidelines programme, the medical technologies evaluation programme, the diagnostics assessment programme or the interventional procedures programme, or will have medicines and prescribing support from the Medicines and Prescribing Centre at NICE. This methods guide relates only to technologies appraised through the technology appraisals programme.

1.2.2 The purpose of an appraisal carried out by the Institute is as described in the Directions from the Secretary of State for Health; that is, to appraise the health benefits and the costs of those technologies notified by the Secretary of State for Health and to make recommendations to the NHS in England and Wales.

1.2.3 Potential topics for technology appraisals come predominantly from the National Institute for Health Research (NIHR) Horizon Scanning Centre. Other sources include individual healthcare professionals, NHS commissioners, and the Department of Health's policy teams. The NICE website provides details on [how NICE selects topics for appraisal](#). Ministers at the Department of Health make the final decision about which topics are referred to NICE for appraisal.

1.2.4 The Department of Health refers technologies for appraisal based on 1 or more of the following criteria:

- Is the technology likely to have a significant health benefit, taken across the NHS as a whole, if given to all patients for whom it is indicated?
- Is the technology likely to have a significant impact on other health-related government policies (for example, reduction in health inequalities)?
- Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated?
- Is there significant inappropriate variation in the use of the technology across the country?
- Is the Institute likely to be able to add value by issuing national guidance? For example, in the absence of such guidance is there likely to be significant controversy over the interpretation or significance of the available evidence on clinical and cost effectiveness?

1.3 *What is technology appraisal?*

The appraisal of a health technology is divided into 3 distinct phases:

- scoping
- assessment
- appraisal.

Scoping

1.3.1 During the scoping process, the Institute determines the appropriateness of the proposed remit and defines the specific questions that each technology appraisal will address. The scope defines the issues of interest (for example, population, potential comparators and potential subgroups) as clearly as possible and the questions that the Appraisal Committee should address when considering the clinical and cost effectiveness of the technology. These questions are fundamental to the assessment process and require an understanding of the context within which to investigate a technology, including currently available care and any alternative technologies for the specific indication. Consultees and commentators are consulted during the scoping process. The Institute revises the scope in response to comments received and develops a final scope that describes the boundaries of the appraisal and the

main issues. The methods and principles that underpin the scoping process are described in detail in [section 2](#).

Assessment

- 1.3.2 The assessment process is a systematic evaluation of the relevant evidence (see [section 3](#)) available on a technology. The aim is to assess a technology's clinical and cost effectiveness for a specific indication, taking account of uncertainty, compared with the appropriate comparator(s) listed in the scope. Assessment has 2 components: a [systematic review](#) of the evidence and an economic evaluation. Assessment, therefore, consists of an analysis of the quality, findings and implications of the available evidence (mainly from research). Strengths, weaknesses and gaps in the evidence are identified and evaluated.
- 1.3.3 An independent academic group reviews the evidence. For MTAs, the academic group is known as the '[Assessment Group](#)', and it conducts an independent systematic review and economic analysis. For STAs, the academic group is the '[Evidence Review Group](#)', and it reviews and critiques the submission provided by the manufacturer or sponsor of a technology. The Evidence Review Group may recommend that the Institute requests additional analyses from the manufacturer or sponsor, and may explore alternative scenarios or conduct further exploratory analyses to address uncertainty in the cost-effectiveness results.

Appraisal

- 1.3.4 Within the appraisal process (see [section 6](#)), an Appraisal Committee considers evidence contained in the reports and analyses produced in the assessment phase and additional information supplied by consultees, commentators, [clinical specialists](#), [patient experts](#) and commissioning experts. The Appraisal Committee considers the evidence and makes a decision, applying judgements on a range of factors.

1.4 *Fundamental principles*

- 1.4.1 The Institute takes into account the clinical and cost effectiveness of a technology, along with other considerations (see [section 6.2](#)), when issuing guidance to the NHS.

- 1.4.2 In general, a technology can be considered clinically effective if, in normal clinical practice, it confers a health benefit, taking account of any harmful effects and opportunity costs. A technology can be considered to be cost effective if its health benefits are greater than the opportunity costs of programmes displaced to fund the new technology, in the context of a fixed NHS budget. In other words, the general consequences for the wider group of patients in the NHS are considered alongside the effects for those patients who may directly benefit from the technology.
- 1.4.3 NICE is committed to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and society as a whole, and to complying fully with its legal obligations on equality and human rights. NICE's equality scheme (see section 7) describes how the Institute meets these commitments and obligations.
- 1.4.4 In formulating its recommendations, the Appraisal Committee will have regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE. The Appraisal Committee will also take into account the Institute's guidance on social value judgements described in the Institute's document, Social value judgements: principles for the development of NICE guidance. This document, developed by NICE's Board, describes the principles NICE should follow when designing the processes used to develop its guidance. In particular it outlines the social value judgements that NICE and its advisory bodies, including Appraisal Committees, should apply when making decisions about the effectiveness and cost effectiveness of interventions.

1.5 *Implementation of NICE guidance*

- 1.5.1 The National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 require clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with NICE technology appraisal recommendations that recommend the relevant health service body provide funding within the period specified. Where NICE recommends that a treatment be funded by the NHS, the Regulations require that the period within which the health service must comply will be stated in the recommendations as three months, except where particular barriers to

implementation within that period are identified. The Institute provides advice and tools to support the local implementation of its guidance. This includes costing tools or statements and audit support for most technology appraisals and additional tools for selected technology appraisals.

2 Developing the scope

2.1 Introduction

- 2.1.1 The 'scoping' process examines the appropriateness of the proposed remit and defines what the appraisal will and will not examine. Scoping determines the nature and content of the evidence to be included in the assessment phase of the appraisal. However, the Appraisal Committee may consider issues that are not defined in the scope if necessary in the light of the evidence provided. Further details of the scoping process, including the identification of interested parties and [consultation](#) on documents, can be found in documents relating to the technology appraisal process (see [section 7](#)) and on our website for the [topic selection process](#).
- 2.1.2 The scope provides a framework for the appraisal. It defines the issues of interest (for example, population, comparators, and health outcome measures) and sets the boundaries for the work undertaken by the independent academic groups and the manufacturer(s) or sponsor(s) of the technology who produce reports for the Appraisal Committee.
- 2.1.3 The issues for consideration in the appraisal that are described in the scope include:
- the disease or health condition and the population(s) for whom treatment with the technology is being appraised
 - the technology (and the setting for its use; for example, hospital [inpatient and outpatient] or community if relevant)
 - the relevant potential comparator technologies (and the setting for their use if relevant)
 - the principal health outcome measures appropriate for the analysis
 - the costs, including when the Department of Health asks NICE to consider costs (savings) to the public sector outside the NHS and personal social services
 - the [time horizon](#) over which health effects and costs will be assessed

- consideration of patient subgroups for whom the technology might be particularly clinically and cost effective
- issues relating to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and society as a whole
- other special considerations and issues that are likely to affect the appraisal, for example, existing relevant NICE guidance and the innovative nature of the technology.

2.2 *Components of the scope*

Background information on the disease or health condition

- 2.2.1 The scope briefly describes the disease or health condition relevant to the technology under appraisal together with appropriate information on its prognosis, epidemiology and alternative treatments currently used in the NHS.

The technology

- 2.2.2 The scope includes information about the marketing authorisation (or CE mark for medical devices) of the technology, and the stage of regulatory approval for technologies not yet licensed. It may include a brief description of the clinical trials on which the licensed indication is based. The scope specifies the mode of administration and the circumstances of use, particularly if different from that of alternative treatments for the same patient group, or when there are several other circumstances in which the technology may be used.

The population

- 2.2.3 The scope defines the population for whom the technology is being appraised as precisely as possible. When the technology is a medicine, the marketing authorisation will generally specify the therapeutic indications. The scope may highlight potential subgroups of the population for whom the clinical or cost effectiveness of the technology might be expected to differ from the overall population, or who require special consideration.

The comparator technologies

- 2.2.4 The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator (see [sections 6.2.1-4](#)). At this stage of the appraisal, identification of comparators should be inclusive.
- 2.2.5 Comparator technologies may include branded and non-proprietary (generic) drugs and biosimilar products.
- 2.2.6 Sometimes both the technology and comparator form part of a [treatment sequence](#) in the pathway of care. In these cases the appraisal may compare alternative treatment sequences.

The evidence base

- 2.2.7 The scoping process should highlight issues about the available evidence base, for example, emerging key trials, important clinical databases, availability of relevant [health-related quality of life](#) data, and the evidence around comparator technologies.

The measures of health outcome

- 2.2.8 As far as possible, the scope identifies principal measures of health outcome(s) that will be relevant for the estimation of [clinical effectiveness](#). That is, they measure health benefits and [adverse effects](#) that are important to patients and/or their carers. The clinical outcome measures usually quantify an impact on survival or health-related quality of life that translates into [quality-adjusted life years \(QALYs\)](#) for the evaluation of cost effectiveness.

The measures of costs

- 2.2.9 The potential impact on resource costs and savings that would be expected from the introduction of the technology should be considered from the [perspective](#) of the NHS and personal social services. In exceptional circumstances, when requested by the Department of Health in the remit for the appraisal, the scope will list requirements for adopting a broader perspective on costs.

Other issues likely to impact upon the appraisal

2.2.10 The scope includes details of:

- related NICE guidance, such as other technology appraisals and clinical guidelines
- related policy developments
- details of service settings related to the technology under appraisal that are either of particular interest or are to be excluded from consideration
- the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during assessment
- issues relating to advancing equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and society as a whole.

3 Evidence

3.1 Introduction

- 3.1.1 Consideration of a comprehensive evidence base is fundamental to the appraisal process. Evidence of various types and from multiple sources may inform the appraisal. To ensure that the guidance issued by the Institute is appropriate and robust, it is essential that the evidence and analysis, and their interpretation, are of the highest standard and are transparent.
- 3.1.2 The evaluation of effectiveness requires quantification of the effect of the technology under appraisal and of the relevant comparator technologies on survival, disease progression and health-related quality of life so that this can be used to estimate QALYs.
- 3.1.3 For costs, evidence requirements include quantifying the effect of the technology on resource use in terms of physical units (for example, days in hospital or visits to a GP) and valuing those effects in monetary terms using appropriate prices and unit costs.
- 3.1.4 In addition to evidence on treatment effects and costs, the appraisal of health technologies requires consideration of a range of other issues, for example:
- the impact of having a condition or disease, the experience of undergoing specific treatments for that condition, and experience of the healthcare system for that condition
 - organisational issues that affect patients, carers or healthcare providers
 - NICE's legal obligations on equality and human rights
 - the requirement to treat people fairly.

3.2 Guiding principles for evidence

- 3.2.1 The evidence submitted to the Appraisal Committee should be:
- relevant to the issue under consideration in terms of patient groups, comparators, perspective, outcomes and resource use as defined in the scope

- inclusive of information on study design, such as the type of study, the circumstances of its undertaking and the rationale for the selection of outcomes, resource utilisation and costs
- assembled systematically and synthesised in a transparent way that allows the analysis to be reproduced
- analysed in a way that is methodologically sound and, in particular, minimises any bias.

To ensure that the evidence base for appraisals is consistent with these principles, NICE has defined a 'reference case' that specifies the methods it considers to be most appropriate for estimating clinical and cost effectiveness in technology appraisals (see [section 5](#)).

3.2.2 There are always likely to be deficiencies in the evidence base available for health technology assessment. For example, small sample sizes may result in some parameters being estimated with a low degree of precision, or evidence on effectiveness might come from outside the UK healthcare system or relate to groups of patients other than those of principal interest to the appraisal. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. Therefore, analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis.

3.3 *Types of evidence*

3.3.1 Whatever the sources of evidence available on a particular technology and patient group, they should be integrated into a systematic review. A systematic review attempts to assemble all the available relevant evidence using explicit, valid and replicable methods in a way that minimises the risk of biased selection of studies. The data from the included studies can be synthesised (known as meta-analysis). All evidence should be critically appraised, and potential biases must be identified (see [section 5.2](#)).

Randomised controlled trials

3.3.2 Randomised controlled trials (RCTs) minimise potential external influences to identify an effect of 1 or more interventions on outcomes. Randomisation aims

to prevent systematic differences between characteristics of participants assigned to different interventions at the start of the trial in terms of both known and unknown (or unmeasured) confounders. The trial should, in principle, provide a minimally biased estimate of the magnitude of any benefits or risks associated with the technology relative to those associated with the control group (participants receiving something other than the technology, for example no treatment, the standard treatment or placebo). RCTs are therefore considered to be most appropriate for measures of relative treatment effect.

- 3.3.3 The relevance of RCT evidence to the appraisal depends on both the external and internal validity of each trial. Internal validity is assessed according to the design and conduct of a trial and includes blinding (when appropriate), the method of randomisation and concealment of allocation, and the completeness of follow-up. Other important considerations are the size and power of the trial, the selection and measurement of outcomes and analysis by intention to treat. External validity is assessed according to the generalisability of the trial evidence; that is, whether the results apply to wider patient groups (and over a longer follow-up) and to routine clinical practice.

Non-randomised and non-controlled evidence

- 3.3.4 The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and end point occur more commonly in non-randomised studies and non-controlled trials than in RCTs.
- 3.3.5 Observational (or epidemiological) studies do not apply an intervention, but instead compare outcomes for people who use the technology under appraisal with outcomes for people who do not use the technology. These studies may be biased in that the people who use the technology may fundamentally differ in their risk of the outcome than the people who do not use the technology. Some observational studies lack a control group, and include only people who receive the technology.
- 3.3.6 Inferences will necessarily be more circumspect about relative treatment effects drawn from studies without randomisation or control than those from RCTs. The potential biases of observational studies should be identified, and ideally quantified and adjusted for. When possible, more than 1 independent

source of such evidence should be examined to gain some insight into the validity of any conclusions.

- 3.3.7 Evidence from sources other than RCTs is also often used for parameters such as the valuation of health effects over time into QALYs, and for costs. Study quality can vary, and so systematic review methods, critical appraisal and sensitivity analyses are as important for review of these data as they are for reviews of data on relative treatment effects from RCTs.

Qualitative research

- 3.3.8 In the context of technology appraisals the main purpose of qualitative research is to explore areas such as patients' experiences of having a disease or condition, their experiences of having treatment and their views on the acceptability of different types of treatment.

Economic evaluations

- 3.3.9 Evidence on cost effectiveness may be obtained from new analyses performed according to the NICE reference case; however, a systematic review of published, relevant evidence on the cost effectiveness of the technology should also be conducted.
- 3.3.10 Economic evaluations should quantify how the technologies under comparison affect disease progression and patients' health-related quality of life, and value those effects to reflect the preferences of the general population.
- 3.3.11 For all parameters (including effectiveness, valuation of health-related quality of life and costs) economic evaluation should systematically consider possible data sources, and avoid selection bias in the choice of sources.

Unpublished and part-published evidence

- 3.3.12 To ensure that the appraisal does not miss important relevant evidence, it is important that attempts are made to identify evidence that is not in the public domain. Such evidence includes unpublished clinical trial data and clinical trial data that are in abstract form only or are incomplete. Such information must be critically appraised and, when appropriate, sensitivity analysis conducted to examine the effects of its incorporation or exclusion.

4 Involvement and participation

NICE will normally receive evidence from:

- an independent academic group
- manufacturers and sponsors of technologies
- national patient or carer groups
- healthcare professional organisations
- clinical specialists, commissioning experts and patient experts
- commissioning bodies.

Detailed information for individual groups participating in an appraisal who wish to submit written or oral evidence is provided in the additional documents listed in section 1.1.3 and is available on the NICE website.

4.1 *Independent academic groups*

4.1.1 A group of independent experts from 1 of a number of academic centres is commissioned by the NHS National Institute for Health Research (NIHR) through the [NIHR Evaluation, Trials and Studies Coordinating Centre \(NETSCC\)](#) to review and critique the available evidence for each technology under appraisal. Groups commissioned for appraisals in the MTA process are referred to as Assessment Groups, whereas those commissioned for appraisals in the STA process are referred to as Evidence Review Groups. The reports they produce are the responsibility of the authors.

Assessment groups (MTA process)

4.1.2 In the MTA process, the Assessment Group independently synthesises the evidence from published information and the submissions from manufacturers and sponsors about the clinical and cost effectiveness of the technology or technologies. The report focuses on the evidence relevant to the scope (see [section 5.1.4](#)).

- 4.1.3 In addition to a systematic review of the evidence on clinical effectiveness and a review of published cost-effectiveness studies, the [assessment report](#) will normally include a cost-effectiveness analysis informed by a review of the clinical-effectiveness evidence. This analysis should conform to the requirements of the reference case (see [section 5](#)).

Evidence review groups (STA process)

- 4.1.4 In the STA process, the Evidence Review Group prepares a report, which assesses the submission provided by the manufacturer or sponsor of the technology (see [section 4.2](#)). The Evidence Review Group may recommend that the Institute request additional analysis from the manufacturer or sponsor, and/or may undertake additional exploratory analyses itself.

4.2 *Manufacturers and sponsors*

- 4.2.1 Submissions are invited from manufacturers and sponsors (organisations who market the technology under licence) of the technology or technologies being appraised. Manufacturers and sponsors should identify all evidence relevant to the appraisal. This includes a list of all studies known to them, including clinical trials, follow-up studies and evidence from disease registries. They may also include relevant study evidence to which they have privileged access and which is not in the public domain. In particular, when technologies are undergoing appraisal immediately before regulatory approval, sufficient details of the clinical trial evidence should be made available to enable the Institute to conduct the appraisal according to the defined scope.
- 4.2.2 At the earliest opportunity, the Institute will ask manufacturers or sponsors to make available details of the studies they intend to include in their submissions. When there is unpublished information, the Institute will request the study reports.
- 4.2.3 In the STA process the manufacturer or sponsor is required to provide a systematic review of the evidence on clinical and cost effectiveness and an assessment of cost effectiveness containing a reference-case analysis based on clinical-effectiveness evidence. This submission forms the principal evidence base to estimate clinical and cost effectiveness. The manufacturer or sponsor

must justify any cost-effectiveness analysis that does not fulfil this reference-case requirement.

4.2.4 Further information on the content of manufacturer and sponsor submissions is available in the [technology appraisal submission templates](#).

4.3 *Patient and carer groups*

- The Institute invites submissions from all patient and carer groups involved in the appraisal.

4.3.1 These written submissions may provide perspectives from patients and carers on:

- the experience of having the condition, or in the case of carers, the experience of caring for someone with the condition
- the experience of receiving care for the condition in the healthcare system
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which may differ from the outcomes measured in the relevant clinical studies and the aspects of health included in generic measures of health-related quality of life)
- the acceptability of different treatments and modes of treatment
- their preferences for different treatments and modes of treatment
- their expectations about the risks and benefits of the technology.

4.3.2 The information is best taken directly from people with the condition (or their family or carers) in the form of written accounts of their experiences and points of view. Narrative summaries, preferably with illustrative quotes, addressing the issues listed in section 4.3.2 are acceptable. Standard qualitative research techniques, such as thematic analysis, facilitate the [synthesis of evidence](#) of this type. Accounts and experiences may be collected and analysed systematically using these qualitative research techniques, but there is no requirement to present the information in this way. The Institute supports the collection of patient and carer evidence by use of a template, by offering the services of the Public Involvement programme, and by providing some financial support.

4.3.3 The Appraisal Committee is interested in a range of patient and carer perspectives, including majority views and views that may be held by only a few patients even if they contradict the majority. It is therefore important to include a range of views, especially when there are differences of opinion.

4.3.4 In the context of a technology appraisal, the Appraisal Committee is interested in limitations in the published research literature identified by patient groups and in particular the extent to which patient-reported outcome measures, or other end points reported in clinical studies, capture outcomes of importance to patients. They may assess research-based evidence from a different perspective to researchers and clinicians and they may judge the evidence according to different criteria. Additionally, it is helpful to have the perspective of patients or carers about how relevant the clinical outcomes and the standardised generic instruments for measuring health-related quality of life (as specified in the reference case, see [section 5.3](#)) are to the disease or condition of the appraisal.

4.4 *Healthcare providers and commissioners of health services*

4.4.1 The Institute invites submissions from all professional bodies and relevant NHS organisations involved in the appraisal, including:

- the Royal Colleges of the appropriate clinical disciplines
- the specialist societies of the appropriate clinical disciplines
- other appropriate professional bodies and NHS organisations including commissioners of NHS services.

4.4.2 Healthcare professionals and commissioners of health services provide a view of the technology in relation to current clinical practice. This puts into context the evidence derived from pre- and post-licensing studies, which often relates to [efficacy](#) and safety under clinical trial conditions rather than effectiveness in routine clinical practice.

4.4.3 The written submissions provide a unique contribution, outlining the professional view of the place of the technology in current clinical practice and in the pathway of care. This includes evidence that relates to some or all of the following:

- Variations between groups of patients, in particular, differential baseline risk of the condition and potential for different subgroups of patients to benefit.
- Identifying appropriate outcome and surrogate outcome measures.
- Significance of side effects or adverse reactions and the clinical benefits.
- Circumstances in which treatment is delivered, including:
 - the need for concomitant treatments
 - the settings in which treatment is delivered (for example, primary or secondary care, or in specialist clinics)
 - the requirements for additional professional input (for example, community care, specialist nursing or other healthcare professionals).
- Relevant potential comparators.
- Information on unpublished evidence. Such information should be accompanied by sufficient details to enable a judgement as to whether it meets the same standards as published evidence and to determine potential sources of bias.
- Evidence from registries and nationally coordinated clinical audit.
- Published clinical guidelines produced by specialist societies.
- The impact of possible guidance on:
 - delivery of care
- education and training requirements of NHS staff
- patients who would use the technology.

4.5 *Clinical specialists, commissioning experts and patient experts*

4.5.1 Three groups of experts – clinical specialists, commissioning experts and patient experts – are selected by the Appraisal Committee Chair from nominations provided by consultees and commentators. These experts provide written evidence and attend the Committee meeting to help in the Committee's discussion of the technology being appraised.

Format of the evidence

- 4.5.2 The Institute asks all experts attending the Committee meeting to submit, in advance, a brief written personal view of the current management of the condition and the expected role and use of the technology in the NHS, as well as to provide oral commentary during the meeting. The purpose of the written personal view is to make the expert's perspective transparent to those who did not attend the meeting. The purpose of the oral commentary provided by the experts is to explore the evidence that is provided in the written submissions from consultees. During the open part of the meeting, clinical specialists, commissioning experts and patient experts are encouraged to interact fully in the debate with the Committee, including responding to and posing questions. The clinical specialists, commissioning experts and patient experts are asked to withdraw from the meeting before the Committee discusses the content of the guidance.
- 4.5.3 Views expressed orally by the experts at the Committee meeting can inform the debate in a variety of ways, including the following:
- Identifying important variations in clinical practice in both the management of the condition and specifically in the current use of the technology. This might include:
 - geographical variations
 - identification of subgroups
 - constraints on local implementation
 - specific issues for implementation that affect patients and carers directly.
 - Identifying the requirements for support to implement any guidance on the technology. This might include:
 - requirements for extra staff or equipment in NHS units
 - education and training requirements for NHS staff and for the patients on how to use the technology
 - special requirements within the community for patients and carers (for example, travel to hospital for treatment)

- ways in which adherence to treatment can be improved.
- Giving personal perspectives on the use of the technology and the difficulties encountered, including the important benefits to patients and the range and significance of adverse effects.
- Providing views on assessing response to treatment and the circumstances in which treatment might be discontinued.
- Identifying subgroups of patients for whom the benefits and risks of treatment might differ.
- Responding to queries that arise from:
 - the lead team (which comprises 3 Committee members who make a presentation to introduce the appraisal topic)
 - issues raised by the Chair and other Committee members
 - issues raised by the Evidence Review Group or the Assessment Group
 - issues raised by other experts
 - issues raised by a response given by the manufacturer or sponsor to a question posed.

5 The reference case

This section details methods for assembling and synthesising evidence on the technology being appraised in order to estimate its clinical and cost effectiveness. The estimates of clinical and cost effectiveness are individual yet interdependent key inputs into the decision-making of the Appraisal Committee. The Institute seeks to promote high-quality analysis and to encourage consistency in analytical approaches, but also acknowledges the need to report studies in other ways to reflect particular circumstances.

5.1 *Framework for estimating clinical and cost effectiveness*

Directions on particular aspects of NICE health technology assessment and economic evaluation are presented below. The position statement of the Institute is set out (in bold), followed by explanation and justification.

The concept of the reference case

5.1.1 The Institute has to make decisions across different technologies and disease areas. It is, therefore, crucial that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To allow this, the Institute has defined a 'reference case' that specifies the methods considered by the Institute to be appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. Submissions to the Institute should include an analysis of results generated using these reference case methods. This does not preclude additional analyses being presented when 1 or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case.

5.1.2 There is considerable debate about the most appropriate methods to use for some aspects of health technology assessment. This uncertainty relates to choices that are essentially value judgements; for example, whose preferences to use (patients or the general public) for valuation of health outcomes. It also includes methodological choices that relate to more technical aspects of an analysis; for example, the most appropriate approach to measuring health-related quality of life. Although the reference case specifies the methods preferred by the Institute, it does not preclude the Appraisal Committee's

consideration of non-reference-case analyses if appropriate. The key elements of analysis using the reference case are summarised in table 5.1.

Table 5.1 Summary of the reference case

Element of health technology assessment	Reference case	Section providing details
Defining the decision problem	The scope developed by NICE	5.1.4 to 5.1.6
Comparator(s)	As listed in the scope developed by NICE	2.2.4 to 2.2.6, 5.1.6, 5.1.14
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	5.1.7, 5.1.8
Perspective on costs	NHS and PSS	5.1.9 and 5.1.10
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	5.1.11 to 5.1.14
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	5.1.15 to 5.1.17
Synthesis of evidence on health effects	Based on systematic review	5.2
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	5.3.1
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	5.3.3

Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	5.3.4
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.4.1
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	5.5.1
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	5.6.1
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; <u>EQ-5D</u> , standardised instrument for use as a measure of health outcome.		

5.1.3 There may be reasons for applying non-reference-case methods. In these cases, the reasons for not applying reference-case methods should be clearly specified and justified, and the likely implications should be quantified. The Appraisal Committee will then make a judgement regarding the weight it attaches to the results of such a non-reference-case analysis.

Defining the decision problem

5.1.4 Estimating clinical and cost effectiveness should begin with a clear statement of the decision problem that defines the technologies being compared and the relevant patient group(s). The decision problem should be consistent with the Institute's scope for the appraisal; any differences must be justified.

5.1.5 The main technology of interest, its expected place in the pathway of care, the comparator(s) and the relevant patient group(s) will be defined in the scope developed by the Institute (see section 2).

5.1.6 When selecting comparators for assessment, give particular consideration to the scope (see section 2), and to the evidence to allow a robust assessment of relative clinical and cost effectiveness.

Perspective

- 5.1.7 For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services.
- 5.1.8 The reference-case perspective on outcomes aims to maximise health gain from available healthcare resources. Some features of healthcare delivery often referred to as 'process characteristics' may ultimately have health consequences, for example, mode of treatment delivery through its impact on adherence. If characteristics of healthcare technologies have a value to people independent of any direct effect on health, the nature of these characteristics should be clearly explained and if possible the value of the additional benefit should be quantified. These characteristics may include convenience and the level of information available for patients.
- 5.1.9 The Institute does not set the budget for the NHS. The appropriate objective of the Institute's technology appraisal programme is to offer guidance that represents an efficient use of available NHS and personal social services resources. For these reasons, the reference-case perspective on costs is that of the NHS and personal social services.
- 5.1.10 Some health technologies may have substantial benefits to other government bodies (for example, treatments to reduce drug misuse may have the effect of reducing crime). These issues should be identified during the scoping stage of an appraisal. Appraisals that consider benefits to the government incurred outside of the NHS and personal social services will be agreed with the Department of Health (and other relevant government bodies as appropriate) and detailed in the remit from the Department of Health and the final scope. For these non-reference-case analyses the benefits and costs (or cost savings) should be presented separately from the reference-case analysis. Productivity costs are not included in either the reference-case or non-reference-case analyses.

Type of economic evaluation

- 5.1.11 For the reference case, cost-effectiveness (specifically cost-utility) analysis is the preferred form of economic evaluation. This seeks to establish whether differences in expected costs between options can be justified in terms of

changes in expected health effects. Health effects should be expressed in terms of QALYs.

- 5.1.12 The focus on cost-effectiveness analysis is justified by the Institute's focus on maximising health gains from a fixed NHS and personal social services budget and the more extensive use and publication of these methods compared with cost-benefit analysis. Currently, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects. If the assumptions that underlie the QALY (for example, constant proportional trade-off and additive independence between health states) are inappropriate in a particular case, then evidence to this effect should be produced and analyses using alternative measures may be presented as an additional non-reference-case analysis.
- 5.1.13 Standard decision rules should be followed when combining costs and QALYs. When appropriate, these should reflect when dominance or extended dominance exists, presented through incremental cost-utility analysis. Incremental cost-effectiveness ratios (ICERs) reported must be the ratio of expected additional total cost to expected additional QALYs compared with alternative treatment(s). In addition to ICERs, expected net monetary or health benefits can be presented using values placed on a QALY gained of £20,000 and £30,000.
- 5.1.14 In exceptional circumstances, if the comparators form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs gained for the class as a whole can be presented.

Time horizon

- 5.1.15 The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.
- 5.1.16 Many technologies have impacts on costs and outcomes over a patient's lifetime. In such instances, a lifetime time horizon for clinical and cost effectiveness is usually appropriate. A lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. For a lifetime time horizon, it is often

necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable (see [section 5.7](#) on modelling). These should include assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions. Analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs.

- 5.1.17 A time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between [treatment options](#), and the differences in costs and health-related quality of life relate to a relatively short period (for example, in the case of an acute infection which has no long term sequelae).

5.2 *Synthesis of evidence on health effects*

- 5.2.1 The objective of the analysis of clinical effectiveness is an unbiased estimate of the mean clinical effectiveness of the technologies being compared. The analysis of clinical effectiveness must be based on data from all relevant studies of the best available quality and should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes, comparison with relevant comparators, and measures of both relative and absolute effectiveness with appropriate measures of uncertainty. The Institute has a preference for RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available.

Systematic review

- 5.2.2 All health effects should be identified and quantified, with all data sources clearly described. In the reference case, evidence on outcomes should be obtained from a systematic review, defined as systematically locating, including, appraising and synthesising the evidence to obtain a reliable and valid overview of the data related to a clearly formulated question^[1].

Relevant studies

- 5.2.3 RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

Study selection and data extraction

- 5.2.4 A systematic review of relevant studies of the technology being appraised should be conducted according to a previously prepared protocol to minimise the potential for bias, and should include studies investigating relevant comparators.
- 5.2.5 Once the search strategy has been developed and literature searching undertaken, a list of possible studies should be compiled. Each study must be assessed to determine whether it meets the inclusion criteria of the review. A log of ineligible studies should be maintained with the rationale for why studies were included or excluded. Having more than 1 reviewer assess all records retrieved by the search strategy increases the validity of the decision. The procedure for resolving disagreements between reviewers should be reported.

Critical appraisal

- 5.2.6 The quality of a study's overall design, its execution, and the validity of its results determines its relevance to the decision problem. Each study meeting the criteria for inclusion should be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies.

Treatment effect modifiers

- 5.2.7 Many factors can affect the overall estimate of relative treatment effects obtained from a systematic review. Some differences between studies occur by chance, others from differences in the characteristics of patients (such as age, sex, severity of disease, choice and measurement of outcomes), care setting,

additional routine care and the year of the study. Such potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline.

Pairwise meta-analysis

- 5.2.8 Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data using measures of outcome that are comparable.
- 5.2.9 The characteristics and possible limitations of the data (that is, population, intervention, setting, sample size and validity of the evidence) should be fully reported for each study included in the analysis and a forest plot included.
- 5.2.10 Statistical pooling of study results should be accompanied by an assessment of heterogeneity (that is, any variability in addition to that accounted for by chance) which can, to some extent, be taken into account using a random (as opposed to fixed) effects model. However, the degree of, and the reasons for, heterogeneity should be explored as fully as possible. Known clinical heterogeneity (for example, because of patient characteristics) may be explored by using subgroup analyses and meta-regression. When there is doubt about the relevance of a particular trial, a sensitivity analysis should exclude that study. If the risk of an event differs substantially between the control groups of the studies in a meta-analysis, an assessment of whether the measure of relative treatment effect is constant over different baseline risks should be carried out. This is especially important when the measure of relative treatment effect is to be used in an economic model and the baseline rate of events in the comparator arm of the model is very different to the corresponding rates in the studies in the meta-analysis.
- 5.2.11 A group of related technologies might have similar but not necessarily identical effects, whether or not recognised as a 'class'. When the Institute is appraising a number of related technologies within a single appraisal, meta-analyses based on individual effects should be carried out. A class effect can be analysed as a sensitivity analysis, unless specified otherwise in the scope for the appraisal.

Indirect comparisons and network meta-analyses

- 5.2.12 Data from head-to-head RCTs should be presented in the reference-case analysis. When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate. The network meta-analysis must be fully described and presented as additional to the reference-case analysis. The Appraisal Committee will take into account the additional uncertainty associated with the lack of direct evidence when considering estimates of relative effectiveness derived from indirect sources only. The principles of good practice for standard pairwise meta-analyses should also be followed in adjusted indirect treatment comparisons and network meta-analyses.
- 5.2.13 The term 'network meta-analysis' includes adjusted indirect comparisons, but also refers to more complex evidence analysis such as 'mixed treatment comparisons'. An 'adjusted indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared directly with each other in head-to-head trials, but have been compared indirectly using a common comparator. Mixed treatment comparisons include both head-to-head trials of treatments of interest (both interventions and comparators) and trials that include 1 of the treatments of interest.
- 5.2.14 Ideally, the network meta-analysis should contain all treatments that have been identified either as an intervention or as appropriate comparators in the scope. Therefore, trials that compare at least 2 of the relevant (intervention or comparator) treatments should be incorporated, even if the trial includes comparators that are not relevant to the decision problem. The principles of good practice for conducting systematic reviews and meta-analyses should be carefully followed when conducting mixed and indirect treatment comparisons. In brief, a clear description of the methods of synthesis and the rationale for how RCTs are identified, selected and excluded is needed. The methods and results of the individual trials included in the network meta-analysis and a table of baseline characteristics for each trial must be documented. If there is doubt about the relevance of a particular trial or set of trials, sensitivity analysis should be presented in which these trials are excluded (or if absent from the base-case analysis, included).

- 5.2.15 The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported. If inconsistency within a network meta-analysis is found, then attempts should be made to explain and resolve these inconsistencies.
- 5.2.16 In all cases when evidence is combined using adjusted indirect comparisons or network meta-analysis frameworks, trial randomisation must be preserved, that is, it is not acceptable to compare results from single treatment arms from different randomised trials. If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty.
- 5.2.17 Evidence from a network meta-analysis must be presented in both tabular form and in graphical formats such as forest plots. The direct and indirect components of the network meta-analysis should be clearly identified and the number of trials in each comparison stated. Results from pairwise meta-analyses using the direct comparisons should be presented alongside those based on the full network meta-analysis.
- 5.2.18 When sufficient relevant and valid data are not available for including in pairwise or network meta-analyses, the analysis may have to be restricted to a narrative overview that critically appraises individual studies and presents their results. In these circumstances, the Appraisal Committee will be particularly cautious when reviewing the results and in drawing conclusions about the relative clinical effectiveness of the treatment options.

5.3 *Measuring and valuing health effects*

- 5.3.1 For the cost-effectiveness analyses health effects should be expressed in QALYs. For the reference case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults.
- 5.3.2 A QALY combines both quality of life and life expectancy into a single index. In calculating QALYs, each of the health states experienced within the time horizon of the model is given a utility reflecting the health-related quality of life associated with that health state. The duration of time spent in each health state is multiplied by the utility. Deriving the utility for a particular health state

usually comprises 2 elements: measuring health-related quality of life in people who are in the relevant health state and valuing it according to preferences for that health state relative to other states (usually perfect health and death).

- 5.3.3 Health-related quality of life, or changes in health-related quality of life, should be measured directly by patients. When it is not possible to obtain measurements of health-related quality of life directly from patients, data should be obtained from the person who acts as their carer in preference to healthcare professionals.
- 5.3.4 The valuation of health-related quality of life measured in patients (or by their carers) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. This valuation leads to the calculation of utility values.
- 5.3.5 Different methods used to measure health-related quality of life produce different utility values; therefore, results from different methods or instruments cannot always be compared. Given the need for consistency across appraisals, one measurement method, the EQ-5D, is preferred for the measurement of health-related quality of life in adults.
- 5.3.6 The EQ-5D is a standardised and validated generic instrument that is widely used and has been validated in many patient populations. The EQ-5D comprises 5 dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. For each of these dimensions it has 3 levels of severity (no problems, some problems, severe problems). The system has been designed so that people can describe their own health-related quality of life using a standardised descriptive system. A set of preference values elicited from a large UK population study using a choice-based method of valuation (the time trade-off method) is available for the EQ-5D health state descriptions. This set of values should be applied to measurements of health-related quality of life to generate health-related utility values.
- 5.3.7 In some circumstances adjustments to utility values, for example for age or comorbidities, may be needed.

- 5.3.8 If not available in the relevant clinical trials, EQ-5D data can be sourced from the literature. When obtained from the literature, the methods of identification of the data should be systematic and transparent. The justification for choosing a particular data set should be clearly explained. When more than 1 plausible set of EQ-5D data is available, sensitivity analyses should be carried out to show the impact of the alternative utility values.
- 5.3.9 When EQ-5D data are not available, these data can be estimated by mapping other health-related quality of life measures or health-related benefits observed in the relevant clinical trial(s) to EQ-5D. The mapping function chosen should be based on data sets containing both health-related quality of life measures and its statistical properties should be fully described, its choice justified, and it should be adequately demonstrated how well the function fits the data. Sensitivity analyses to explore variation in the use of the mapping algorithms on the outputs should be presented.
- 5.3.10 In some circumstances the EQ-5D may not be the most appropriate. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence on the lack of content validity for the EQ-5D should be provided, demonstrating that key dimensions of health are missing. This should be supported by evidence that shows that EQ-5D performs poorly on tests of construct validity and responsiveness in a particular patient population. This evidence should be derived from a synthesis of peer-reviewed literature. In these circumstances alternative health-related quality of life measures may be used and must be accompanied by a carefully detailed account of the methods used to generate the data, their validity, and how these methods affect the utility values.
- 5.3.11 When necessary, consideration should be given to alternative standardised and validated preference-based measures of health-related quality of life that have been designed specifically for use in children. The standard version of the EQ-5D has not been designed for use in children. An alternative version for children aged 7–12 years is available, but a validated UK valuation set is not yet available.
- 5.3.12 A new version of the EQ-5D, the EQ-5D-5L, has been developed in which there are 5 levels of severity (no problem, slight problems, moderate problems, severe problems and unable to or extreme problems) for each of the 5 dimensions of health (see section 5.3.6). The EQ-5D-5L may be used for reference-case

analyses. The descriptive system for the EQ-5D-5L has been validated, but no valuation set to derive utilities currently exists. Until an acceptable valuation set for the EQ-5D-5L is available, the validated mapping function to derive utility values for the EQ-5D-5L from the existing EQ-5D (-3L) may be used (available from www.euroqol.org).

In August 2017, NICE issued a [position statement](#) on the use of the EQ-5D-5L valuation set. Companies and academic groups should refer to this statement.

5.4 *Equity considerations in cost-effectiveness analysis*

- 5.4.1 In the reference case, an additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit.
- 5.4.2 The estimation of QALYs, as defined in the reference case, implies a particular position regarding the comparison of health gained between individuals. Therefore, in the reference case, an additional QALY is of equal value regardless of other characteristics of the individuals, such as their socio-demographic characteristics, their age, or their level of health. The Committee has discretion to consider a different [equity](#) position, and may do so in certain circumstances and when instructed by the NICE Board (see [section 6](#)).

5.5 *Evidence on resource use and costs*

NHS and personal and social services costs

- 5.5.1 For the reference case, costs should relate to resources that are under the control of the NHS and personal and social services. These resources should be valued using the prices relevant to the NHS and personal and social services. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.
- 5.5.2 The public list prices for technologies (for example, pharmaceuticals or medical devices) should be used in the reference-case analysis. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case

analysis to best reflect the price relevant to the NHS. The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing Information Tool ([eMIT](#)); focusing on medicines in the National Generics Programme Framework for England. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed. When a reduced price is available through a patient access scheme that has been agreed with the Department of Health, the base-case analysis should include the costs associated with the scheme. The review date for the appraisal will be informed by the period of time over which the manufacturer or sponsor can guarantee any such pricing agreements.

- 5.5.3 For medicines that are predominantly prescribed in primary care, prices should be based on the Drug Tariff.
- 5.5.4 In the absence of a published list price and price agreed by a national institution (as may be the case for some devices), the price submitted by the manufacturer may be used, provided that it is nationally and publicly available.
- 5.5.5 Healthcare resource groups (HRGs) are a valuable source of information for estimating resource use. HRGs are standard groupings of clinically similar treatments that use common levels of healthcare resources. The national average unit cost of an HRG is reported as part of the annual mandatory collection of reference costs from all NHS organisations in England. The use of these costs can reduce the need for local micro-costing (costing of each individual component of care related to the use of a technology). Care must be taken to ensure that all relevant HRGs have been taken into account. For example, the cost of hospital admission for a serious condition may not account for time spent in critical care, which is captured and costed as a separate HRG.
- 5.5.6 Data based on HRGs may not be appropriate in all circumstances (for example, when the new technology and the comparator both fall under the same HRG, or when the mean cost does not reflect resource use in relation to the new technology under appraisal). In such cases, other sources of evidence, such as micro-costing studies, may be more appropriate. When cost data are taken from literature, the methods used to identify the sources should be defined. When several alternative sources are available, a justification for the costs chosen

should be provided and discrepancies between the sources explained. When appropriate, sensitivity analysis should be used to assess the implications for results of using alternative data sources.

- 5.5.7 Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis. Costs that are considered to be unrelated to the condition or technology of interest should be excluded.
- 5.5.8 If introduction of the technology requires changes in infrastructure, costs or savings should be included in the analysis.
- 5.5.9 When a group of related technologies is being appraised as part of a 'class' of treatments, an analysis using the individual unit costs specific to each technology should normally be presented in the reference case. Exceptionally, if there is a very wide range of technologies and costs to be considered, then analyses using the weighted mean cost and the highest and lowest cost estimates should be presented.
- 5.5.10 Value added tax (VAT) should be excluded from all economic evaluations, but included in calculation of the budgetary impact when the resources in question are liable for this tax.

Non-NHS and non-personal and social services costs

- 5.5.11 Some technologies may have a substantial impact on the costs (or cost savings) to government bodies other than the NHS. Exceptionally, these costs may be included if specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS and personal social services costs, and not included in the ICER.
- 5.5.12 Costs borne by patients may be included when they are reimbursed by the NHS or personal social services. When the rate of reimbursement varies between patients or geographical regions, such costs should be averaged across all patients. Where there are costs borne by patients that are not reimbursed by

the NHS and personal social services, these may be presented separately. Productivity costs should be excluded.

- 5.5.13 When care by family members, friends or a partner might otherwise have been provided by the NHS or personal social services it may be appropriate to consider the cost of the time of providing this care, even when adopting a NHS or personal social services perspective. All analyses including the time spent by family members of providing care should be presented separately. A range of valuation methods exists to cost this type of care. Methods chosen should be clearly described and sensitivity analyses using other methods should be presented. Personal social service savings should also be incorporated.

5.6 *Discounting*

- 5.6.1 Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. For the reference case, the same annual discount rate should be used for both costs and benefits (currently 3.5%).
- 5.6.2 The specific discount rate varies across jurisdictions and over time. The Institute considers that it is usually appropriate to discount costs and health effects at the same annual rate of 3.5%, based on the recommendations of the UK Treasury for the [discounting](#) of costs.
- 5.6.3 Sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis (see section 6.2.19).

5.7 *Modelling methods*

- 5.7.1 Full documentation and justification of structural assumptions and data inputs should be provided. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be undertaken.
- 5.7.2 Modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness in a format relevant to the Appraisal Committee's decision-making process. Models are required for

most technology appraisals. Situations when modelling is likely to be required include those when:

- all the relevant evidence is not contained in a single trial
- patients participating in trials do not represent the typical patients likely to use the technology within the NHS
- intermediate outcome measures are used rather than effect on health-related quality of life and survival
- relevant comparators have not been used or trials do not include evidence on relevant populations
- clinical trial design includes crossover (treatment switching) that would not occur in clinical practice
- costs and benefits of the technologies extend beyond the trial follow-up period.

5.7.3 Providing an all-embracing definition of what constitutes a high-quality model is not possible. In general, estimates of treatment effect should be based on the results of the systematic review, structural assumptions should be fully justified and data inputs should be clearly documented and justified in the context of a valid review of the alternatives.

5.7.4 The methods of quality assurance used in the development of the model should be detailed and the methods and results of model validation should be provided. In addition, the results from the analysis should be presented in a disaggregated format and should include a tabular presentation of information on estimates of life-years gained, mortality rates (at separate time points if appropriate) and the frequency of selected clinical events predicted by the model.

5.7.5 Clinical end points that reflect how a patient feels, functions, or how long a patient survives are regarded as more informative than surrogate end points (such as laboratory tests and imaging findings). When the use of 'final' clinical end points is not possible and 'surrogate' data on other outcomes are used to infer the effect of treatment on mortality and health-related quality of life, evidence in support of the surrogate-to-final end point outcome relationship must be provided together with an explanation of how the relationship is quantified for use in modelling. The usefulness of the surrogate end point for

estimating QALYs will be greatest when there is strong evidence that it predicts health-related quality of life and/or survival. In all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified.

- 5.7.6 Clinical trial data generated to estimate treatment effects may not sufficiently quantify the risk of some health outcomes or events for the population of interest or may not provide estimates over a sufficient duration for the economic analysis. The methods used to identify and critically appraise sources of data for economic models should be stated and the choice of particular data sets should be justified with reference to their suitability to the population of interest in the appraisal.
- 5.7.7 Modelling is usually required to extrapolate costs and health benefits over an extended time horizon. Assumptions used to extrapolate the impact of treatment over the relevant time horizon should have both external and internal validity and be reported transparently. The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials. Internal validity should be explored and when statistical measures are used to assess the internal validity of alternative models of extrapolation based on their relative fit to the observed trial data, the limitations of these statistical measures should be documented. Alternative scenarios should also be routinely considered to compare the implications of different methods for extrapolation of the results. For example, for duration of treatment effects, scenarios might include when the treatment benefit in the extrapolated phase is: (i) nil; (ii) the same as during the treatment phase and continues at the same level; or (iii) diminishes in the long term.
- 5.7.8 In RCTs, participants randomised to the control group are sometimes allowed to switch treatment group and receive the active intervention. In these circumstances, when intention-to-treat analysis is considered inappropriate, statistical methods that adjust for treatment switching can also be presented. Simple adjustment methods such as censoring or excluding data from patients who crossover should be avoided because they are very susceptible to selection bias. The relative merits and limitations of the methods chosen to explore the impact of switching treatments should be explored and justified with respect to

the method chosen and in relation to the specific characteristics of the data set in question. These characteristics include the mechanism of crossover used in the trial, the availability of data on baseline and time-dependent characteristics, and expectations around the treatment effect if the patients had remained on the treatment to which they were allocated.

5.8 *Exploring uncertainty*

- 5.8.1 It is important for the model to quantify the decision uncertainty associated with a technology (that is, the probability that a different decision would be reached if the true cost effectiveness of each technology could be ascertained before making the decision).
- 5.8.2 Models are subject to uncertainty around the structural assumptions used in the analysis. Examples of structural uncertainty may include how different states of health are categorised and how different pathways of care are represented. These structural assumptions should be clearly documented and the evidence and rationale to support them provided. The impact of structural uncertainty on estimates of cost effectiveness should be explored by separate analyses of a representative range of plausible scenarios.
- 5.8.3 Examples of when this type of scenario analysis should be conducted are:
- when there is uncertainty about the most appropriate assumption to use for extrapolation of costs and outcomes beyond trial follow-up
 - when there is uncertainty about how the pathway of care is most appropriately represented in the analysis
 - when there may be economies of scale (for example, in appraisals of diagnostic technologies).
- 5.8.4 Uncertainty about the appropriateness of the methods used in the reference case can also be dealt with using sensitivity analysis, but these analyses must be presented separately.
- 5.8.5 A second type of uncertainty arises from the choice of data sources to provide values for the key parameters, such as different costs and utilities, estimates of relative effectiveness and their duration. The implications of different estimates

of key parameters must be reflected in sensitivity analyses (for example, through the inclusion of alternative data sets). Inputs must be fully justified and uncertainty explored by sensitivity analysis using alternative input values.

5.8.6 The choice of data sources to include in an analysis may not be clear-cut. In such cases, the analysis should be re-run, using the alternative data source or excluding the study about which there is doubt, and the results reported separately. Examples of when this type of sensitivity analysis should be conducted are:

- when alternative sets of plausible data on the health-related utility associated with the disease or intervention are available
- when there is variability between hospitals in the cost of a particular resource or service, or the acquisition price of a particular technology
- when there are doubts about the quality or relevance of a particular study in a meta-analysis or network meta-analysis.

5.8.7 A third source of uncertainty arises from parameter precision, once the most appropriate sources of information have been identified (that is, the uncertainty around the mean health and cost inputs in the model). Distributions should be assigned to characterise the uncertainty associated with the (precision of) mean parameter values. Probabilistic sensitivity analysis is preferred. This enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions chosen for probabilistic sensitivity analysis should not be arbitrarily chosen, but chosen to represent the available evidence on the parameter of interest, and their use should be justified. Formal elicitation methods are available if there is a lack of data to inform the mean value and associated distribution of a parameter. If there are alternative plausible distributions that could be used to represent uncertainty in parameter values, this should be explored by separate probabilistic analyses of these scenarios.

- 5.8.8 Evidence about the extent of correlation between individual parameters should be carefully considered and reflected in the probabilistic analysis. Assumptions made about the correlations should be clearly presented.
- 5.8.9 The computational methods used to implement an appropriate model structure may occasionally present challenges in conducting probabilistic sensitivity analysis. The use of model structures that limit the feasibility of probabilistic sensitivity analysis should be clearly specified and justified. Models should always be fit for purpose, and should enable a thorough consideration of the decision uncertainty associated with the model structure and input parameters. The choice of a 'preferred' model structure or programming platform should not result in the failure to adequately characterise uncertainty.
- 5.8.10 Appropriate ways of presenting uncertainty in cost-effectiveness data parameter uncertainty include confidence ellipses and scatter plots on the cost-effectiveness plane (when the comparison is restricted to 2 alternatives) and cost-effectiveness acceptability curves. The presentation of cost-effectiveness acceptability curves should include a representation and explanation of the cost-effectiveness acceptability frontier. Uncertainty should also be presented in tabular form. In addition to details of the expected mean results (costs, outcomes and ICERs), the probability that the treatment is cost effective at maximum acceptable ICERs of £20,000–£30,000 per QALY gained and the error probability (that the treatment is not cost effective) should also be presented, particularly when there are more than 2 alternatives.
- 5.8.11 The use of univariate and best- or worst-case sensitivity analysis is an important way of identifying parameters that may have a substantial impact on the cost-effectiveness results and of explaining the key drivers of the model. However, such analyses become increasingly unhelpful in representing the combined effects of multiple sources of uncertainty as the number of parameters increase. The use of probabilistic sensitivity analysis can allow a more comprehensive characterisation of the parameter uncertainty associated with all input parameters.

5.9 *Companion diagnostics*

- 5.9.1 The use of a technology may be conditional on the presence or absence of a particular biomarker (for example a gene or a protein). If a diagnostic test to

establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness. A sensitivity analysis should be provided without the cost of the diagnostic test. When appropriate, the diagnostic accuracy of the test for the particular biomarker of treatment efficacy should be examined and, when appropriate, incorporated in the economic evaluation.

5.9.2 The appraisal will take account of any requirements of the marketing authorisation, including tests to be completed and the definition of a positive test. In clinical practice in the NHS, it may be possible that an alternative diagnostic test procedure to that used in the clinical trials of the technology is used. When appropriate, the possibility that using an alternative test (which may differ in diagnostic accuracy from that used in the clinical trials) may affect selection of the patient population for treatment and the cost effectiveness of the treatment will be highlighted in the appraisal guidance.

5.9.3 It is expected that assessments of multiple companion diagnostic test options will generally be undertaken in the NICE diagnostics assessment programme. For further information see the [NICE diagnostics assessment programme manual](#).

5.10 *Analysis of data for patient subgroups*

5.10.1 For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing estimates of clinical and cost effectiveness separately for each relevant subgroup of patients. The characteristics of patients in the subgroup should be clearly defined and should preferably be identified on the basis of an expectation of differential clinical or cost effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors. When possible, potentially relevant subgroups will be identified at the scoping stage with consideration being given to the rationale for expecting a subgroup effect. However, this does not preclude the identification of subgroups later in the process; in particular, during the deliberations of the Appraisal Committee.

- 5.10.2 Given the Institute's focus on maximising health gain from limited resources, it is important to consider how clinical and cost effectiveness may differ because of differing characteristics of patient populations. Typically, the capacity to benefit from treatment will differ between patients, and this may also impact on the subsequent cost of care. There should be a clear justification and, if appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Post hoc data 'dredging' in search of subgroup effects is to be avoided and will be viewed sceptically.
- 5.10.3 The estimate of the overall net treatment effect of an intervention is determined by the baseline risk of a particular condition or event and/or the relative effects of the technology compared with the relevant comparator treatment. The overall net treatment effect may also be determined by other features of the people comprising the population of interest. It is therefore likely that relevant subgroups may be identified in terms of differences in 1 or more contributors to absolute treatment effects.
- 5.10.4 For subgroups based on differences in baseline risk of specific health outcomes, systematic identification of data to quantify this is required. It is important that the methods for identifying appropriate baseline data for the purpose of subgroup analysis are provided in sufficient detail to enable replication and critical appraisal.
- 5.10.5 Care should be taken to specify how subgroup analyses are undertaken, including the choice of scale on which any effect modification is defined. The statistical precision of all subgroup estimates should be reflected in the analysis of parameter uncertainty. The characteristics of the patients associated with the subgroups presented should be clearly specified to allow the Appraisal Committee to judge the appropriateness of the analysis with regard to the decision problem.
- 5.10.6 The standard subgroup analyses performed in RCTs or systematic reviews seek to determine whether there are differences in relative treatment effects between subgroups (through the analysis of interactions between the effectiveness of the technology and patient characteristics). The possibility of differences emerging by chance, particularly when multiple subgroups are reported, is high and should be taken into account. Pre-specification of a particular subgroup in the study or review protocol, with a clear rationale for

anticipating a difference in efficacy and a prediction of the direction of the effect, will increase the credibility of a subgroup analysis.

- 5.10.7 In considering subgroup analyses, the Appraisal Committee will take specific note of the biological or clinical plausibility of a subgroup effect in addition to the strength of the evidence in favour of such an effect (for example, if it has a clear, pre-specified rationale and is consistent across studies). The evidence supporting biological or clinical plausibility for a subgroup effect should be fully documented, including details of statistical analysis.
- 5.10.8 Individual patient data are preferred, if available, for the estimation of subgroup-specific parameters. However, as for all evidence, the appropriateness of such data will always be assessed by considering factors such as the quality of the analysis, how representative the available evidence is to clinical practice and how relevant it is to the decision problem.
- 5.10.9 Consideration of subgroups based on differential cost may be appropriate in some circumstances; for example, if the cost of managing a particular complication of treatment is known to be different in a specific subgroup.
- 5.10.10 When considering subgroups, the Appraisal Committee pays particular attention to its legal obligations on equality and human rights.
- 5.10.11 Types of subgroups that are not considered relevant are those based solely on the following factors:
- subgroups based solely on differential treatment costs for individuals according to their social characteristics
 - subgroups specified in relation to the costs of providing treatment in different geographical locations in the UK (for example, when the costs of facilities available for providing the technology vary according to location).
- 5.10.12 Analysis of 'treatment continuation rules', whereby cost effectiveness is maximised based on continuing treatment only in those who achieve a specified 'response' within a given time, should not be analysed as a separate subgroup. Rather, the strategy involving the 'continuation rule' should be analysed as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. This enables the costs

and health consequences of factors such as any additional monitoring associated with the continuation rule to be incorporated into the economic analysis. Additional considerations for continuation rules include:

- the robustness and plausibility of the end point on which the rule is based
- whether the 'response' criteria defined in the rule can be reasonably achieved
- the appropriateness and robustness of the time at which response is measured
- whether the rule can be incorporated into routine clinical practice
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective
- considerations of fairness with regard to withdrawal of treatment from people whose condition does not respond to treatment.

5.11 *Presentation of data and results*

Presenting data

5.11.1 All parameters used to estimate clinical and cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous , mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed. For probabilistic analyses, the distributions used to characterise the uncertainty in input parameters should be documented and justified. As much detail as possible on the data used in the analysis should be provided.[variables](#)

Presenting expected cost-effectiveness results

5.11.2 The expected value of each component of cost and expected total costs should be presented; expected QALYs for each option compared in the analysis should also be detailed in terms of their main contributing components. ICERs should be calculated as appropriate.

5.11.3 The main individual components comprising both costs and QALYs for the intervention and control treatment pathways should be tabulated. For QALYs this includes presenting the life-year component separately. The costs and

QALYs associated with different stages of the disease should also be presented separately.

5.12 *Impact on the NHS*

Implementation of NICE guidance

- 5.12.1 Information on the net impact of the implementation of the health technology on the NHS (and personal and social services, when appropriate) is required.
- 5.12.2 As outlined in more detail below, when possible, the information on NHS impact should include details on key epidemiological and clinical assumptions, resource units and costs with reference to a general England and Wales population, and patient or service base (for example, per 100,000 population, per average primary care trust or per ward).

Implementation or uptake and population health impact

- 5.12.3 Evidence-based estimates of the current baseline treatment rates and expected appropriate implementation or uptake or treatment rates of the appraised and comparator technologies in the NHS should be supplied. In addition, an estimate of the resulting health impact (for example, QALYs or life-years gained) in a given population should ideally be attempted. These should take account of the condition's epidemiology and the appropriate levels of access to diagnosis and treatment in the NHS. It should also highlight any key assumptions or uncertainties.

Resource impact

- 5.12.4 Implementation of a new health technology will have direct implications for the provision of units of the appraised and comparator technologies (for example, doses of drugs or theatre hours) by the NHS. In addition, the technology may have a knock-on impact (increase or decrease) on other NHS and personal and social services resources, including alternative or avoided treatment and resources required to support the use of the new technology. These might include:

- staff numbers and hours

- training and education
- support services (for example, laboratory tests)
- service capacity or facilities (for example, hospital beds, clinic sessions, diagnostic services and residential home places).

5.12.5 Any likely constraints on the resources required to support the implementation of the appraised technology should be highlighted, and comment should be made on the impact this may have on the implementation timescale.

Costs

5.12.6 Estimates of net NHS (and personal and social services, when appropriate) costs of the expected resource impact should be provided to allow effective national and local financial planning. The costs should be disaggregated by appropriate generic organisational (for example, NHS, personal and social services, hospital or primary care) and budgetary categories (for example, drugs, staffing, consumables or capital). When possible, this should be to the same level and detail as that adopted in resource unit information. If savings are anticipated, the extent to which these finances can actually be realised should be specified. Supplied costs should also specify the inclusion or exclusion of VAT. The cost information should be based on published cost analyses or recognised publicly available databases or price lists.

5.12.7 If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored.

5.12.8 The Institute produces costing tools to allow individual NHS organisations and local health economies to quickly assess the impact guidance will have on local budgets. Details of how the costing tools are developed are available in the Institute's document, [Assessing cost impact: methods guide](#).

^[1] The independent academic groups follow general guidelines for conducting systematic reviews published by the Centre for Reviews and Dissemination at the University of York ([Systematic Reviews: CRD's guidance for undertaking reviews in health care](#)).

6 The appraisal of the evidence and structured decision-making

6.1 Introduction

6.1.1 The purpose of this section is to explain how the Appraisal Committee appraises the evidence and makes the judgements that lead to its final conclusions.

6.1.2 The Appraisal Committee is an independent advisory body. Members include people who work in the NHS, relevant academic disciplines, pharmaceutical and medical devices industries and lay members. The Appraisal Committee makes recommendations to the Institute regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the Appraisal Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The Institute is responsible for the dissemination of the final guidance to the NHS.

6.1.3 When formulating its recommendations to the Institute, the Appraisal Committee has discretion to consider those factors it believes are most appropriate to each appraisal. In doing so, the Appraisal Committee has regard to the provisions and regulations of the Health and Social Care Act 2012 relating to NICE, and NICE's legal obligations on equality and human rights. The Act expects NICE, in undertaking its general duties, to have regard to:

- The broad balance between the benefits and costs of providing health services or social care in England.
- The degree of need of people in England for health services or social care.
- The desirability of promoting innovation in providing health services or social care in England.

6.1.4 In reaching its decision, the Appraisal Committee bases its recommendations on the evidence presented, including statements from consultees and commentators and the views expressed by clinical specialists, commissioning experts and patient experts at the Committee meeting. Formulating the 'Considerations' section of the guidance represents an important component of the Appraisal Committee's work. This section identifies the key evidence taken into account by the Appraisal Committee and its views on this evidence. It highlights any areas of contention and uncertainty that have arisen during the

Appraisal Committee's discussions of the evidence and presents a general description of the Committee's views on the written and oral inputs that have informed their decision.

6.1.5 Usually, the Appraisal Committee's provisional recommendations are released in an appraisal consultation document for widespread consultation with consultees, commentators and the public. In reviewing responses to consultation, the Committee is principally interested in comments on its preliminary recommendations within the context of the evidence base reviewed at its first meeting and its consideration of that evidence. The comments received on the key issues identified at the first meeting are carefully reviewed.

6.1.6 The Appraisal Committee considers the impact of the consultation comments on:

- the preliminary recommendations on the use of the technology
- the other sections of the appraisal consultation document
- recommendations for further research
- issues for implementation, including:
 - resource availability to support implementation (for example, workforce planning and training, and new clinics)
 - the extent of any changes in current clinical practice
 - the implementation criteria agreed between the Institute and the Department of Health
- the timing of the appraisal review, because of the timing and potential impact of research in progress (for example, new RCTs).

6.1.7 The Appraisal Committee considers the comments and, if appropriate amends its recommendations, exercising judgement on the nature and importance of the comments from consultation. The content of the 'Considerations' section is modified to clarify the key evidence considered by the Appraisal Committee, its views on this evidence and any areas of contention that have arisen during the appraisal. This section also highlights, in general terms, the written and oral inputs that the Appraisal Committee has used to inform its judgement.

- 6.1.8 The Appraisal Committee takes into account advice from the Institute on the appropriate approach to making scientific and social value judgements. Advice on social value judgements is informed by the work of the [Citizens Council](#), NICE's advisory bodies, and NICE's Board, as well as legislation on human rights, discrimination and equality as reflected in NICE's equality scheme. Principles that describe the social value judgements that should, generally, be considered by the Appraisal Committee have been provided in the Institute's document, [Social value judgements: principles for the development of NICE guidance](#).
- 6.1.9 The credibility of the guidance produced by the Institute is dependent on the transparency of the Appraisal Committee's decision-making process. It is crucial that the Appraisal Committee's decisions are explained clearly with reference to all the available evidence, and that the contributions of clinical specialists, commissioning experts, patient experts and the views of people who responded to consultation during the appraisal are considered. The reasoning for the Committee's decision will be explained, with reference to the factors that have been taken into account, in the 'Considerations' section of the guidance.
- 6.1.10 The language and style used in the documents produced by the Committee are governed by the following principles:
- The need for clarity in explaining how the Appraisal Committee has come to its conclusions. Of particular importance is the 'Considerations' section of the guidance document, which summarises the key issues that have been debated and the rationale for the conclusions drawn. It also includes a table that documents how the Appraisal Committee has taken account of each of the main components of the decision.
 - The understanding that the text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This requires careful judgement so that enough information and justification is given in the appraisal consultation document or final appraisal determination to enable the reader to understand what evidence the Appraisal Committee considered and, if appropriate, who provided that evidence.
- 6.1.11 The Appraisal Committee is not empowered to alter the Direction from the Secretary of State for Health on the implementation of the Institute's guidance regarding the mandatory requirement placed upon health commissioners to make funds available for implementation of the Institute's appraisal guidance within 3 months of publication. However, the Appraisal Committee may

consider circumstances in which this implementation period should be varied and advise the Institute accordingly. When appropriate, the Committee's consideration is limited to those circumstances in which it is apparent that either the technology cannot be acquired and/or the NHS will not be in a position to use it within the 3-month period.

- 6.1.12 The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics. For technologies that are not subject to licensing procedures (for example, medical devices), evidence of acceptable quality of manufacturing processes, such as the CE mark, will be required and the technology will be evaluated in the context of the instructions for use. Exceptionally, the Department of Health may direct the Appraisal Committee to make recommendations about a technology outside of the terms of its marketing authorisation or instructions for use.
- 6.1.13 Evidence relating to use of the technology under appraisal outside the terms of its marketing authorisation may be considered during the assessment phase of the appraisal and may inform the Appraisal Committee's deliberations regarding the licensed use of the drug.
- 6.1.14 The Committee is not able to make recommendations on the pricing of technologies to the NHS but can consider a patient access scheme subject to the arrangements detailed in the technology appraisal process guide(s).

6.2 *Appraisal of the evidence*

Structured decision-making: comparators

- 6.2.1 The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the clinical and cost-effectiveness evidence.
- 6.2.2 When selecting the most appropriate comparator(s), the Committee will consider:
- established NHS practice in England
 - the natural history of the condition without suitable treatment

- existing NICE guidance
- cost effectiveness
- the licensing status of the comparator.

6.2.3 The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s). When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative.

6.2.4 The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. Long-standing treatments often lack a sponsor to support the licensing process. Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use.

Structured decision-making: clinical effectiveness and health-related factors

6.2.5 The Appraisal Committee has the discretion to take account of the full range of clinical studies that have been carried out and is not expected to restrict itself to considering only certain categories of evidence. This requires the Appraisal Committee to consider all of the evidence presented to it, including RCTs, observational studies and any qualitative evidence related to the experiences of patients, carers and clinical specialists who have used the technology being appraised or are familiar with the relevant condition. In evaluating the evidence base, the Appraisal Committee will exercise its judgement when deciding

whether particular forms of evidence are fit for purpose in answering specific questions.

6.2.6 The importance given to these various kinds of evidence depends on both the overall balance and quality of the evidence from different sources, and the suitability of a particular type of evidence to address issues under consideration. In general, greater importance is given to evidence derived from high-quality studies with methodology designed to minimise bias.

6.2.7 The Appraisal Committee's judgements on clinical effectiveness take account of the following factors:

- The nature and quality of the evidence derived from:
 - the analysis of the independent academic groups
 - the written submissions of the consultees
 - the views expressed by the clinical specialists, particularly their experience of the technology in clinical practice
 - the views of the patient experts and carers on the experiences of patients who have used the technology.
- Uncertainty generated by the evidence and differences between the evidence submitted for licensing and that relating to effectiveness in clinical practice.
- The possible differential benefits or adverse outcomes in different groups of patients.
- The impact of benefits and adverse outcomes associated with the technology as seen from the patient's perspective.
- The position of the technology in the overall pathway of care and the alternative treatments that are established in clinical practice.

6.2.8 The extent to which the above factors are taken into account in making judgements about the evidence of clinical effectiveness is a matter for the Committee's discretion.

6.2.9 In the reference case, the Committee will regard all QALYs as being of equal weight. However, when considering the overall health benefits, the Appraisal

Committee can accept analysis that explores a QALY weighting that is different from that of the reference case when a technology appraisal concerns a 'life-extending treatment at the end of life', or in other circumstances when instructed by the NICE board.

6.2.10 In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

6.2.11 When the conditions described in section 6.2.10 are met, the Appraisal Committee will consider:

- the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age and
- the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the normal range of maximum acceptable ICERs, with a maximum weight of 1.7.

6.2.12 Treatments recommended following the application of the 'end-of-life' criteria listed in section 6.2.10 will not necessarily be regarded or accepted as standard comparators for future appraisals of new treatments introduced for the same

condition. Second and subsequent extensions to the marketing authorisations for the same product will be considered on their individual merits.

Amendments have been made to sections 6.2.10–12 to support the joint NHS England and NICE proposals for the management of the Cancer Drugs Fund from April 2016.

Structured decision-making: cost effectiveness

- 6.2.13 The Institute is asked to take account of the overall resources available to the NHS when determining cost effectiveness. Therefore, decisions on the cost effectiveness of a new technology must include judgements on the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new technology.
- 6.2.14 The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the Committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases. Therefore, the Committee may require more robust evidence on the effectiveness and cost effectiveness of technologies that are expected to have a large impact on NHS resources.
- 6.2.15 The Appraisal Committee takes account of how the incremental cost effectiveness of the technology being appraised relates to other interventions or technologies currently or potentially applied in the NHS. In addition, as far as possible, the Committee will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals.
- 6.2.16 When the evidence on key parameters used to estimate cost effectiveness (for example, clinical effectiveness and effect on health-related quality of life) has serious limitations and/or when a variety of assumptions have been necessary in the [cost-effectiveness modelling](#), the additional uncertainty this generates is a key factor in underpinning the judgements of the Committee. The Appraisal Committee is likely to consider more favourably technologies for which evidence on cost effectiveness is underpinned by the best-quality clinical data than those for which supporting evidence is dependent to a large extent on

theoretical modelling alone. However, the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases.

6.2.17 The Committee's judgements on cost effectiveness are influenced by the following factors:

- The strength of the supporting clinical-effectiveness evidence.
- The robustness and appropriateness of the structure of the economic models. In particular, the Committee considers carefully whether the model reflects the decision problem at hand and the uncertainties around the assumptions on which the model structure is based.
- The plausibility of the inputs into, and the assumptions made, in the economic models.
- The Committee's preferred modelling approach, taking into account all of the economic evidence submitted.
- The range and plausibility of the ICERs generated by the models reviewed.
- The likelihood of decision error and its consequences.

6.2.18 The Appraisal Committee will consider carefully which individuals benefit most from the technology and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost effectiveness. The Appraisal Committee may recommend the use of an intervention for subgroups of the population only when there is clear evidence that the characteristics defining the subgroup influence the effectiveness and/or cost effectiveness of the intervention.

6.2.19 In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the

Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.

Structured decision-making: non-health factors

6.2.20 In general the Committee uses the most plausible ICER as the primary consideration when making judgements about the acceptability of technologies as a cost-effective use of NHS resources. However, its overall conclusions are also affected by the following additional considerations:

- Whether or how its judgements have a bearing on broader social considerations to the extent that these are covered by [NICE's principles on social value judgements](#).
- Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health as part of the remit.

6.2.21 The concept that underlies the Committee decision-making is that of the opportunity cost of programmes that could be displaced by the introduction of new technologies. This way, NICE seeks to maximise the health benefit gained from a fixed NHS budget. This principle is correct if the sole purpose of the health service is to improve health. While this may be the primary purpose of the NHS, it is acknowledged that care delivered by the NHS could have other benefits that are considered socially valuable but are not directly related to health and are not easily captured in a cost per QALY analysis. Techniques exist to consider the trade-off between health benefits and non-health benefits quantitatively. These techniques require that all relevant criteria are identified in advance, quantified and then weighted to reflect aspects of social value in a way that can be regarded as legitimate by all stakeholders. At present the introduction of such techniques into the Committee's decision-making is considered unsuitable. Therefore the Committee will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related.

6.3 *Decision-making*

- 6.3.1 The Appraisal Committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective or below which it would. Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies. NICE does not have complete information about the costs and QALYs from all competing healthcare programmes in order to define a precise maximum acceptable ICER. However, NICE considers that it is most appropriate to use a range as described in sections 6.3.2 to 6.3.5. Furthermore, consideration of the cost effectiveness of a technology is a necessary, but is not the sole, basis for decision-making. Consequently, the Institute considers technologies in relation to this range of maximum acceptable ICERs, such that the influence of other factors upon the decision to recommend a technology is greater when the ICER is closer to the top of the range.
- 6.3.2 Below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a technology is normally based on the cost-effectiveness estimate and the acceptability of a technology as an effective use of NHS resources. When the estimated ICERs presented are less than £20,000 per QALY gained and the Committee judges that particular interventions should not be provided by the NHS, the recommendations will make specific reference to the Committee's view on the plausibility of the inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for example, by sensitivity analysis or limitations to the generalisability of findings regarding effectiveness.
- 6.3.3 Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:
- The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented.
 - Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained.

- The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.
- The technology meets the criteria for special consideration as a 'life-extending treatment at the end of life' (see section 6.2.10)
- Aspects that relate to non-health objectives of the NHS (see sections 6.2.20 and 6.2.21).

6.3.4 As the ICER of an intervention increases in the range of £20,000 to £30,000 per QALY gained, the Committee's judgement about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed in section 6.3.3.

6.3.5 Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, with regard to the factors listed in section 6.3.3.

6.4 *Research recommendations*

6.4.1 When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted. Before issuing such recommendations the Committee will consider the following factors:

- the need for and potential value to the NHS of additional evidence that can inform the development of NICE guidance and clinical practice on the use of the technology
- the uncertainty in the analysis and what could be gained by reconsidering the decision in the light of research findings
- whether the research is feasible in circumstances when the Appraisal Committee recommends the intervention for NHS use outside the context of research
- irrecoverable costs incurred from introducing the technology

- the likely net benefits for all NHS patients of use only in a research setting during the time that the recommended research is being conducted.

In considering these factors the Committee will balance the potential net benefits to current NHS patients of a recommendation not restricted to research with the potential net benefits to both current and future NHS patients of being able to produce guidance and base clinical practice on a more secure evidence base.

6.4.2 Recommendations on the use of technologies only in the context of research will not include consideration of which organisation (public or private) will fund the research. The Appraisal Committee will consider:

- the likelihood that the research needed will be commissioned and successfully report
- the time it is likely to take for research findings to be available to inform subsequent NICE guidance and clinical practice
- other factors which may impact on the value of evidence generation, such as other research that is underway or likely to be commissioned and completed.

In considering these factors the Committee may seek advice from research commissioners, the wider research and clinical communities and consultees.

6.4.3 When the Committee recommends use of a technology and that research is conducted, it considers the factors in sections 6.4.1 and 6.4.2. The Committee will need to be satisfied that the additional research is feasible in the circumstances in which the intervention has been recommended.

6.4.4 In all cases, when technologies are being recommended only in the context of research, the Committee will explore whether overall, the potential value to the NHS of the recommended research is likely to represent good value in the context of limited research resources.

7 Further information

7.1 *NICE project team and Steering Group*

Project team

Meindert Boysen

Programme Director, Technology Appraisals, NICE

Janet Robertson

Associate Director, Technology Appraisals, NICE

Lynn Woodward

Assistant Project Manager, Centre for Health Technology Evaluation, NICE

Steering Group

Professor Carole Longson (Chair)

Director, Centre for Health Technology Evaluation, NICE

Professor Andrew Stevens

Chair, Appraisal Committee

Dr Amanda Adler

Chair, Appraisal Committee and Consultant Physician, Addenbrookes Hospital

Professor Martin Buxton

Professor of Health Economics, Brunel University

Meindert Boysen

Programme Director, Technology Appraisals, NICE

Professor Peter Littlejohns (until December 2011)

Clinical and Public Health Director, NICE

7.2 *NICE Methodology Working Party*

Professor Andrew Stevens (Chair)

Chair, Appraisal Committee and Professor of Public Health, University of Birmingham

Dr Amanda Adler

Chair, Appraisal Committee and Consultant Physician, Addenbrookes Hospital

Dr Edwina Affie

Director West Midlands Commissioning Support Unit and Senior Lecturer, University of Birmingham

Lizzie Amis

Senior Public Involvement Adviser, Public Involvement Programme, NICE

Dr Hanan Bell

Technical Adviser, Diagnostics Assessment Programme, NICE

Meindert Boysen

Programme Director, Technology Appraisals, NICE

Professor John Brazier

Professor of Health Economics, University of Sheffield

Professor Martin Buxton

Professor of Health Economics, Brunel University

Dr Claire Cheong-Leen

Commissioning Support Appraisals Service

Dr Julia Earnshaw

Director of Health Outcomes, GlaxoSmithKline

Simon Ellis

Associate Director, Public Health Interventions, NICE

Cecilia Fenerty

Consultant Ophthalmic Surgeon, Manchester Royal Eye Hospital

Dr Sarah Garner

Associate Director, Research and Development, NICE

Prashanth Kandaswamy

Senior Technical Adviser, Centre for Clinical Practice, NICE

Professor Jos Kleijnen

Director, Kleijnen Systematic Reviews Ltd

Lizzy Latimer

Technical Adviser, Medical Technologies Evaluation Programme, NICE

Professor Carole Longson

Director, Centre for Health Technology Evaluation, NICE

Professor Jonathan Michaels

Honorary Professor of Clinical Decision Science, University of Sheffield

Dr Bhash Naidoo

Technical Adviser, Technology Appraisals, NICE

Professor Stephen Palmer

Professor of Health Economics, University of York

Danny Palnoch

Senior Economic Adviser, Department of Health

Martin Price

Head of Market Access, Janssen

Simon Reeve

Head of Clinical and Cost effectiveness, Department of Health

Janet Robertson

Associate Director, Technology Appraisals, NICE

Professor Matt Stevenson

Professor of Health Technology Assessment, University of Sheffield

Dr Catherine Swann

Associate Director, Centre for Public Health Excellence, NICE

Dr Paul Tappenden

Senior Research Fellow, University of Sheffield

Michael Wallace

Director, Health Economics and Reimbursement, Johnson & Johnson Medical Devices and Diagnostics, UK

Laura Weir

Head of Policy and Campaigns, Multiple Sclerosis Society

Professor Gordon Wilcock

Professor of Clinical Geratology, John Radcliffe Hospital

The following attended 1 or more meetings of the working party on behalf of a working party member:

Warren Cowell

HTA policy, Pfizer Pharmaceuticals

Dr Sally Doss

Technical Adviser, Medical Technologies Evaluation Programme, NICE

Tarang Sharma

Senior Analyst, Research and Development, NICE

Dr John Stevens

Lecturer in Bayesian Statistics in Health Economics, University of Sheffield

Specialist advisers to the Working Party

Professor Tony Ades

Professor of Public Health Science, University of Bristol

Professor John Brazier

Professor of Health Economics, University of Sheffield

Professor Karl Claxton

Professor of Health Economics, University of York

Professor Nancy Devlin

Director of Research, Office of Health Economics

Dr Sofia Dias

Research Associate, University of Bristol

Jenni Field

Associate Director, Costing, NICE

Dr Ruth Garside

Senior Research Fellow, Peninsula College of Medicine and Dentistry

Dr Elisabeth George

Associate Director, Technology Appraisals, NICE

Dr Pall Jonsson

Technical Adviser, Technology Appraisals, NICE

Professor Mike Kelly

Director, Centre for Public Health Excellence, NICE

Professor Katherine Payne

Professor of Health Economics, University of Manchester

Fiona Rinaldi

Technical Adviser, Technology Appraisals, NICE

Professor Mark Sculpher

Professor of Health Economics, University of York

Dr Sophie Staniszewska

Senior Research Fellow, Royal College of Nursing Institute

Jonathan Tosh

Research Fellow, University of Sheffield

Dr Allan Wailoo

Reader in Health Economics, University of Sheffield

Doris-Ann Williams

Director, British in Vitro Diagnostics Association.

7.3 *Bibliography*

Related documents that describe other aspects of the Institute's methods and processes referred to in this guide are detailed below. These documents are available from the [NICE website](#) and links to the website are provided for each document.

- [Guide to the single technology appraisal process](#)
- [Guide to the multiple technology appraisal process](#)
- [Guide to the technology appraisal appeal process](#)
- [Single technology appraisal \(STA\): specification for manufacturer/sponsor submission of evidence](#)
- [Patient carer organisation consultee template](#)
- [Professional organisation consultee template](#)
- [NHS organisation consultee template](#)
- [Process for advising on the feasibility of implementing a patient access scheme](#)
- [Diagnostics assessment programme manual](#)
- [Social value judgements: principles for the development of NICE guidance, second edition](#)
- [Into practice guide](#)
- [Assessing resource impact process manual](#)
- [NICE's equality scheme](#)

Glossary

Absolute risk reduction (or increase)

The arithmetic difference between the event rates in 2 groups in a clinical study.

Abstract

A summary of a study, which may be published alone or as an introduction to a full scientific paper.

Adherence

The extent to which a person follows the health advice agreed with healthcare professionals. It may also be referred to as 'compliance'.

Adverse effect

A consequence other than that which was intended. Adverse effects relate specifically to drugs or other treatments or interventions that a person is receiving – they are a toxic reaction.

Appraisal Committee

A standing advisory committee of the Institute. Includes people who work in the NHS, people representing patient and carer organisations, lay members, people from relevant academic disciplines and the pharmaceutical and medical device industries.

Assessment Group

An independent assessment group commissioned by the NHS Research and Development Health Technology Assessment (HTA) programme to produce an independent review of the evidence for technologies being appraised within the multiple technology appraisal (MTA) process.

Assessment report

A critical review of the clinical and cost effectiveness of a health technology or technologies being appraised within the multiple technology appraisal (MTA) process. It is prepared by the Assessment Group. To prepare the report, the Assessment Group carries out a review of the published literature and the submissions from manufacturers and sponsors.

Baseline

Used to describe the initial set of measurements taken at the beginning of a study (after a run-in period, when applicable).

Bias

Systematic (as opposed to random) deviation of the results of a study from the 'true' results.

Blinding

When patients, caregivers, researchers and outcome assessors are kept unaware of the interventions patients have received in a study.

Carer

In this guide the term 'carer' refers to a person who provides unpaid care by looking after a relative, friend or partner who needs support because of ill health, frailty or disability.

Case-control study

A comparative observational study in which the investigator compares people who have experienced an event (for example, developed a disease) with people who have not (controls), and collects data to determine possible causes of the event.

CE mark

The abbreviation of 'Conformité Européene'. This mark indicates that the manufacturer has conformed with all the obligations required by European law applying to health, safety and environmental protection legislation. The CE mark allows a manufacturer to sell their products within the European market.

Citizens Council

A group of 30 people drawn from all walks of life who bring the public's views to NICE decision-making. The Citizens Council tackles challenging questions about values, such as fairness and need.

Class (of drugs in a NICE technology appraisal)

A group of drugs with the same or similar mechanisms of action. These drugs may or may not have the same basic chemical structure. However, there may be differences between drugs within a class, such as the side effects associated with them.

Clinical audit

A quality improvement process that measures patient care and outcomes through a structured or detailed review of care against explicit criteria, and takes action to improve it if necessary.

Clinical effectiveness

The extent to which an intervention produces an overall health benefit, taking into account beneficial and adverse effects, in routine clinical practice. It is not the same as efficacy.

Clinical specialist

In technology appraisals, clinical specialists act as expert witnesses to the Appraisal Committee. They are selected on the basis of specialist expertise and personal knowledge of the technology and/or other treatments for the condition. They provide a view of the technology within current clinical practice, and insights not typically available in the published literature.

Cohort study

A retrospective or prospective follow-up study. People in the study are grouped on the basis of whether or not they have been exposed to a suspected risk factor or intervention. A cohort study can be comparative, but the study investigator has no control over who is or isn't exposed.

Commentator

An organisation that engages in the appraisal process but is not asked to prepare a submission dossier. Commentators are invited to comment on the draft scope document, the assessment report and the appraisal consultation document (ACD). They receive the final appraisal determination (FAD) for information only, and do not have the right of appeal. These organisations are manufacturers of comparator technologies, Healthcare Improvement Scotland, the relevant National Collaborating Centre, related research groups, and other groups when appropriate.

Comorbidity

A disease or condition a patient has in addition to the disease being studied or treated.

Comparator

The standard intervention against which the intervention under appraisal is compared. The comparator can be no intervention, for example best supportive care.

Confidence interval (CI)

A range of values for an unknown population parameter (for example, blood pressure) with a stated 'confidence' (conventionally 95%) that it contains the true value. The range is calculated from sample data, and generally includes the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of ranges will actually contain the true value.

Confounding

In a study, confounding occurs when the effect of an intervention on an outcome is distorted because of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.

Constant proportional trade-off

The proportion of remaining life that a person would trade off for a given quality improvement is independent of the amount of remaining life.

Construct validity

The extent to which a measure correlates with other measures or 'constructs' in a manner consistent with theory (for example, the extent to which a generic measure of quality of life correlates with other established measures of disease severity).

Consultation

The process that allows stakeholders and individuals to comment on initial versions of NICE guidance and other documents (for example, the draft scope) so that their views can be taken into account when the final version is being produced.

Consultee

An organisation that participates in the appraisal of a technology. Consultees can comment on the draft scope, the assessment report or [Evidence Review Group report](#), and the appraisal consultation document (ACD) during the consultation process. Consultee organisations can nominate clinical specialists, commissioning experts and patient experts to present their personal views to the Appraisal Committee. All consultees are given the opportunity to appeal against the final appraisal determination (FAD).

Control

An explicitly defined comparator against which the effects of an intervention are compared in a clinical study.

Cost-benefit analysis

An economic evaluation that expresses both costs and outcomes of an intervention in monetary terms. Benefits are valued in monetary terms using valuations of people's observed or stated preferences, such as the willingness-to-pay approach.

Cost-effectiveness acceptability curves

A graph that plots a range of possible maximum acceptable ICERs on the horizontal axis against the probability (chance) that the intervention will be cost effective at that ICER on the vertical axis. In technology appraisals, cost-effectiveness acceptability curves are a means of representing the uncertainty surrounding the cost-effectiveness estimates in relation to the decision.

Cost-effectiveness analysis

An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart

attacks avoided, or cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness frontier

A region on a plot that shows the probability that the technology with the highest expected net benefit is cost effective.

Cost-effectiveness model

An explicit mathematical framework which is used to represent clinical decision problems and incorporate evidence from a variety of sources to estimate costs and health outcomes.

Cost-effectiveness plane

A graphical illustration of cost effectiveness. The horizontal axis represents the difference in effect between the intervention and the comparator. The vertical axis represents the difference in cost.

Decision problem

A clear description of the interventions, patient populations, outcome measures and perspective adopted in a health technology evaluation, relating specifically to the decision(s) that the evaluation is designed to inform.

Director of the Centre for Health Technology Evaluation

The Director of the Centre for Health Technology Evaluation is responsible for the delivery of the technology appraisal programme. The Director is also responsible for ensuring that appraisals are conducted in accordance with the published appraisal process and methodology.

Discounting

Costs and benefits incurred today are usually valued more highly than costs and benefits occurring in the future. Discounting health benefits reflects society's preference for benefits to be experienced in the present rather than the future. Discounting costs reflects society's preference for costs to be experienced in the future rather than the present.

Dominance

An intervention is dominated if it has higher costs and worse outcomes than an alternative intervention.

Effectiveness

See 'Clinical effectiveness'.

Efficacy

The extent to which an intervention is effective when studied under controlled research conditions.

End point

In a research study, an event or outcome that can be measured and constitutes 1 of the target outcomes of the trial.

Epidemiological study

The study of a disease within a population, which includes defining its incidence and prevalence and examining the roles of external influences (for example, infection or diet) and interventions on the disease.

Equity

Fair distribution of resources or benefits.

European Medicines Agency

A decentralised agency of the European Union responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

Evidence

Information on which a decision or guidance is based. Evidence is obtained from a range of sources, including randomised controlled trials, observational studies and expert opinion (of clinical professionals and/or patients/carers).

Evidence Review Group

An independent assessment group commissioned by the NHS Research and Development Health Technology Assessment (HTA) programme to produce an independent assessment of the evidence submitted by the manufacturer or sponsor of a technology being appraised within the single technology appraisal (STA) process.

Evidence Review Group report

A critical assessment of the evidence submitted by the manufacturer of a technology being appraised within the single technology appraisal (STA) process. It is prepared by the Evidence Review Group.

Extended dominance

The incremental cost-effectiveness ratio (ICER) for a given treatment alternative is higher than that of the next, more effective, alternative (that is, it is dominated by the combination of 2 alternatives and should not be used to calculate appropriate ICERs).

External validity

The degree to which the results of an observation, study or review are likely to hold true in a population or clinical practice setting outside of the study population/setting. See also 'Internal validity'.

Extrapolation

In data analysis, predicting the value of a parameter outside the range of observed values.

Forest plot

A common way of presenting the results of a systematic review and meta-analysis. The estimates of treatment effects, along with their confidence intervals, are plotted relative to a vertical line indicating no difference between the intervention and control in the included study. From this plot, an impression of the distribution of the estimates of effect in all included studies can be gained.

Generalisability

The extent to which the results of a study conducted in a particular patient population and/or a specific context will apply for another population and/or in a different context.

Health-related quality of life

A combination of a person's physical, mental and social wellbeing.

Health technology

Any method used by those working in health services to promote health, prevent and treat disease, and improve rehabilitation and long-term care. Technologies in this context are not confined to new drugs or medical technologies.

Healthcare Resource Groups (HRGs)

These groups provide a way of categorising the treatment of patients so that the use of resources can be monitored and evaluated. Each HRG refers to a group of health-related activities or services that have been judged to consume a similar level of resources.

Heterogeneity

Used in meta-analyses and systematic reviews to describe when the results or estimates of effects of a treatment from separate studies seem to be very different (for example, the size of treatment effects may vary across studies, or some studies may indicate beneficial treatment effects whereas others suggest adverse treatment effects). Such difference in results may occur by chance, because of variation in study quality or because of variation in populations, interventions, or methods of outcome measurement in the included studies.

Inclusion criteria (literature review)

Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental cost-effectiveness ratio (ICER)

The ratio of the difference in the mean costs of a technology compared with the next best alternative to the differences in the mean outcomes.

Indication (specific)

The use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Indirect comparison

An analysis comparing interventions that have not been compared directly within a head-to-head randomised trial.

Intention-to-treat (ITT) analysis

An analysis of the results of a randomised controlled trial in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

Intermediate outcome

Outcomes that are related to the outcome of interest but may be more easily assessed within a clinical study (for example, blood pressure reduction is related to the risk of a stroke).

Internal validity

The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study. It refers to the integrity of the study design and is a prerequisite for applicability (external validity) of a study's findings. See also 'External validity'.

Life-years gained

Average years of life gained per person as a result of the intervention.

Marketing authorisation

An authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) or European Commission to market a medicinal product.

Medicines and Healthcare products Regulatory Agency (MHRA)

The Executive Agency of the Department of Health that protects and promotes public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

Meta-analysis

A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome.

Mixed treatment comparison

An analysis that compares 2 or more interventions using a combination of direct evidence (from head-to-head trials of the interventions of interest) and indirect evidence (trials that do not compare the interventions of interest directly).

Multiple technology appraisal (MTA)

The name given to the NICE process in which appraisals of more than 1 technology, or a single technology for a broad set of indications, are conducted.

National Institute for Health Research (NIHR)

The NIHR commissions and funds NHS, social care and public health research, and makes this research available to support decision-making by professionals, policy makers and patients.

Natural history of a disease

The progression of a disease when untreated.

Net benefit

The net benefit can be expressed in health (for example, using quality-adjusted life years [QALYs]) or monetary terms. Net health benefit is the difference between the total expected QALYs and the health expected to be forgone elsewhere (the total expected costs divided by the maximum acceptable incremental cost-effectiveness ratio [ICER] value). The net monetary benefit is the

difference between the monetary value of total expected QALYs (expected QALYs multiplied by the maximum acceptable ICER value) and total expected costs.

NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)

One of the activities of NETSCC is the management of the NIHR health technology assessment (HTA) programme. This programme produces independent research information about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS. Technology assessment reports are commissioned by the HTA programme on behalf of NICE to inform its national clinical guidance to the NHS.

Non-reference-case analysis

An analysis that does not use methods specified in the reference case considered by the Institute to be the most appropriate for the Appraisal Committee's purpose.

Observational study

A retrospective or prospective study in which the investigator observes the natural course of events with or without control groups (for example, cohort and case-control studies).

Opportunity cost

The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Outcome

The measure of the possible results of treatment with a preventive or therapeutic intervention. Outcome measures can be either intermediate or final end points. See also 'Intermediate outcome'.

Pairwise comparisons

Comparisons that compare each of the technologies of interest in a series of separate analyses. For example, if there are 3 treatments (A, B and C) being compared, they could be compared in a single combined analysis (that is, A compared with B compared with C) or as a series of pairwise comparisons (that is A compared with B, A compared with C, and B compared with C).

Parameter

A measurable or quantifiable characteristic. For example, the relative treatment effect of a technology may be a parameter in an economic model.

Parameter uncertainty

Uncertainty about the mean values of parameters (for example, health outcomes, utilities and resource use) included in the model.

Patient expert

Acts as an expert witness to the Appraisal Committee. Patient experts have used the technology either personally or as part of a representative group. They provide a view on the risks and benefits of the technology from personal experience as a patient or carer, and an understanding of the wider range of patient and/or carer views.

Perspective (in economic evaluation)

The viewpoint from which an economic evaluation is conducted. The viewpoint may be that of the patient, hospital/clinic, healthcare system or society.

Primary research

A study generating original data rather than analysing data from existing studies (which is called secondary research).

Quality-adjusted life year (QALY)

An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs incorporate changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social, and other factors) of life. Used to measure benefits in cost-utility analysis.

Quality of life

See 'Health-related quality of life'.

Random effects model

In meta-analysis, a model allowing for heterogeneity between studies. The simplest models allow for a single random effect term, and more complicated models can allow for different levels of heterogeneity.

Randomisation

Allocation of participants in a research study to 2 or more alternative groups using a chance procedure such as computer-generated random numbers. This approach is used to attempt to ensure there is an even distribution of participants with different characteristics between groups and reduces bias and confounding.

Randomised controlled trial (RCT)

A comparative study in which people are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.

Reference case

When estimating clinical and cost effectiveness, the reference case specifies the methods considered by NICE to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources.

Relative risk (RR)

The number of times more likely or less likely an event is to happen in 1 group compared with another (calculated as the risk of the event in group A divided by the risk of the event in group B). The RR is usually expressed as the risk of the event in the intervention group divided by the risk of the event in the comparator group. In this case, an RR of less than 1 indicates that there is less risk of the event with the intervention than the comparator.

Relative treatment effect

The effect of a treatment relative to another treatment or control, for example measured by relative risk (RR).

Remit

The brief given to the Institute by the Department of Health and Welsh Assembly Government when a technology is referred to NICE for appraisal.

Sensitivity analysis

A way of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

One-way simple sensitivity analysis (univariate analysis)

Each parameter is varied individually to isolate the consequences of the parameter on the results of the study.

Multi-way simple sensitivity analysis (scenario analysis)

Two or more parameters are varied at the same time and the overall effect on the results is evaluated.

Threshold sensitivity analysis

The critical value of parameters above or below which the conclusions of the study will change are identified.

Probabilistic sensitivity analysis

Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).

Single technology appraisal (STA)

The name given to the NICE process in which appraisals of single technologies for 1 indication are conducted.

Structural uncertainty

Uncertainty relating to the range of assumptions and judgements necessary in constructing a model. This can include design features of the model (for example, the assumed standard pathway of care) as well as judgements about the relevance of evidence, assumptions about appropriate distributions for parameters and alternative methods of estimation.

Synthesis of evidence

A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion to answer a defined clinical question. This can include systematic review (with or without meta-analysis), and qualitative and narrative summaries.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings are used. Statistical meta-analysis may or may not be used.

Technology

See 'Health technology'.

Technology assessment

The process of evaluating the clinical, economic and other evidence on the use of a technology to formulate guidance on its most efficient use.

Time horizon

The time span used in the NICE appraisal that reflects the period over which the main differences in health effects and use of healthcare resources between interventions are expected to be experienced.

Time trade-off

A method used to measure utility (for example, health states). The utility value is measured by finding the point at which the respondent cannot choose between 2 scenarios. For chronic illness,

the choice is between the illness for a period of time and perfect health for a shorter time, both followed by death. For short-term illness, the choice is between the illness for a period of time and a worse health state for a shorter time, both followed by the same specified outcome.

Treatment options

The choice of interventions that are available for a specific condition.

Treatment sequence

Used to describe when the intervention being evaluated and the comparator are used in succession in the management of a condition.

Utility

A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

Variable

A measurement that can vary within a study (for example, the age of participants). Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

ISBN: 978-1-4731-0119-7