



*National Institute for
Health and Clinical Excellence*

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**Guide to the methods
of technology appraisal**

Guide to the methods of technology appraisal

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This document is one of a set that describes the process and methods that NICE uses to undertake technology appraisals and provide guidance for the organisations invited to contribute to these appraisals. For further information, please go to www.nice.org.uk

It replaces the 'Guide to the methods of technology appraisal' published in April 2004.

The document is available from the NICE website (www.nice.org.uk) or from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference number N1618).

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Contents

Acknowledgements	3
List of abbreviations	3
Foreword	4
<hr/>	
1 Introduction	6
1.1 The methods of technology appraisal	6
1.2 Health technologies and their selection	7
1.3 What is technology appraisal?	7
1.4 Fundamental principles	9
1.5 Implementation of NICE guidance	9
<hr/>	
2 Developing the scope	10
2.1 Introduction	10
2.2 Components of the scope	11
2.3 Consultation on the draft scope	12
<hr/>	
3 Evidence for assessment and appraisal	14
3.1 Introduction	14
3.2 Evidence for relative treatment effects	14
3.3 Evidence for cost effectiveness	16
3.4 Evidence for other appraisal considerations	17
<hr/>	
4 Suppliers of evidence, commentary and analysis	19
4.1 Health technology assessment	19
4.2 Manufacturers and sponsors	20
4.3 Patient/carer groups	22
4.4 Healthcare professionals	24
4.5 Clinical specialists and patient experts	25
<hr/>	

5	Clinical and cost effectiveness and NHS impact	27
5.1	Guiding principles	27
5.2	Framework for estimating clinical and cost effectiveness	29
5.3	Synthesising evidence on outcomes	34
5.4	Measuring and valuing health effects	38
5.5	Evidence on resource use and costs	40
5.6	Discounting	41
5.7	Modelling methods	42
5.8	Characterisation of potential bias and uncertainty	43
5.9	Presentation of data and results	44
5.10	Analysis of data for patient subgroups	47
5.11	Identifying future research needs from the evidence	49
5.12	Reflecting equity considerations in cost-effectiveness analysis	49
5.13	Impact on the NHS	50
<hr/>		
6	The appraisal of the evidence and decision-making	52
6.1	Introduction	52
6.2	Appraisal Committee meetings	54
<hr/>		
	Appendix A: NICE project team and Steering Group	61
	Appendix B: NICE Methodology Working Party and specialist advisers	62
	Appendix C: Bibliography	65
	Appendix D: Glossary	66
<hr/>		

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The Institute is grateful to the members of the NICE Methodology Working Party (see appendix B) 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.

List of abbreviations

ACD	Appraisal consultation document
FAD	Final appraisal determination
HRG	Healthcare resource group
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
MTA	Multiple technology appraisal
NCCHTA	National Coordinating Centre for Health Technology Assessment
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
STA	Single technology appraisal

Foreword

The National Institute for Health and Clinical Excellence (NICE, or the Institute) provides guidance to the NHS in England and Wales 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 Scotland and Northern Ireland.

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 2004. 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 two companion documents to this guide: 'Guide to the technology appraisal process' and 'Guide to the single technology appraisal (STA) process' (see appendix C). A review of these documents is currently underway; further information on the updated documents will be made available on the NICE website.

This document indicates the kind of information and analysis that the Appraisal Committee will find most helpful. Substantive departures from the 'Guide to the methods of technology appraisal' should therefore not be made without the previous agreement of the Director of the Centre for Health Technology Evaluation.

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 would like to encourage further development of the methods of technology appraisal. Innovative approaches to any aspect of technology appraisal will therefore be considered, if necessary, as additions to the reference case. Work of this sort should be agreed with the Director of the Centre for Health Technology Evaluation before submission of evidence to the Institute.

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.

The Institute is aware that, currently, there is a national shortage of the skills required for technology appraisal that affects manufacturers and sponsors and urges universities and professional associations to contribute to remedying the shortage. The Institute suggests that manufacturers and sponsors of technologies who lack the relevant methodological skills in-house should seek them elsewhere rather than attempt a submission of evidence that may fall short of the standards expected. Advice on where to find such skills is normally available from senior academic and other experts or through their professional associations.

1 Introduction

1.1 The methods of technology appraisal

- 1.1.1 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 aims to introduce the general methodological concepts underlying each stage of the appraisal process and to describe what is required of participants considering submission of evidence to NICE.
- 1.1.2 The Institute has two appraisal processes: the multiple technology appraisal (MTA) process and the single technology appraisal (STA) process. Although there are differences between the two processes, the principles relating to decision-making and the methods of assessment are the same.
- 1.1.3 As well as this methods guide, there are companion documents describing the Institute's appraisal processes (see appendix C).
- 'Guide to the technology appraisal process' (for MTAs).
 - 'Guide to the single technology appraisal (STA) process'.
- 1.1.4 The Institute's appraisal process relies on information and input from a number of sources, including independent assessment groups (see section 4.1.1), manufacturers and sponsors, healthcare professionals and patient/carer representatives. This methods guide is the foundation for the following documents aimed at individual groups participating in an appraisal (see appendix C).
- 'Contributing to a technology appraisal: a guide for patient/carer groups'.
 - 'Contributing to a technology appraisal: a guide for healthcare professional groups'.
 - 'Contributing to a technology appraisal: a guide for manufacturers and sponsors'.
 - 'Contributing to a technology appraisal: a guide for NHS organisations'.
 - 'Single technology appraisal (STA): specification for manufacturer/sponsor submission of evidence'.
 - 'Technology appraisal process: guidance for appellants'.
- 1.1.5 Documents describing all the Institute's methods and processes are available on the Institute's website (www.nice.org.uk) and from NICE publications (telephone 0845 003 7783 or email publications@nice.org.uk). Links to the website location for documents referred to in this guide are provided in appendix C. The Institute regularly reviews its methods and processes and the documentation may be subject to change.
- 1.1.6 The Institute is aware that many people who are not experts in health technology appraisal will read this document. A glossary of terms has therefore been included (see appendix D).

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 NICE include:

- pharmaceuticals
- medical devices
- diagnostic techniques
- surgical procedures
- other therapeutic technologies
- health promotion activities.

1.2.2 The purpose of the appraisal carried out by the Institute is as described in the Directions from the Secretary of State for Health (see appendix C); 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 from several sources, including healthcare professionals, the general public, the Department of Health's national clinical directors and policy teams, and the National Horizon Scanning Centre. Further details on the topic selection process and how to suggest a topic for appraisal are provided on the NICE website. Ministers at the Department of Health have responsibility for the final decision about which topics are referred to NICE.

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

- Is the technology likely to result in 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 result in 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 three distinct phases.

- Scoping.
- Assessment.
- Appraisal.

Scoping

- 1.3.1 During the scoping process, the Institute determines the appropriateness of the remit and the specific questions that are to be addressed for each technology appraisal. The scope defines the issues of interest (for example, population, comparators and potential subgroups) as clearly as possible and the questions that should be addressed by the Appraisal Committee when considering the clinical and cost effectiveness of the technology. The questions to be addressed by the appraisal are fundamental to the assessment process and require an understanding of the context within which a technology is to be investigated, 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 issues that will be investigated. The methods and principles that underpin the scoping process are described in detail in section 2.

Assessment

- 1.3.2 The assessment process (see section 3) is a systematic evaluation of the relevant evidence available on a technology. The aim is to produce an estimate, taking account of uncertainty, of a technology's clinical and cost effectiveness for a specific indication. Assessment normally has two mutually dependent components: a systematic review of the evidence and an economic evaluation. Assessment, therefore, consists of an objective analysis of the quality, findings and implications of the (mainly research) evidence available as it relates to the appraisal question and context. Strengths, weaknesses and gaps in the evidence are identified and evaluated.
- 1.3.3 The assessment process always includes a review of the evidence by an independent assessment group. For MTAs, the Assessment Group conducts an independent systematic review and economic analysis. For STAs, the Evidence Review Group reviews the submission provided by the manufacturer or sponsor of a technology and provides a critique of this submission. The Evidence Review Group may recommend that the Institute requests additional analysis from the manufacturer or sponsor, and may undertake sensitivity analysis (that is, exploring alternative scenarios and the uncertainty in the cost-effectiveness results).

Appraisal

- 1.3.4 The appraisal process (see section 6) is a consideration of the reports and analyses produced in the assessment phase within the context of additional information supplied by consultees, commentators, clinical specialists, patient experts and the general public. The Appraisal Committee considers the evidence available and then formulates an appraisal decision, applying judgements on the importance of a range of factors that may differ from appraisal to appraisal. Although there is a boundary between

assessment and appraisal, it is not precisely defined and judgement in the assessment process about, for example, choice of outcome measures to be investigated will influence the appraisal process.

1.4 Fundamental principles

- 1.4.1 The Institute takes into account the clinical and cost effectiveness of a technology, along with other specified considerations, when issuing guidance to the NHS.
- 1.4.2 In general, technologies can be considered clinically effective if, in normal clinical practice, they confer an overall health benefit, taking account of any harmful effects, when compared with relevant alternative treatments. Technologies can be considered to be cost effective if their health benefits are greater than the opportunity costs measured in terms of the health benefits associated with programmes that may be displaced to fund the new technology. 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 of interest.
- 1.4.3 The Institute is committed to promoting equality, eliminating unlawful discrimination and actively considering the implications of its guidance for human rights. The Institute will take into account relevant provisions of legislation on human rights, discrimination and equality. 'NICE's equality scheme and action plan 2007–2010' (see appendix C) 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 of NICE's Establishment Orders, relevant legislation and Directions from the Secretary of State for Health. The Appraisal Committee will also take into account the Institute's guidance on the consideration of social value judgements described in the Institute's document, 'Social value judgements: principles for the development of NICE guidance' (see appendix C).

1.5 Implementation of NICE guidance

- 1.5.1 The Secretary of State for Health has directed that the NHS provides funding and resources for technologies that have been recommended through the NICE technology appraisals programme normally within 3 months from the date that the guidance is published. The Institute provides advice and tools to support the local implementation of its guidance. Costing tools and support for audit are produced for all technology appraisals; additional implementation support tools are produced for selected technology appraisals. The Institute's document, 'How to put NICE guidance into practice' (see appendix C), provides advice on the implementation of NICE guidance.

2 Developing the scope

2.1 Introduction

- 2.1.1 The 'scoping' process examines the appropriateness of the proposed remit and defines in detail what the appraisal will and will not examine. Scoping is an important step because it determines the nature and content of the evidence 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 and topic selection process (see appendix C).
- 2.1.2 The purpose of a scope is to provide a framework for the appraisal. The scope defines the issues of interest (for example, population and comparators) as clearly as possible and sets the boundaries for the work undertaken by those producing reports for the Appraisal Committee, including the independent assessment groups and the manufacturer(s) or sponsor(s) of the technology.
- 2.1.3 Potential consultees and commentators are consulted on the proposed remit and draft scope. This consultation process is designed to ensure that relevant issues have been considered and that the focus and boundaries of the appraisal have been clearly defined in the final scope.
- 2.1.4 The issues for consideration in the appraisal, including the parameters of clinical and cost effectiveness, that are described in the scope include:
- the clinical problem 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 comparator technologies (and the setting for their use if relevant)
 - the principal health outcome measures appropriate for the analysis
 - the costs to be assessed
 - the time horizon over which benefits and costs will be assessed
 - consideration of patient subgroups for whom the technology might potentially be particularly clinically and cost effective
 - issues relating to equalities legislation and/or the prevention of discrimination that may require special consideration
 - other special considerations and issues that are likely to affect the appraisal; for example, existing relevant NICE guidance.

2.2 Components of the scope

Background information on the clinical problem

- 2.2.1 The scope describes the disease (or other clinical problem) relevant to the new technology together with appropriate information on the prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS.

The technology

- 2.2.2 Information is required about the marketing authorisation (or CE mark for medical devices) of the technology, and the stage of regulatory approval for unlicensed technologies. The circumstances of use are carefully specified, particularly if these differ from the circumstances in which alternative treatments for the same patient group are used, or when there are several alternative circumstances in which the technology itself may be used.

The population

- 2.2.3 The population for whom the technology is being appraised is defined as precisely as possible. When the technology is a medicine, this will usually be determined by the therapeutic indications specified in the marketing authorisation. 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 subgroups that require special consideration.

The comparator technologies

- 2.2.4 Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment. There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice. For example, this may occur when new technologies are used inconsistently across the NHS. Relevant comparator technologies may also include those that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope but that are used routinely for the indication in the NHS. Comparator technologies may include branded and non-proprietary (generic) drugs. Sometimes both technology and comparator form part of a treatment sequence, in which case the appraisal may need to compare alternative treatment sequences. The scoping process aims to specify the comparator technologies as precisely as the technology under appraisal. Evidence providers will need to give due regard to all the above considerations when selecting comparator technologies for analyses in the evidence submissions.

The evidence base

- 2.2.5 The scoping process is a good opportunity to highlight issues about the available evidence base; for example, emerging key trials, important clinical databases, and the evidence around comparator technologies.

The health outcome measures

- 2.2.6 As far as possible, principal measures of health outcome are identified in the scope. For the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant; that is, they measure health benefits and adverse effects that are important to patients and/or their carers. The clinical outcome measures would usually be expected to have an impact on survival or health-related quality of life (HRQL) and be able to be translated into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness.

The measures of costs

- 2.2.7 The potential impact on resource costs and savings for the NHS and personal social services (PSS) that would be expected from the introduction of the technology is presented.

The time horizon over which benefits and costs are assessed

- 2.2.8 The time span used in the appraisal usually reflects the period over which the main differences between technologies (from the point of view of their likely health effects and use of healthcare resources) are expected to be experienced, taking into account the limitations of supporting evidence. A lifetime horizon should normally be adopted if a treatment affects survival at a differential rate when compared with the relevant comparator.

Special considerations and other issues likely to impact upon the appraisal

- 2.2.9 When appropriate, the scope also includes brief details of other considerations that could form part of the appraisal. This may include:
- related NICE guidance, such as clinical guidelines
 - related policy developments, such as the National Service Frameworks
 - details of specific patient subgroups or service settings, either of particular interest or to be excluded from consideration
 - issues relating to equalities and the prevention of discrimination.

2.3 Consultation on the draft scope

- 2.3.1 During consultation on the proposed remit and draft scope, interested parties are asked for their views on an appropriate remit for the appraisal and important issues to be considered. This consultation process is important to define the relevant issues to be considered and, in particular, to:

- describe the clinical problem, including the proposed place of the technology in the clinical pathway of care
- identify relevant comparator technologies
- highlight issues regarding the available evidence base (for example, emerging key trials)
- identify subgroups for separate analysis and/or consideration
- identify key health outcomes, including HRQL
- identify any equality or diversity issues that need to be taken into consideration.

3 Evidence for assessment and appraisal

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 be relevant to the appraisal. These are outlined in the sections below. 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 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
 - balanced and not selected to support a specific case
 - inclusive of all study design information, such as the type of study, the circumstances of its undertaking and the selection of outcomes and costs
 - comprehensive in the description of the analysis undertaken, which should include an intention-to-treat analysis (that is, when patients are analysed in the groups to which they are randomised in the trials regardless of any subsequent changes to the treatment given)
 - fit for purpose, that is, it contributes to an overall assessment of benefit of the technology, including HRQL and resource use.
- 3.1.3 The analyses and modelling should be methodologically sound and, in particular, minimise any bias (for example, by using evidence from randomised controlled trials [RCTs] to estimate relative treatment effects; by presenting the explicit criteria by which studies are included and excluded; and by using resource-use data that are representative of typical NHS costs).
- 3.1.4 Economic models should also:
- be replicable
 - have face validity (that is, be plausible)
 - be open to external scrutiny.

3.2 Evidence for relative treatment effects

Introduction

- 3.2.1 The treatment effect of a technology can be summarised as the difference between the duration and state of health or HRQL (including the impact of any adverse effects of treatment) that would be experienced on average by patients receiving the technology and that experienced by the same group were they to receive alternative care.

- 3.2.2 The primary research methods and designs that are used to measure the treatment effect can be broadly categorised into experimental or observational studies. The most reliable evidence about the relative treatment effects of a technology is obtained from experimental studies with high internal and external validity. For an assessment of internal validity, the different types of study design can be ranked according to design features that affect their validity for estimating relative treatment effect, ranging from RCTs to uncontrolled observational studies.
- 3.2.3 The potential for bias, including performance, measurement and attrition bias, is greater in studies lower in the ranking. However, it is important to recognise that, even for the analysis of relative treatment effects, RCT data are often limited to selected populations and may include comparator treatments and short time spans that do not reflect routine or best NHS practice. Therefore, good-quality non-randomised studies may be needed to supplement RCT data. In addition, the value of evidence from anywhere in the ranking will depend on its quality and relevance to the appraisal (as defined in the scope).
- 3.2.4 If relevant, up-to-date and well-conducted systematic reviews that include studies least open to bias are available, these should be considered.

Randomised controlled trials

- 3.2.5 RCTs are designed to minimise potential external influences so that the effects of one or more interventions in a precisely defined patient group are isolated. Randomisation aims to prevent selection bias in the allocation of interventions to participants and ensure balance between the intervention groups in known and unknown factors. The outcome of the trial should, in principle, be a minimally biased estimate of the magnitude of any benefits or risks associated with the technology relative to those that are associated with the control. RCTs are therefore considered to be most appropriate for measures of relative treatment effect.
- 3.2.6 The Institute has a strong preference for evidence from 'head-to-head' RCTs that directly compare the technology with the appropriate comparator in the relevant patient groups. When such evidence is available and includes relevant outcome evidence, this is preferred over other study designs.
- 3.2.7 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 features of the design and conduct of a trial that are important for eliminating bias. These features include blinding (when appropriate), the method of randomisation and concealment of allocation, and the completeness of follow-up. Other important considerations are the size 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, the applicability of the results to wider patient groups over a longer follow-up than is reported in the trials and to routine clinical practice, including appropriate comparator technologies.

Non-RCT evidence

- 3.2.8 Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. The problems of confounding, lack of blinding, incomplete follow-up and lack of a clear denominator and endpoint will usually be much worse in non-randomised studies than in RCTs. But in some circumstances, evidence from these studies will be needed in addition to RCT data, in particular to estimate relative treatment effect over longer time horizons or to measure particular outcomes that have not been included in the RCTs. In the absence of valid RCT evidence, evidence from studies least open to bias will be considered preferentially with reference to the inherent limitations of the specific design.
- 3.2.9 Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.
- 3.2.10 Whatever the sources of evidence available on a particular technology and patient group, they will be integrated into a systematic review with explicit, valid and replicable methods (see section 5.3).

3.3 Evidence for cost effectiveness

- 3.3.1 In considering cost effectiveness, it is likely that evidence from other study designs in addition to that from RCTs will be necessary.
- 3.3.2 The evidence requirements for economic evaluations include the quantification of the effect of the technologies under comparison on the course of the relevant disease, the impact of those effects on patients' HRQL and the valuation of those impacts to reflect the preferences of the general population.
- 3.3.3 For costs, evidence requirements include quantifying the effect of the technologies 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. The types of evidence required will differ according to the parameter being estimated.
- 3.3.4 For all parameters (including effectiveness, valuation of HRQL and costs) a systematic consideration of possible data sources is required, and the selection of sources to justify a particular outcome must be avoided.
- 3.3.5 Evidence on cost effectiveness may be obtained from new analyses; however, a systematic review of published, relevant evidence on the cost effectiveness of the technology should also be conducted.

3.4 Evidence for other appraisal considerations

Introduction

- 3.4.1 In addition to evidence on treatment effect and cost effectiveness, the appraisal of health technologies requires consideration of a range of other issues. A variety of types of evidence generated from a range of sources, of both quantitative and qualitative origin, is relevant to these areas.

Acceptability, appropriateness and preference

- 3.4.2 Information on whether a health technology is considered to be an acceptable or appropriate technology (compared with alternative technologies) by patients, carers or healthcare professionals is useful. Individuals or groups may prefer particular health technologies, for example, because of the frequency or nature of adverse events or the route or frequency of administration. The health impact of most of these factors (for example, adverse events) is expected to be reflected in the estimation of HRQL. In addition, individuals or groups may be concerned about the ethics of using a particular technology. These are relevant considerations for an appraisal because they influence judgements on the usefulness of technologies, inform the nature of choice between alternative technologies and provide important evidence on the extent to which these considerations have been adequately captured in measurements of HRQL. Evidence relevant to these considerations can come in various forms, be based on quantitative or qualitative measurements, and originate from a range of sources that have different methodological strengths and weaknesses. Such evidence includes literature reviews, adverse effect/adherence/continuation data collected in research studies, patient surveys (for example, of adverse effects or preferences) and summarised testimonies from clinical specialists and patients.

Feasibility and impact

- 3.4.3 Health technologies may be clinically and cost effective but it may also be necessary to consider organisational issues that impact on patients and carers or those providing care. Such factors may affect the feasibility or rate of a technology's implementation (for example, the location or availability of specialist services) or the size of the impact of implementation (for example, knock-on effects on support services or staff recruitment and training requirements). Evidence on these factors may take a variety of forms, including case studies and implementation and evaluation studies.

Equity and equality

- 3.4.4 The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic

analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups.

- 3.4.5 The Institute is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. The Institute consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

4 Suppliers of evidence, commentary and analysis

The Institute will normally be supplied with evidence from:

- an independent assessment group (the 'Assessment Group' for MTAs and the 'Evidence Review Group' for STAs)
- manufacturers and sponsors of technologies
- national patient/carer groups
- healthcare professionals
- clinical specialists and patient experts.

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 1.1.4 and is available on the Institute's website.

4.1 Health technology assessment

Independent assessment groups

- 4.1.1 For each technology appraisal an independent assessment group, made up of a panel of independent experts from one of a number of academic centres, is commissioned by the NHS Health Technology Assessment Programme through the National Coordinating Centre for Health Technology Assessment (NCCHTA) to critically review the available evidence concerning a 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.
- 4.1.2 In the MTA process, the Assessment Group prepares the assessment report, which is an independent synthesis of the evidence from published information and the submissions from manufacturers and sponsors about the clinical and cost effectiveness of the technology/technologies. The report provides a systematic review of the literature and a review of manufacturer and sponsor economic models submitted to the Institute. It usually includes a new assessment of cost effectiveness based on an economic model.
- 4.1.3 The Assessment Group also consults clinical and methodological experts, and patient groups, when gathering evidence for the assessment report.
- 4.1.4 The assessment report is not an exhaustive review of all the information on a given technology. The report is focused on the evidence relevant to the decision problem defined in the scope and based upon the assessment protocol. There is no specific cut-off point in the hierarchy of evidence acceptable. The type of evidence accepted is pragmatically determined by the quantity and quality of evidence available for each indication under assessment, and for the interpretation of each of the outcome measures in question. The extent to which the Assessment Group uses submitted

evidence depends on how closely it fits with the criteria defined in the assessment protocol, following recognised methodological guidance.

- 4.1.5 In the STA process, the Evidence Review Group prepares the Evidence Review Group report, which is a critical appraisal of the submission provided by the manufacturer or sponsor of the technology. If the Evidence Review Group is concerned about any assumptions made in the submitted analyses, it may recommend that the Institute requests additional analysis from the manufacturer or sponsor, and/or may undertake additional analysis themselves.
- 4.1.6 The report produced by either the Assessment Group or the Evidence Review Group is an important part of the input into the appraisal, but it is not the only evidence that informs the Appraisal Committee's consideration of the technology under appraisal. These independent academic reports are the responsibility of the authors, namely the Assessment Group or Evidence Review Group. These groups do not propose recommendations on the use of the technology for the NHS; this final responsibility rests with the Institute.

4.2 Manufacturers and sponsors

Submissions from 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 sponsored by them or known to them, in the form of all clinical trials, follow-up studies and evidence from disease registers. 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 in the period immediately before the expected date of regulatory approval, care should be taken so that sufficient detail of the clinical trial evidence is made available to enable the Institute to conduct the appraisal according to the defined scope.
- 4.2.2 At the earliest opportunity, manufacturers will be asked to make available details of the studies they intend to include in their submissions. When there is extensive unpublished information, the Assessment Group or Evidence Review Group may request the study reports before the submission date.

Summary of requirements for submissions by manufacturers and sponsors

- 4.2.3 Submissions should normally include the following.
- A complete list of all studies concerning the health technology within the disease area in which it is being appraised. These studies may be sponsored by manufacturers or sponsors or known to them (the Institute may request further information on studies included in the list).

- The main submission should, as a minimum, include the following.
 - The aims of treatment and current approved indications for the technology.
 - An overview of the current treatment pathway, including how the technology is expected to fit into the treatment pathway.
 - An assessment of clinical effectiveness, containing a critical appraisal, interpretation and synthesis of clinical-effectiveness evidence.
 - A tabulation of the values and sources of the key parameters to be used in the assessment of cost effectiveness.
 - An assessment of cost effectiveness containing a reference-case analysis of cost effectiveness based on the synthesis of clinical-effectiveness evidence. A justification for any cost-effectiveness analysis not fulfilling the reference-case requirement is essential.
 - An assessment of resource impact containing estimates of the impact of the technology on the NHS, including uptake/treatment rates, population health gain, resource implications and financial costs.
- An appendix containing supporting documentation for data and analyses contained and referenced in the main submission. Documentation contained in the appendix for data and analyses not used in the main submission will not be assessed.
- An appendix containing excluded evidence with the rationale for exclusion.
- An executable electronic copy of the model (without password protection) used in the cost-effectiveness analysis.

4.2.4 When published guidance is to be reviewed for the purposes of consideration of re-appraisal, the minimum requirement will be that all new evidence should be provided and accompanied by a synopsis of the previous evidence submitted for the original appraisal. The evidence requirements for each specific review appraisal will normally be outlined during the scoping stage.

4.2.5 Manufacturers and sponsors should refer to the relevant supporting document detailed in section 1.1.3 before submitting evidence. In addition, further information on the content of manufacturer and sponsor submissions is available in the Institute's documents: 'Contributing to a technology appraisal: a guide for manufacturers and sponsors' and 'Single technology appraisal (STA): specification for manufacturer/sponsor submission of evidence' (see appendix C).

Unpublished and part-published evidence

4.2.6 To ensure that all relevant evidence is taken into account, it is important that attempts are made to identify evidence that is not in the public domain. Such evidence includes data from unpublished clinical trials and additional data from trials that have either been published in abstract form only or for which only selected information has been reported. All such information must be critically appraised and sensitivity analysis conducted to examine the effects of its incorporation or exclusion.

Evidence submitted in confidence

- 4.2.7 Under exceptional circumstances, the Institute will accept unpublished evidence under agreement of confidentiality; for example, if the information is commercially sensitive ('commercial in confidence') or if its use might adversely affect future publication rights ('academic in confidence'). To ensure that the appraisal process is as transparent as possible, it is highly desirable that evidence pivotal to the Committee's decisions should be available publicly. Ideally, all the evidence seen by the Appraisal Committee should be available to consultees and commentators. Manufacturers and sponsors (as well as all others submitting evidence) are therefore required to keep 'in confidence' restrictions to a minimum, provide the rationale for submitting material as confidential and permit the Institute to acknowledge that it exists.
- 4.2.8 A checklist on the submission of confidential information must be completed by manufacturers or sponsors when submitting evidence. For information on good practice on the submission of confidential information see details of an agreement between the Institute and the Association of the British Pharmaceutical Industry (see appendix C).

4.3 Patient/carer groups

- 4.3.1 Submissions are invited from all patient/carer groups involved in the appraisal. Patient evidence can include the views, assessments and evaluations of:
- individual patients
 - individual carers
 - groups (such as groups of patients, carers or voluntary organisations that represent patients).

Evidence submitted to NICE

- 4.3.2 Patient evidence refers to any information originating from patients and/or carers that may inform the appraisal of a technology.
- 4.3.3 There are two principal reasons for presenting patient evidence.
- Patients and carers are a unique source of expert information about the personal impact of a disease and its treatment, which can help set the correct scope for the assessment of the evidence and enable the realistic interpretation of the clinical and economic data as the appraisal progresses.
 - Patient evidence can identify limitations in the published research literature; in particular, the failure to capture the true concerns of individual patients related to HRQL over and above measurements using standardised instruments (such as questionnaires) developed using psychometric techniques.
- 4.3.4 For the purpose of informing its technology appraisals, the Institute is looking for a concise and balanced overview that reflects the range of patient and carer perspectives,

including majority views and potentially important views that may be held by only a few patients. The Institute is interested in capturing a range of patient and carer views on, and experiences of, living with the condition, and the impact of a technology on a patient's symptoms and physical, social, psychological and emotional state. It is also interested in what it might be like living without the technology being appraised. Patient evidence is most useful when presented as a synthesis of information, balancing positive and negative views, rather than as a series of individual testimonials.

Dimensions of patient experience

4.3.5 Patient experience of treatment and therapy can be classified under broad headings that reflect different elements of patient experience.

- Experience of disease diagnosis and the types of treatment that are available, including the specific technology being appraised.
- Comparing and managing life with and without the technology.
- Changes and adjustments to patients/carers' lives that are associated with the process of initiating and maintaining treatment with the technology.
- Changes induced by the effects of the technology itself.
- Experience of disease progression with or without treatment.

4.3.6 Within each of the elements above, patient evidence may provide information about patient and carer perspectives on:

- living with the condition
- outcomes that patients value most from the technology
- perceived risks and benefits of the technology
- the difference (both positive and negative) the technology could make to:
 - the physical wellbeing of patients (for example, symptoms, pain, mobility and disability)
 - lifestyles and the choices that matter to patients/carers (for example, impact on daily activities, work, hobbies, social life and relationships)
 - the psychological health of patients/carers (for example, mood, anxiety and distress)
 - the emotional health of patients/carers (for example, wellbeing and impact on relationships)
 - the balance between HRQL and length of life
 - the various treatment choices that matter to patients/carers
 - the impact on the lives of family members and carers.

4.4 Healthcare professionals

- 4.4.1 Submissions are invited from all professional bodies 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.

Evidence submitted to NICE

- 4.4.2 Healthcare professionals provide a view of the technology within the context of current clinical practice. This view is not typically available from the published literature. It is important because it extends the evidence that is 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.
- Patient group variations, in particular, differential baseline risk of the condition and capacity for different subgroups of patients to benefit.
 - The identification of appropriate outcome measures and the appropriate use of surrogate outcome measures.
 - The relative significance of side effects/adverse reactions and the clinical benefits.
 - The particular 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).
 - The treatments that are currently used in routine NHS practice and whether these are different from what is considered to be best practice, particularly when published trials are not recent or do not closely follow UK practice.
 - Information on recent and informal unpublished evidence (any such additional information must be accompanied by sufficient detail to enable a judgement to be made as to whether it meets the same standards as the published evidence and to enable potential sources of bias to be determined).
 - Evidence from registries and nationally coordinated clinical audit.
 - Published clinical guidelines produced by specialist societies accompanied by the evidence hierarchy on which they are based.
 - Evidence from and assessment of current clinical practice, especially the use of the technology and relevant comparators 'off licence'.

- The impact of possible guidance on:
 - the delivery of care
 - the education and training requirements of NHS staff
 - patients who would use the technology.

4.5 Clinical specialists and patient experts

4.5.1 Two groups of experts – clinical specialists and patient experts – are selected by the Committee Chair from nominations provided by (non-manufacturer) consultees and commentators. Clinical specialists and patient experts provide written evidence and attend the Committee meeting to help in the discussion of the technology being appraised.

Format of the evidence

4.5.2 The experts attending the Committee meeting are asked to submit, in advance, a brief written personal view of the current management of the condition, the (expected) role of the technology and its use in the NHS, as well as to provide oral commentary during 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 and patient experts are encouraged to interact fully in the debate with the Committee, including responding to and posing questions. The clinical specialists 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 usefully inform the debate in a variety of ways, including the following.

- Identifying important variations in clinical practice in both the management of the condition in general and specifically in the current use of the technology. This might include:
 - geographical variations
 - the identification of subgroups
 - constraints on local implementation
 - specific issues for implementation that affect patients and carers directly.
- Identifying the requirements, and importance of support, for the implementation of 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 concordance with 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 as perceived by patients.
- Providing views on the nature of any rules, informal or formal, for starting and stopping use of the technology. This might include the requirement for additional analysis:
 - to identify appropriate subgroups of patients for treatment with the technology
 - to assess response to treatment and the potential for discontinuation.
- Responding to queries that arise from:
 - the lead team presentation (the lead team being two Committee members who make a brief presentation to introduce the topic of the appraisal, see section 6.2.2)
 - issues raised by the Chair and other Committee members
 - issues raised by other experts.

5 Clinical and cost effectiveness and NHS impact

This section details what the Institute considers to be appropriate 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, individually, key inputs into the decision-making of the Appraisal Committee. It should also be emphasised that they are interdependent because comprehensive, transparent and reproducible synthesis of all relevant evidence on health effects is needed for high-quality, cost-effectiveness analysis. In describing these methods, the Institute seeks to promote high-quality analysis and to encourage consistency in analytical approaches. However, the Institute acknowledges the need for the flexibility to report studies in other ways to reflect particular circumstances.

5.1 Guiding principles

Clinical and cost effectiveness

5.1.1 To inform the Appraisal Committee's decision-making, the analytical framework within which evidence is synthesised to estimate clinical and cost effectiveness needs to exhibit a number of important features.

- Consistency of submissions is needed to ensure comparability of methods and results between appraisals of different technologies and over time.
- Relevant comparators for the technology being appraised are those routinely used in the NHS, and therapies regarded as best practice when this differs from routine practice.
- All relevant evidence of the best available quality needs to be assembled systematically and synthesised in a transparent and reproducible manner.
- Costs to the NHS and the PSS should be reported.
- Measures of health-related benefits should be comparable to those of other appraisals when possible to promote consistency and to enable them to be compared with benefits from other technologies that may be displaced if the technology under appraisal is adopted.
- The time horizon should be sufficient to reflect important cost and benefit differences between the technologies being compared.
- The uncertainty surrounding the estimates of clinical and cost effectiveness needs to be fully expressed.

Synthesis and modelling

5.1.2 The process of assembling evidence for health technology assessment needs to be systematic. That is, evidence must be identified, quality assessed and, when appropriate, pooled using explicit criteria and justifiable and reproducible methods.

These principles apply to all categories of evidence that are used to estimate clinical and cost effectiveness, evidence for which will typically be drawn from a number of different sources. These sources might include cohort studies for parameters relating to the natural history of the condition, randomised trials for relative treatment effects, and cross-sectional surveys for resource use and costs. When assembling the evidence it is essential to consider how bias can be minimised, especially when non-randomised studies are included.

- 5.1.3 It is essential that clinical and cost effectiveness is considered over an appropriate time horizon to reflect UK practice and patients, and to compare treatment options that represent routine care and/or current best practice for the relevant patient groups. Therefore, it will be necessary to construct an analytical framework within which to synthesise the available evidence so that estimates of clinical and cost effectiveness can be made that are relevant to the clinical decision-making context. This framework will usually require the development of a model using aggregated or individual patient data to estimate parameters. Further details of modelling methods are provided in section 5.7.

Requirements for evidence

- 5.1.4 The requirements for evidence of effectiveness include the quantification of the effect of the technologies on disease progression and patients' HRQL, and the valuation of those effects in a manner that reflects the preferences of the general population.
- 5.1.5 Data are required to quantify the effect of the technologies on use of resources in terms of physical units (for example, days in hospital or volume of drugs used) and valuing those effects in monetary terms using appropriate prices and unit costs.
- 5.1.6 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 subgroups 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 use the best evidence available, be explicit about data limitations and any 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.

Diagnostic technologies

- 5.1.7 Diagnostic technologies can be used in different ways (for example, for disease identification, monitoring of disease progression and treatment, assessment of disease prognosis, or initial screening) and this should be reflected in the evidence submitted to the Institute.

- 5.1.8 Evidence for the appraisal of diagnostic technologies should normally incorporate evidence on the accuracy of the diagnostic technology. It is also important to incorporate the predicted changes in health outcomes and costs as a result of treatment decisions based on the test result.
- 5.1.9 The general principles guiding the assessment of the clinical and cost effectiveness of diagnostic technologies should be the same as for other technologies. However, particular consideration of the methods of analysis may be required, especially in relation to evidence synthesis. Evidence for the effectiveness of diagnostic technologies should include the costs and outcomes for people whose test results lead to an incorrect diagnosis as well as those who are correctly diagnosed.
- 5.1.10 As for other technologies, RCTs have the potential to capture the pathway of care involving diagnostic technologies, but their feasibility and availability may be limited. Other study designs should be assessed on the basis of their fitness for purpose, taking into consideration the aim of the study (for example, to evaluate outcomes, or to evaluate sensitivity and specificity) and the purpose of the diagnostic technology.

Analysis of uncertainty

- 5.1.11 It is essential that the Appraisal Committee is able to fully appreciate the uncertainty and limitations associated with the clinical and cost-effectiveness evidence. Consideration of the uncertainty and limitations of the evidence base is needed to provide a robust evaluation of the expected costs and health effects of a technology, to assess whether existing evidence is sufficient for recommending the routine use of a technology, and to enable consideration of the possible consequences of an uncertain decision for the NHS. This requires the appropriate use of rigorous methods to assess the implications of uncertainty, including the uncertainty around the appropriate structure of the economic model, the choice of sources and analyses to inform the estimates of costs and health effects, and the precision with which these are known. This quantification of decision uncertainty may then feed into subsequent decisions about the need for future research. More detail about dealing with uncertainty in analyses is presented in sections 5.8 and 5.9. More detail on how the Appraisal Committee considers uncertainty in reaching its decisions is presented in section 6.2.

5.2 Framework for estimating clinical and cost effectiveness

Directions on particular aspects of economic evaluation are presented below. When applicable, the position statement of the Institute is set out (in italics), followed by explanation and justification.

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 the Institute	5.2.5 & 5.2.6
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective on costs	NHS and PSS	5.2.7 to 5.2.10
Perspective on outcomes	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 & 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and/or carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years.

The concept of the reference case

- 5.2.1 *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 the most 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 one or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case.*
- 5.2.2 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 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 HRQL. The reference case specifies the methods considered by the Institute to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. 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.
- 5.2.3 There may be important barriers to applying reference-case methods. In these cases, the reasons for a failure to meet the reference case should be clearly specified and justified, and the likely implications should, as far as possible, 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.
- 5.2.4 For consultees making submissions to the Institute, it is important that any data that might provide an input into the reference case are clearly and fully presented. This is particularly important when consultees hold relevant data that are not in the public domain. In this situation, the data provided by the consultees may provide an important input into the consideration of economic analyses submitted to the Institute.

Defining the decision problem

- 5.2.5 *Estimating clinical and cost effectiveness should begin with a clear statement of the decision problem. This will require a definition and justification of the technologies being compared and the relevant patient group(s) to be treated. These characteristics should be consistent with the Institute's scope for the appraisal.*

- 5.2.6 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).

Perspective

- 5.2.7 *For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or, when relevant, other people (principally carers). The perspective adopted on costs should be that of the NHS and PSS. Technologies for which a substantial proportion of the costs (or cost savings) are expected to be incurred outside of the NHS and PSS, or which are associated with significant non-resource effects other than health, should be identified during the scoping stage of an appraisal. In these exceptional circumstances, information on costs to other government bodies, when these are not reflected in HRQL measures, may be reported separately from the reference-case analysis. The intention to include such data will normally be agreed with the Department of Health before finalisation of the remit.*
- 5.2.8 The reference-case perspective on outcomes is consistent with an objective of maximising health gain from available healthcare resources. Some features of healthcare delivery that are often referred to as 'process characteristics' may ultimately have health consequences; for example, the mode of treatment delivery may have health consequences through its impact on concordance with treatment. When there are significant characteristics of healthcare technologies that have a value to people that is independent of any direct effect on health, these should be noted. These characteristics include the convenience with which healthcare is provided and the level of information available for patients.
- 5.2.9 The Institute works in a specific context; in particular, it 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 PSS resources. For these reasons, the reference-case perspective on costs is that of the NHS and PSS.
- 5.2.10 Some health technologies may have a substantial impact on non-health outcomes or costs to other government bodies (for example, treatments to reduce illicit drug misuse may have the effect of reducing drug-related crime). These issues should be identified during the scoping stage of an appraisal. Appraisals that will include consideration of costs incurred outside of the NHS and PSS will always 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) to other government bodies should be presented separately from the reference-case analysis. Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses.

Type of economic evaluation

- 5.2.11 *For the reference case, cost-effectiveness (specifically cost–utility) analysis is the preferred form of economic evaluation. This seeks to establish whether differences in costs between options can be justified in terms of changes in health effects. Health effects should be expressed in terms of QALYs.*
- 5.2.12 The focus on cost-effectiveness analysis is justified by the more extensive use and publication of these methods compared with cost–benefit analysis and the focus of the Institute on maximising health gains from a fixed NHS/PSS budget. Given its widespread use, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and HRQL effects. It is recognised that alternative measures exist (for example, the healthy-year equivalent), but few economic evaluations have used these methods and their strengths and weaknesses are not fully established. If the assumptions underlying QALYs (for example, constant proportional trade-off and additive independence between health states) are considered 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.

Time horizon

- 5.2.13 *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.*
- 5.2.14 Many technologies have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic diseases. In such instances, a lifetime time horizon for clinical and cost effectiveness is appropriate. A lifetime time horizon is also required for any mortality component in order to quantify the implications of any differential survival effect between alternative technologies. For a lifetime time horizon, extrapolation modelling is often necessary. When the impact of treatment beyond the results of the clinical trials is uncertain, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects should be presented (see section 5.7 on modelling). Such assumptions should include the limiting assumption of no further benefit as well as more optimistic assumptions. Analyses that limit the time horizon to periods shorter than the expected impact of treatment are not usually considered to provide the best estimates of costs and benefits.
- 5.2.15 A time horizon shorter than lifetime could be justified if there is no differential mortality effect between options, and the differences in costs and HRQL relate to a relatively short period (for example, in the case of an acute infection). Consideration of the time horizon and the uncertainty around the extrapolation of data beyond the duration of the clinical trials is a critical component of the appraisal.

5.3 Synthesising evidence on outcomes

5.3.1 *The objective of the analysis of clinical effectiveness is the production of an unbiased estimate of the mean clinical effectiveness of the technologies being compared. The analysis of clinical effectiveness should 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.*

Systematic review

- 5.3.2 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 the systematic location, inclusion, appraisal and synthesis of evidence to obtain a reliable and valid overview of the data related to a clearly formulated question¹.
- 5.3.3 Assessments of diagnostic technologies should follow the general principles of systematic reviews as recommended here for other healthcare technologies. However, it is recognised that the specifics of, for example, the meta-analysis of studies of the sensitivity and specificity of diagnostic tests are different from reviews of the effects of therapeutic interventions. This is an area of active methodological research.

Relevant studies

- 5.3.4 Head-to-head RCTs provide the most valid evidence of relative treatment effect. However, such evidence may not always be available and may not be sufficient to quantify baseline health effects. 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

- 5.3.5 A systematic review should be conducted according to a previously prepared protocol to minimise the potential for bias. The protocol specifies the characteristics of the review, thereby reducing the risk of bias and ensuring that the review is reproducible.
- 5.3.6 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 exclusion to allow assessment of the robustness of

¹ The Institute's assessment groups follow general guidelines for conducting systematic reviews published by the NHS Centre for Reviews and Dissemination (Undertaking Systematic Reviews of Research on Effectiveness. York: NHS Centre for Reviews and Dissemination).

the literature search and study selection processes. The validity of the decision process is increased if more than one reviewer assesses all records retrieved by the search strategy. The procedure for resolving disagreements between reviewers should be reported.

Critical appraisal

- 5.3.7 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore 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

- 5.3.8 Many factors can potentially affect the overall estimate of relative treatment effects obtained from a systematic review. Some differences between studies occur by chance. Other common causes of differences in results arise 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, because clinical techniques develop, the year of the study. Such potential treatment effect modifiers need to be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline.

Meta-analysis

- 5.3.9 *Synthesis of outcome data through meta-analysis is appropriate provided there are sufficient relevant and valid data that use measures of outcome that are comparable.*
- 5.3.10 Forest plots are a useful tool for illustrating individual study results. 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.
- 5.3.11 Statistical pooling should be accompanied by an assessment of heterogeneity (that is, any variability in addition to that accounted for by chance). Statistical heterogeneity in results 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, due to patient characteristics, or intervention dose or frequency) may be managed by judicious use of subgroup analyses and meta-regression. When there is doubt about the relevance of a particular trial, a sensitivity analysis should be undertaken that examines the effect of excluding such trials. 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 decision model and the baseline rate in the model is very different to the control event rates of the studies in the meta-analysis.

- 5.3.12 A group of related technologies, whether or not they are formally identified as part of a recognised 'class', might have similar but not necessarily identical effects. When the Institute is appraising a number of related technologies within a single appraisal, analyses based both on a class effect and individual effects should normally be undertaken, unless specified otherwise in the final scope for the appraisal.

Indirect and mixed treatment comparisons

- 5.3.13 *Data from head-to-head RCTs should be presented in the reference-case analysis, if available. When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. This mixed treatment comparison must be fully described and presented as additional to the reference-case analysis (a 'mixed treatment comparison' includes trials that compare the interventions head-to-head and indirectly). When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used (an 'indirect comparison' is a synthesis of data from a network of trials). The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.*
- 5.3.14 The Institute has a preference for data from head-to-head RCTs and these should be presented in the reference-case analysis when available.
- 5.3.15 An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions. A 'mixed treatment comparison' refers to an analysis that includes trials that compare the interventions of interest head-to-head and trials that compare them indirectly. The principles of good practice for systematic reviews and meta-analyses should be carefully followed when conducting mixed and indirect treatment comparisons. The rationale for the identification and selection of the RCTs should be explained, including the rationale for the selection of treatment comparisons that have been included. A clear description of the methods of synthesis is required. The methods and results of the individual trials should be documented. If there is doubt about the relevance of a particular trial, sensitivity analysis should also be presented

in which these trials are excluded. The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported.

- 5.3.16 There may be circumstances in which data from head-to-head RCTs are less than ideal (for example, the sample size may be small or there may be concerns about the external validity). In such cases additional evidence from mixed treatment comparisons can be considered. In these cases, mixed treatment comparisons should be presented separately from the reference-case analysis and a rationale for their inclusion provided. Again, the principles of good practice apply.
- 5.3.17 When multiple technologies are being appraised, data from RCTs (when available) that compare each of the technologies head-to-head should be presented in a series of pairwise comparisons. Consideration may be given to presenting an additional analysis using a mixed treatment comparison framework. In these situations, the Appraisal Committee will consider the results of both analyses with particular reference to the methods of synthesis and the appropriateness of the inclusion or exclusion of studies.
- 5.3.18 There may be situations when data from head-to-head RCTs of the technologies (and/or comparators) are not available. In these circumstances, indirect treatment comparison analyses should be considered.
- 5.3.19 When evidence is combined using indirect or mixed treatment comparison frameworks, trial randomisation must be preserved. A comparison of the results from single treatment arms from different randomised trials is not acceptable unless the data are treated as observational and appropriate steps taken to adjust for possible bias and increased uncertainty.
- 5.3.20 Analyses using indirect or mixed treatment comparison frameworks may include comparator interventions (including placebo) that have not been defined in the scope of the appraisal if they are relevant to the development of the network of evidence. The rationale for the inclusion and exclusion of comparator interventions should be clearly reported. Again, the principles of good practice apply.
- 5.3.21 Evidence from a mixed treatment comparison may be presented in a variety of ways. The network of evidence may be presented in tabular form. It may also be presented diagrammatically as long as the direct and indirect treatment comparisons are clearly identified and the number of trials in each comparison is stated.
- 5.3.22 When sufficient relevant and valid data are not available for including in meta-analyses of head-to-head trials, or mixed or indirect comparisons, the analysis may have to be restricted to a qualitative overview that critically appraises individual studies and presents their results. In these circumstances, the Appraisal Committee will be particularly cautious when reviewing the results of analysis.

5.4 Measuring and valuing health effects

- 5.4.1 *For cost-effectiveness analysis, the value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.*
- 5.4.2 The QALY is a measure of a person's length of life weighted by a valuation of their HRQL over that period. The HRQL 'weighting' usually comprises two elements: the description of changes in HRQL itself and a valuation of that description of HRQL. Information on changes in HRQL as a result of treatment should be reported directly by patients (and directly by carers when the impact of treatment on the carer's health is also important). The valuation of changes in HRQL reported by patients should be based on public preferences elicited using a choice-based method in a representative sample of the UK population.
- 5.4.3 When it is not possible to obtain information on changes in patients' HRQL directly from patients, then data should be obtained from their carer (not from healthcare professionals). The valuation of changes in HRQL measured in patients (or carers) should be based on a valuation of public preferences from a representative sample of the UK population.
- 5.4.4 To quantify the effects of technologies on HRQL, the EQ-5D (a standardised and validated generic instrument) is preferred. Different classification systems produce different utility values; therefore, results from the use of different systems cannot always be compared. Given the comparative nature of the Institute's work and the need for consistency across appraisals, a single classification system, the EQ-5D, is preferred for the measurement and valuation of HRQL.
- 5.4.5 The EQ-5D is a widely used measure of HRQL and has been validated in many different patient populations. The EQ-5D comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. The system has been designed so that people can describe their own HRQL 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 classification system. This set of values can be applied to people's self-reported descriptions of their HRQL to generate health-related utility values.

- 5.4.6 Data using the EQ-5D instrument may not always be available. When EQ-5D data are not available, methods can be used to estimate EQ-5D utility data by mapping (also known as ‘cross-walking’) EQ-5D utility data from other HRQL measures included in the relevant clinical trial(s). This can be done if an adequate mapping function can be demonstrated and validated. Mapping should be based on empirical data and the statistical properties of the mapping function should be clearly described.
- 5.4.7 When EQ-5D utility data are not available, direct valuations of descriptions of health states based on standardised and validated HRQL measures included in the relevant clinical trial(s) may be submitted. In these cases, the valuation of descriptions should use the time trade-off method in a representative sample of the UK population, with ‘full health’ as the upper anchor, to retain methodological consistency with the methods used to value the EQ-5D.
- 5.4.8 Data that have been collected directly in relevant clinical trials using condition-specific, preference-based measures should be presented in a separate economic analysis.
- 5.4.9 The EQ-5D may not be an appropriate measure of health-related utility in all circumstances. If the EQ-5D is considered inappropriate, empirical evidence should be provided on why the properties of the EQ-5D are not suitable for the particular patient population. These properties may include the content validity, construct validity, responsiveness and reliability of EQ-5D. When an alternative measure is preferred, those submitting analysis should provide reasons, supported by empirical data on the properties of the instrument used. They should also indicate any evidence that will help the Committee understand to what extent their choice of instrument has impacted on the valuation of the QALYs gained. If direct valuations of descriptions of health states based on HRQL measures other than the EQ-5D are used, the valuation methods must be comparable to those used for the EQ-5D (see section 5.4.5).
- 5.4.10 It is recognised that the current version of the EQ-5D has not been designed for use in children. When necessary, consideration should be given to alternative standardised and validated preference-based measures of HRQL, such as the Health Utility Index 2 (HUI 2), that have been designed specifically for use in children.
- 5.4.11 When health-related utility values have been 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. Health-related utility data that do not meet the criteria for the reference case should be accompanied by a carefully detailed account of the methods used to generate the data and a consideration of how these methods may affect the values. When more than one plausible set of health-related utility data are available, a sensitivity analysis should be undertaken.

5.5 Evidence on resource use and costs

NHS and PSS costs

- 5.5.1 *For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.*
- 5.5.2 When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the reference-case analysis. Sensitivity analysis should assess the implications of variations from this price. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and can be consistently available across the NHS, and if the period for which the specified price is available is guaranteed. In these circumstances, advice will be taken from institutions such as the NHS Purchasing and Supply Agency (PASA) or Welsh Health Supplies. The review date for the appraisal will be informed by the period of time over which any such agreements can be guaranteed.
- 5.5.3 In the absence of a published list price and price agreed by a national institution (as may be the case for some diagnostic technologies), the price submitted by the manufacturer may be used, provided that it is nationally and publicly available.
- 5.5.4 Given the perspective in the reference case, it is appropriate for the financial costs relevant to the NHS/PSS to be used as the basis of costing, though these may not always reflect the full social opportunity cost of a given resource. As far as possible, estimates of unit costs and prices for particular resources should be used consistently across appraisals. A first point of reference in identifying such costs and prices should be any current official listing published by the Department of Health and/or the Welsh Assembly Government.
- 5.5.5 The methods of identification of resource use and unit cost data are not as well defined as for evidence for the identification of clinical effectiveness. National data based on healthcare resource groups (HRGs), such as the Payment by Results tariff, are a valuable source of information and should be considered for use when they are appropriate and available. Data based on HRGs may not be appropriate in all circumstances (for example, when the definition of the HRG is broad or the mean cost probably does not reflect resource use in relation to the 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.

- 5.5.6 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.
- 5.5.7 If introduction of the technology requires additional infrastructure to be put in place, consideration should be given to including such costs in the analysis.
- 5.5.8 When a group of related technologies are 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 highest and lowest cost estimates should be presented as a minimum.
- 5.5.9 Value added tax (VAT) should be excluded from all economic evaluations but included in budget impact calculations at the appropriate rate (currently 17.5%) when the resources in question are liable for this tax.

Non-NHS and non-PSS costs

- 5.5.10 Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been 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/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).
- 5.5.11 Costs borne by patients may be included when they are reimbursed by the NHS or PSS. When the rate of reimbursement varies between patients or geographical regions, such costs should be averaged across all patients. Productivity costs and costs borne by patients that are not reimbursed by the NHS and PSS should be excluded.

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, an annual discount rate of 3.5% should be used for both costs and benefits. When results are potentially sensitive to the discount rate used, consideration should be given to sensitivity analyses that use differential rates for costs and outcomes and/or that vary the rate between 0% and 6%.*

5.6.2 The need to discount to a present value is widely accepted in economic evaluation, although the specific rate is variable across jurisdictions and over time. The Institute considers it appropriate to discount costs and health effects at the same rate. The annual rate of 3.5%, based on the recommendations of the UK Treasury for the discounting of costs, should be applied to both costs and health effects.

5.7 Modelling methods

5.7.1 *The models used to synthesise available evidence to generate estimates of clinical and cost effectiveness for the Institute's needs should follow accepted guidelines. 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 As described in section 5.1.3, 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 where:

- all the relevant evidence is not contained in a single trial
- patients participating in trials do not match the typical patients likely to use the technology within the NHS
- intermediate outcomes measures are used rather than effect on HRQL and survival
- relevant comparators have not been used or trials do not include evidence on relevant subgroups
- the long-term costs and benefits of the technologies extend beyond trial follow-up.

5.7.3 Providing an all-embracing definition of what constitutes a high-quality model is not possible, but some guidelines are available. In general, all 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. This is particularly important to avoid outlying values being selected that create a bias analogous to the selection bias produced when using one or two clinical trials from a selection of several relevant trials. Estimates of treatment effect should be based on the results of the systematic review. Modelling is often required to extrapolate costs and health benefits over an extended time horizon. Assumptions used to extrapolate treatment effects should have clinical validity, be reported transparently and be clearly justified. Alternative scenarios should be considered to compare the implications of different assumptions around extrapolation for the results. For example, for the 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.

- 5.7.4 Trial data may not be sufficient to quantify baseline risk of some health outcomes or events for the population of interest. Quantifying the baseline risk of health outcomes and how the disease would naturally progress with the comparator intervention can be a useful step when estimating absolute health outcomes in the economic analysis. Relative treatment effects observed in randomised trials may then be applied to data on the baseline risk of health outcomes for the populations or subgroups of interest. The methods used to identify and critically appraise sources of data for these estimates should be stated and justified.
- 5.7.5 If the use of the technology is conditional on the outcome of a diagnostic test, the accuracy of the test and associated costs should be incorporated into the assessments of clinical and cost effectiveness.
- 5.7.6 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. This should include presenting 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.

5.8 Characterisation of potential bias and uncertainty

- 5.8.1 *It is important to identify potential selection bias in the inputs to the model and 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 It is recognised that it is necessary to make assumptions when constructing a model. The potential bias and consequential uncertainty is sometimes referred to as 'structural uncertainty'. Examples of structural uncertainty may include the categorisation of different states of health and the representation of different pathways of care. 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 A second type of potential bias arises from the selective use of data sources to provide values for the key parameters, such as different costs and utilities, estimates of relative effectiveness and their longevity. The implications of different estimates of key parameters must be reflected in sensitivity analyses (for example, through the inclusion of alternative scenarios). Inputs must be fully justified and uncertainty explored by sensitivity analysis using alternative input values.

- 5.8.4 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.
- 5.8.5 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.
- 5.8.6 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.
- 5.8.7 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 express uncertainty.

5.9 Presentation of data and results

Presenting data

- 5.9.1 *All parameters used to estimate clinical and cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, 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.*

Presenting expected cost-effectiveness results

- 5.9.2 *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.*
- 5.9.3 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. Consideration should also be given to presenting separately the costs and QALYs associated with different stages of the disease. Standard decision rules should be followed when combining costs and QALYs. These should reflect any situation in which dominance or extended dominance exists. 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. When models consist of non-linear combinations of parameters, probabilistic sensitivity analysis should be used to generate mean costs and QALYs. In such models, setting parameters to their mean values will not provide the correct estimates of mean costs and QALYs.

Dealing with uncertainty around structural assumptions in cost-effectiveness analysis

- 5.9.4 *Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.*
- 5.9.5 An important element of uncertainty around cost-effectiveness results arises from the uncertainty in the structure of the decision model. The analysis of the uncertainty in all parameters for decision uncertainty assumes that factors such as a model's structure and data inputs are considered to be appropriate. However, these characteristics of the model are also subject to uncertainty, which should be identified and formally examined using sensitivity analysis.
- 5.9.6 Common examples of when this type of sensitivity 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).

- 5.9.7 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.

Dealing with uncertainty around the selection of data sources in cost-effectiveness analysis

- 5.9.8 *The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.*

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

- when alternative sets of plausible data on the health-related utility associated with the disease/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 mixed treatment comparison.

Dealing with parameter uncertainty in cost-effectiveness analysis

- 5.9.10 *All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.*
- 5.9.11 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 two 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 thresholds 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 two alternatives.
- 5.9.12 The use of univariate and best/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 complete characterisation of the parameter uncertainty associated with all input parameters. Within a probabilistic analysis the contribution of the uncertainty in each parameter to overall decision uncertainty and its consequences can be achieved using expected-value-of-information methods.

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 the provision of 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 a priori expectation of differential clinical or cost effectiveness due to 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 the expectation of 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, but 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 one 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 are often based on differences in relative treatment effects (through the analysis of interactions between the effectiveness of the technology and patient characteristics). The possibility of differences emerging by chance, particularly when numerous subgroups are reported, should be explored.
- 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. 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, the representativeness of the available evidence and relevance 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 The Appraisal Committee will pay particular attention to its obligations with respect to legislation on human rights, discrimination and equality when considering subgroups.
- 5.10.11 Types of subgroups that are not considered relevant are those based solely on the following factors.
- Individual utilities for health states and patient preference.
 - 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 within 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 consideration for continuation rules include:

- the robustness and plausibility of the endpoint 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
- issues with respect to withdrawal of treatment from non-responders and other equity considerations.

5.11 Identifying future research needs from the evidence

5.11.1 *Candidate topics for future research can be identified on the basis of evidence gaps identified by the systematic review and cost-effectiveness analysis. These may be best prioritised by considering the value of additional information in reducing the degree of decision uncertainty.*

5.11.2 Part of the analysis of uncertainty is to identify the parameter and structural uncertainties to which the decision is most sensitive. This information can then be fed into decisions about future research priorities. As part of cost-effectiveness analysis, formal value-of-information methods are available that use probabilistic sensitivity analysis to establish the value for money of additional research to reduce parameter uncertainty and how that research should be focused.

5.11.3 Recommendations for further research are prioritised using processes and criteria agreed by the Institute's Research and Development Advisory Committee. The Institute promotes research recommendations to organisations that fund research, such as the NHS Research and Development Programme.

5.12 Reflecting equity considerations in cost-effectiveness analysis

5.12.1 *In the reference case, an additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit.*

5.12.2 The estimation of QALYs, as defined in the reference case, implies a particular position regarding the comparison of health gained between individuals. Therefore, an additional QALY is of equal value regardless of other characteristics of the individuals, such as their socio-demographic details, or their pre- or post-treatment level of health. There are

several unresolved methodological issues concerning how and in what circumstances to apply additional weights to QALY calculations. Until such issues are resolved, the use of differential QALY weights is not recommended as part of the reference case.

5.13 Impact on the NHS

Implementation of NICE guidance

- 5.13.1 *Information on the net impact of the implementation of the health technology on the NHS (and PSS, when appropriate) is required.*
- 5.13.2 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/uptake and population health impact

- 5.13.3 Evidence-based estimates of the current baseline treatment rates and expected appropriate implementation/uptake/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

- 5.13.4 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 PSS 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/facilities (for example, hospital beds, clinic sessions, diagnostic services and residential home places).
- 5.13.5 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

- 5.13.6 Estimates of net NHS (and PSS, 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, PSS, 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.
- 5.13.7 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.
- 5.13.8 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, 'Developing costing tools: methods guide' (see appendix C).

6 The appraisal of the evidence and 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, patient and carer organisations, relevant academic disciplines, and pharmaceutical and medical devices industries. 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 to recommend against the use of treatments if the benefits to patients are unproven or 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 of NICE's Establishment Orders and legislation on human rights, discrimination and equality. In undertaking appraisals of healthcare technologies, the Institute is expected to take into account Directions from the Secretary of State for Health (see appendix C) as follows.
- The broad balance of clinical benefits and costs.
 - The degree of clinical need of patients with the condition or disease under consideration.
 - Any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of the Institute by the Secretary of State and any guidance issued by the Secretary of State.
 - The potential for long-term benefits to the NHS of innovation.
- 6.1.4 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. Guidelines that describe the social value judgements that should, generally, be considered by the Appraisal Committee are provided in the Institute's document, 'Social value judgements: principles for the development of NICE guidance' (see appendix C).
- 6.1.5 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, and that the contributions of clinical specialists, 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.

- 6.1.6 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.
 - 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 (ACD) or final appraisal determination (FAD) to enable the reader to understand what evidence the Appraisal Committee considered and, if appropriate, who provided that evidence.
- 6.1.7 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.
- 6.1.8 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. It can, however, consider unlicensed comparator technologies if these are used regularly in the NHS. Long-standing treatments often lack a sponsor to support the licensing process. In exceptional cases, the Appraisal Committee may make recommendations outside of the marketing authorisation if directed to do so by the Department of Health. The availability of evidence relating to such 'off licence' use of the technology 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. For technologies that are not subject to the licensing procedures (for example, medical devices), evidence of acceptable quality of manufacturing processes, such as the CE mark, will be required.
- 6.1.9 The Committee is not able to make recommendations on the pricing of technologies to the NHS.

6.1.10 The remainder of this guide describes the sequence of the discussions that take place at the Appraisal Committee's meetings to develop guidance and the ways in which the various inputs from consultees and commentators are used to inform the Appraisal Committee's conclusions.

6.2 Appraisal Committee meetings

Introduction

6.2.1 In reaching its decision, the Appraisal Committee will derive its recommendations directly from the evidence base, together with statements from consultees and commentators, and the views expressed by clinical specialists 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 view of this evidence. It describes the Appraisal Committee's thoughts on each aspect of the guidance. It highlights the 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 of the written and oral inputs that have informed their decision.

6.2.2 At the first Appraisal Committee meeting, normally two members of the Appraisal Committee (the 'lead team'), or occasionally members of the NICE technical team, make a brief presentation to the other members to introduce the topic of the appraisal. The presentation usually includes:

- an overview of the condition for which the technology is indicated, including the epidemiology and pathophysiology relevant to the Appraisal Committee's considerations
- an overview of the technology and its place in the pathway of care for the condition and relevant alternative treatments/comparators
- an overview of the evidence of clinical effectiveness
- an overview of the evidence of cost effectiveness and, when appropriate, clarification and critique of the economic models received
- identification of issues of importance for consideration by the Appraisal Committee to facilitate the discussion.

The presentation does not pre-empt the Committee's debate or the formulation of the guidance.

6.2.3 If there are any outstanding issues following the meetings, the Committee, through the Institute, may seek clarification from the consultees, clinical and patient experts, and the independent assessment group.

The role of the clinical specialists and patient experts

- 6.2.4 The invited clinical specialists and patient experts are present for the discussions of the Committee at its first meeting and are encouraged to interact fully in the debate with the Committee, including both responding to and posing questions. They are not required to make additional presentations to the Committee and are asked to withdraw for the final part of the meeting when the Committee discusses the content of the guidance.

The role of the independent assessment groups

- 6.2.5 The independent assessment groups are known as the Assessment Group (for MTAs) or the Evidence Review Group (for STAs). Members of the independent assessment group are invited to attend all the meetings of the Appraisal Committee to assist them in clarifying aspects of the evidence base covered in their written documentation. The independent assessment group is not involved in the decision-making or drafting of the guidance and has no direct input into this process.

Functions of the Chair

- 6.2.6 The functions of the Chair of the Appraisal Committee are to:

- keep the Committee's discussions within the remit and scope of the appraisal topic
- highlight general considerations associated with the appraisal and identify key issues raised in the lead team presentation and during the discussion with the experts
- guide the Committee in discussion regarding the importance of issues raised.

In addition, the Chair ensures that the Committee considers:

- the relevant factors listed in the Directions of the Secretary of State for Health
- the opportunity costs associated with the use of the technology (that is, implications for healthcare programmes for other patient groups that may be displaced)
- the relevant factors listed in the Institute's guidance on social value judgements
- the views expressed by the clinical specialists and patient experts
- the relevant legislation on human rights, discrimination and equality
- the uncertainties in the evidence base.

Appraising clinical effectiveness

- 6.2.7 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 consideration of only certain categories of evidence. This requires the Appraisal Committee to consider all of the evidence it deems relevant, from RCTs to observational studies and any qualitative evidence related to the experiences of patients, carers and clinical experts 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

scientific and clinical judgement when deciding whether particular forms of evidence are fit for purpose in answering specific questions.

- 6.2.8 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.
- 6.2.9 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 assessment 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 greater risk of adverse events in different groups of patients.
 - The risks (adverse effects) and benefits of 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 available.
- 6.2.10 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.
- 6.2.11 When evidence of effectiveness is either absent or weak, the Appraisal Committee may recommend that particular interventions are used within the NHS only in the context of research. Factors that will be considered before issuing such recommendations include the following.
- The intervention should have a reasonable prospect of providing benefits to patients in a cost-effective way.
 - The research can realistically be set up, is already planned, or is already recruiting patients.
 - There is a real prospect that the research will inform future NICE guidance.
 - The broad balance of the benefits and costs of conducting the research are favourable.

6.2.12 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.

Appraising 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 more 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/technologies currently being 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 The Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the cost-effectiveness evidence.
- 6.2.17 When the evidence on key parameters used to estimate cost effectiveness (for example, clinical effectiveness and effect on HRQL) 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 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. Taking this into account, 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.
- 6.2.18 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.

- 6.2.19 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 influences the effectiveness and/or cost effectiveness of the intervention.
- 6.2.20 The Committee will take into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: age; sex/gender or sexual orientation; people's income, social class or position in life; race or ethnicity; disability; and conditions that are or may be, in whole or in part, self-inflicted or are associated with social stigma.
- 6.2.21 The Appraisal Committee does not use a precise ICER threshold 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 threshold to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies. The Institute does not have complete information about the costs and QALYs from all competing healthcare programmes in order to define a precise threshold. However, the Institute considers that it is most appropriate to use a threshold range as described in sections 6.2.22 to 6.2.25. 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 threshold range, 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.
- 6.2.22 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.

6.2.23 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 HRQL 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 QALY measure.

6.2.24 As the ICER of an intervention increases in the £20,000 to £30,000 range, 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 above.

6.2.25 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 above.

6.2.26 The Institute has a strong preference for expressing health gains in terms of QALYs. In most circumstances, when the health gain is expressed in terms of life-years gained, the range of most plausible 'life-years gained' ICERs that are acceptable will be substantially lower than those described above. In these circumstances, the Committee will impute a plausible QALY value from the estimated life-years gained. The exact adjustment that the Committee makes will take account of the differences between QALYs and life-years gained. It will be guided by reference to the population norms for HRQL for the affected population, but will generally be lower than this for a sick population.

Review of consultation comments

6.2.27 The Appraisal Committee's provisional recommendations are released as an ACD 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.

6.2.28 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 ACD
- 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 need to suggest that the Institute should consider recommending varying their advice to the Department of Health regarding the application of implementation criteria agreed with the Department of Health
- the need to reconsider the timing of the appraisal review, such as the timing and potential impact of research in progress (for example, new RCTs).

6.2.29 The Appraisal Committee considers the comments and, when appropriate, amends its recommendations exercising its own 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 view of this evidence and the 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 on areas of conflict.

6.2.30 The final recommendations undergo a number of drafting stages with the Appraisal Committee before a FAD is agreed.

6.2.31 The final review of the FAD and approval for distribution for appeal is the responsibility of the Institute's Guidance Executive. During this phase, the Committee Chair is consulted to ensure that the Committee's deliberations are fully reflected in the FAD that is sent out for consultation. Subject to any appeal, the FAD will form the Institute's guidance on the use of the appraised technology.

6.2.32 If an appeal is held and some or all of the appellants' points have been upheld, the Committee may need to meet again to review the appraisal. Under these circumstances, the Committee may require further evidence from consultees, clinical specialists, patient experts and the independent assessment group.

Appendix A: NICE project team and Steering Group

Project team

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Dr Louise Longworth

Technical Adviser, Centre for Health Technology Evaluation, NICE

Kim Turner

Project Manager, Centre for Health Technology Evaluation, NICE

Steering Group

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Professor David Barnett

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Professor Tony Culyer

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Professor Peter Littlejohns

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The following attended one or more meeting of the working party on behalf
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Dr Elisabeth George
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Appendix C: Bibliography

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

- [Guide to the technology appraisal process](#) (reference N0514)
- [Guide to the single technology appraisal \(STA\) process](#) (reference N1117)
- [Contributing to a technology appraisal: a guide for patient/carer groups](#) (reference N0516)
- [Contributing to a technology appraisal: a guide for healthcare professional groups](#) (reference N0517)
- [Contributing to a technology appraisal: a guide for manufacturers and sponsors](#) (reference N0518)
- [Contributing to a technology appraisal: a guide for NHS organisations](#) (reference N0519)
- [Technology appraisal process: guidance for appellants](#) (reference N0520)
- [Single technology appraisal \(STA\): specification for manufacturer/sponsor submission of evidence](#)
- [Social value judgements: principles for the development of NICE guidance](#)
- [How to put NICE guidance into practice](#) (reference N0943)
- [Developing costing tools: methods guide](#)
- [NICE's equality scheme and action plan 2007–2010](#)
- [Agreement between the Association of the British Pharmaceutical Industry \(ABPI\) and the National Institute for Clinical Excellence \(NICE\) on guidelines for the release of company data into the public domain during a health technology appraisal](#)
- [Directions and Consolidating Directions to the National Institute for Health and Clinical Excellence 2005](#) (from the Secretary of State for Health)

Appendix D: Glossary

Absolute risk The probability of an event or outcome occurring (for example, an adverse reaction to the drug being tested) in the people in the study group.

Abstract 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; may also be referred to as 'compliance'.

Adverse event An undesirable effect of a health technology.

Aggregated data Data presented as the sum of all the resources and costs involved.

Appraisal Committee Standing advisory committee of the Institute. Members include people who work in the NHS, patient/carer organisations, relevant academic disciplines and pharmaceutical and medical devices 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 protocol Written instructions for the conduct and analysis that forms the basis of the assessment report produced by the Assessment Group.

Assessment report A critical review of the clinical and cost effectiveness of a health technology/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 study participants, caregivers, researchers and outcome assessors are kept unaware about the interventions that people have been allocated to in a study.

Case-control study Comparative observational study in which the investigator selects people who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

CE mark Abbreviation of 'Conformité Européene'. The marking 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 freely circulate their products within the European marketplace.

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

Class (of drugs in NICE technology appraisal) A group of drugs with the same or similar mechanism of action. These drugs may or may not have the same basic chemical structure. However, there may be differences between drugs within a class, for example, in side-effect profile.

Clinical audit A quality improvement process that seeks to improve patient care and outcomes through a structured or detailed review of care against explicit criteria and the implementation of change.

Clinical effectiveness The extent to which an intervention produces an overall health benefit, taking into account beneficial and adverse effects, in routine clinical practice.

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 on the use of the technology and/or other treatments for the condition. They provide a view of the technology within current clinical practice, with insights not typically available in the published literature.

Cohort study A retrospective or prospective follow-up study. People included 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 exposed or not.

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, NHS Quality Improvement Scotland, the relevant National Collaborating Centre, other related research groups and other groups when appropriate.

Commercial in confidence See 'In confidence material'.

Comorbidity Coexistence of a disease, or more than one disease, in a person 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 with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals 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 accepts an invitation to participate 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 representing patients/carers and professionals can nominate clinical specialists 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 using, for example, the willingness-to-pay approach.

Cost-effectiveness acceptability curves A graph that plots a range of possible cost-effectiveness thresholds on the horizontal axis against the probability (chance) that the intervention will be cost effective 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 of interest and the comparator. The vertical axis represents the difference in cost.

Data synthesis Combining evidence from different sources.

Decision problem A clear description of the interventions, patient populations, outcome measures and perspective adopted in a health technology evaluation, which relates 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 active when studied under controlled research conditions.

Endpoint In a research study, an event or outcome that can be measured and constitutes one 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.

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 provided 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.

Exclusion criteria (clinical study) Criteria that define who is not eligible to participate in a clinical study.

Experimental study (analytic study) A study with an explicit control group that allows testing of a hypothesis.

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 two other 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.

General-population-generated utility weightings Weightings for utilities that are derived from studies in the general population. See also 'Utility'.

Health-related quality of life (HRQL) A combination of a person's physical, mental and social wellbeing; not merely the absence of disease.

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 items of sophisticated equipment.

Healthcare Resource Groups (HRGs) These groups provide a way of categorising the treatment of patients to monitor and evaluate the use of resources. Each HRG refers to a group of health-related activities or services that have been judged to consume a similar level of resources.

Healthy-year equivalent A measure of health-related quality of life (HRQL) used in cost–utility analysis. It is the hypothetical number of years spent in perfect health which could be considered equivalent to the actual number of years spent in a defined imperfect health state. It differs from a quality-adjusted life year (QALY) because not only is it based on the person's preferences for the duration of their life, but also on the person's preferences for their health state.

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.

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

Inclusion criteria (literature review) Explicit criteria used to decide which studies should be considered as potential sources of evidence.

In confidence material Information (for example, the findings of a research project) defined as 'confidential' because its public disclosure could have an impact on the commercial interests of a particular company or the academic interests of a research or professional organisation.

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 defined 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 an RCT 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 the context of 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 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.

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 two 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 in head-to-head trials).

Multiple technology appraisal (MTA) The name given to the NICE process in which appraisals of more than one technology, or a single technology for more than one indication, are conducted.

National Coordinating Centre for Health Technology Assessment (NCCHTA)

Part of the Wessex Institute for Health Research and Development at the University of Southampton. The NCCHTA coordinates the Health Technology Assessment (HTA) programme on behalf of the NHS Research and Development programme. The aim of the HTA programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who make policy for, use, manage and work in the NHS.

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 cost-effectiveness threshold value). The net monetary benefit is the difference between the monetary value of total expected QALYs (expected QALYs multiplied by the threshold value) and total expected costs.

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

Observational study 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 that may stem from exposure to a preventive or therapeutic intervention. Outcome measures can be either intermediate or final endpoints. 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 three treatments (A, B and C) being compared, they could be compared in a single combined analysis (that is, A versus B versus C) or as a series of pairwise comparisons (that is A versus B, A versus C, and B versus 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 population 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 experience of using the technology either personally or as part of a representative group. They provide an individual 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/carer views.

Patient-level data Information on the outcome and cost of treatment collected for individual patients.

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).

Product licence An authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to market a medicinal product.

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 have the advantage of incorporating 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 the heterogeneity between studies. The simplest models allow for a single random effect term; more complicated models can allow for different levels of heterogeneity.

Randomisation Allocation of participants in a research study to two 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 thus 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 one 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 one indicates that the intervention is better than the comparator.

Relative treatment effect The effect of a treatment relative to another treatment or control, such as measured by a 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 each 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).

Sensitivity (of a test) The proportion of individuals classified as positive by the gold (or reference) standard, who are correctly identified by the study test.

Single technology appraisal (STA) The name given to the NICE process in which appraisals of single technologies for one indication are conducted.

Specificity (of a test) The proportion of individuals classified as negative by the gold (or reference) standard, who are correctly identified by the study test.

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 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 relating to use of a technology to formulate guidance on its most efficient use.

Test accuracy How good a test is at determining whether a person truly does or does not have a target condition. Accuracy can be expressed in a number of ways but most commonly as sensitivity and specificity.

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 two 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 is available for a specific condition.

Treatment sequence 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.

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