

Guide to the Methods of Technology Appraisal

April 2004

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About this document

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.

The documents in the set, which will be published during 2004, are:

- *Guide to the Technology Appraisal Process* (reference N0514)
- *Guide to the Methods of Technology Appraisal* (reference N0515)
- *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)

These documents are available from the NICE website (www.nice.org.uk) or from the NHS Response Line (telephone 0870 1555 455 and quote the appropriate reference number).

Note: this set of documents replaces the Technology Appraisals Process Series published in June 2001.

Nothing in this document shall restrict any disclosure of information by the Institute that is required by law (including in particular but without limitation the Freedom of Information Act 2000).

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Foreword

The National Institute for Clinical Excellence (NICE, or the Institute) provides guidance to the NHS in England and Wales on the use of selected new and established technologies. The Institute undertakes appraisals of health technologies at the request of the Department of Health and the Welsh Assembly Government. The appraisal by the Institute encompasses the clinical and cost effectiveness of a technology in the context of its use in the NHS as a whole.

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 all aspects of appraisal methodology and is a guide for all organisations considering submitting evidence to the Technology Appraisal Programme of the Institute. It has been developed through a process of literature review, workshop discussion and review.

This document indicates the kind of data and analysis that the Appraisal Committee will find most helpful in accomplishing its task. Substantive departures from this document should therefore not be made without the previous agreement of the Appraisal Programme Director.

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 for the methods informing the Appraisal Committee's decision-making to adopt a consistent approach regarding cost-effectiveness analysis. 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 that is presently undeveloped or where there is no agreed standard would therefore be considered, if necessary, as additions to the reference case. Work of this sort should be agreed with the Appraisal Programme Director.

Before making submissions for an individual appraisal, the perspective and presentation of evidence may be discussed with the Appraisal Programme Director and/or the Technical Lead. However, there are limits to the extent to which the Institute's staff can engage in discussions about submissions. The Scoping Workshop at the beginning of the appraisal process provides an opportunity to discuss methods.

The Institute sponsors research into the methods of technology appraisal and welcomes suggestions to the Appraisal Programme Director 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. We suggest 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.

Acknowledgements

The Institute is very grateful to the members of the Methodology Working Party (see Appendix A) for their contribution to the development of this document. It is also very grateful to the members of the four Task Groups (see Appendix B) who took part in a series of meetings to discuss, prepare and edit the text that forms the basis of this document.

List of abbreviations

HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
NCCHTA	National Coordinating Centre for Health Technology Assessment
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial

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 assessment and appraisal within the context of the NICE appraisal process. The aims are to introduce the general methodological concepts underlying each stage of the appraisal process and to describe what is required of participants considering the submission of evidence to NICE.
- 1.1.2 Accompanying this methodological guidance document is a companion document describing the Institute's appraisal process, *Guide to the Technology Appraisal Process*.
- 1.1.3 The Institute's appraisal process relies on information and input from a number of sources, including the Assessment Group (see section 4.1.1), manufacturers and sponsors, healthcare professionals and patient/carer representatives. This document is the foundation for the following detailed documents addressing issues of relevance to individual groups participating in an appraisal.
- ▶ *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*
 - ▶ *Technology Appraisal Process: Guidance for Appellants*
- 1.1.4 These documents will be published during 2004 and will be available on the Institute's website (www.nice.org.uk) and from the NHS Response Line (see the inside front cover for details).
- 1.1.5 The Institute is aware that many who are not expert in technology appraisal will read this document. A basic glossary of terms has therefore been included (Appendix C, page 40).
- 1.1.6 The preappraisal and appraisal processes are summarised in Figures 1–3 (pages 3 to 6).

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 and the Welsh Assembly Government. 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 of the Secretary of State for Health and the Welsh Assembly Government: that is, to appraise the health benefits and the costs of those technologies notified by the Secretary of State for Health and the Welsh Assembly Government and to make recommendations to the NHS in England and Wales.
- 1.2.3 The Department of Health and the Welsh Assembly Government select technologies for appraisal based on one or more of the following criteria:¹
- ▶ 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?

¹ Further information about the process for selecting technologies for referral to the Institute can be obtained in England from the Head of the NICE Liaison Unit, Department of Health, Quarry House, Quarry Hill, Leeds, LS2 7UE (www.doh.gov.uk/nice/index.htm) and in Wales from Head of Performance, Quality and Regulation Division 2, NHS Quality Division, Welsh Assembly Government, Cathays Park, Cardiff, CF1 3NQ.

- 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 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.

1.3.1 Scoping

- 1.3.1.1 During the scoping process, the Institute determines the specific questions to be addressed for each technology appraisal so as to define the issues of interest (for example, population, comparators) as clearly as possible and the questions that should be addressed by the Appraisals Committee when considering the clinical and cost effectiveness of the technology. Consultees and commentators are consulted during the scoping process. The Institute revises the scope in response to comments received and develops a final scoping document that describes the boundaries of the appraisal and the parameters that will be investigated. The scope is further developed into a protocol for the technology assessment. The scoping process is described in detail in chapter 2.

1.3.2 Assessment

- 1.3.2.1 The assessment process (see also chapter 3) is a systematic and independent evaluation of the relevant evidence available on the technology; the aim is to produce an estimate, including uncertainty, of its 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. The assessment process requires an understanding of the appraisal question and the context within which it is to be addressed, covering, for example, currently available care, any alternative technologies, and appropriate methods of comparing the technologies. This 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 Appraisal

- 1.3.3.1 The appraisal process (see also chapter 6) is a consideration of the outputs of the assessment process within the context of additional information supplied by consultees, commentators, clinical specialists and patient experts. The Appraisal Committee considers the evidence available in the Assessment Report and elsewhere. The Committee then formulates an appraisal decision, applying judgements on the importance of a range of factors that differ from appraisal to appraisal. While 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 Interpreting clinical and cost effectiveness

- 1.4.1 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 alternatives. They can also be considered cost effective if their health benefits are greater than their opportunity cost 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 directly benefit from the technology of interest.

Figure 1 Steps in developing the scope.

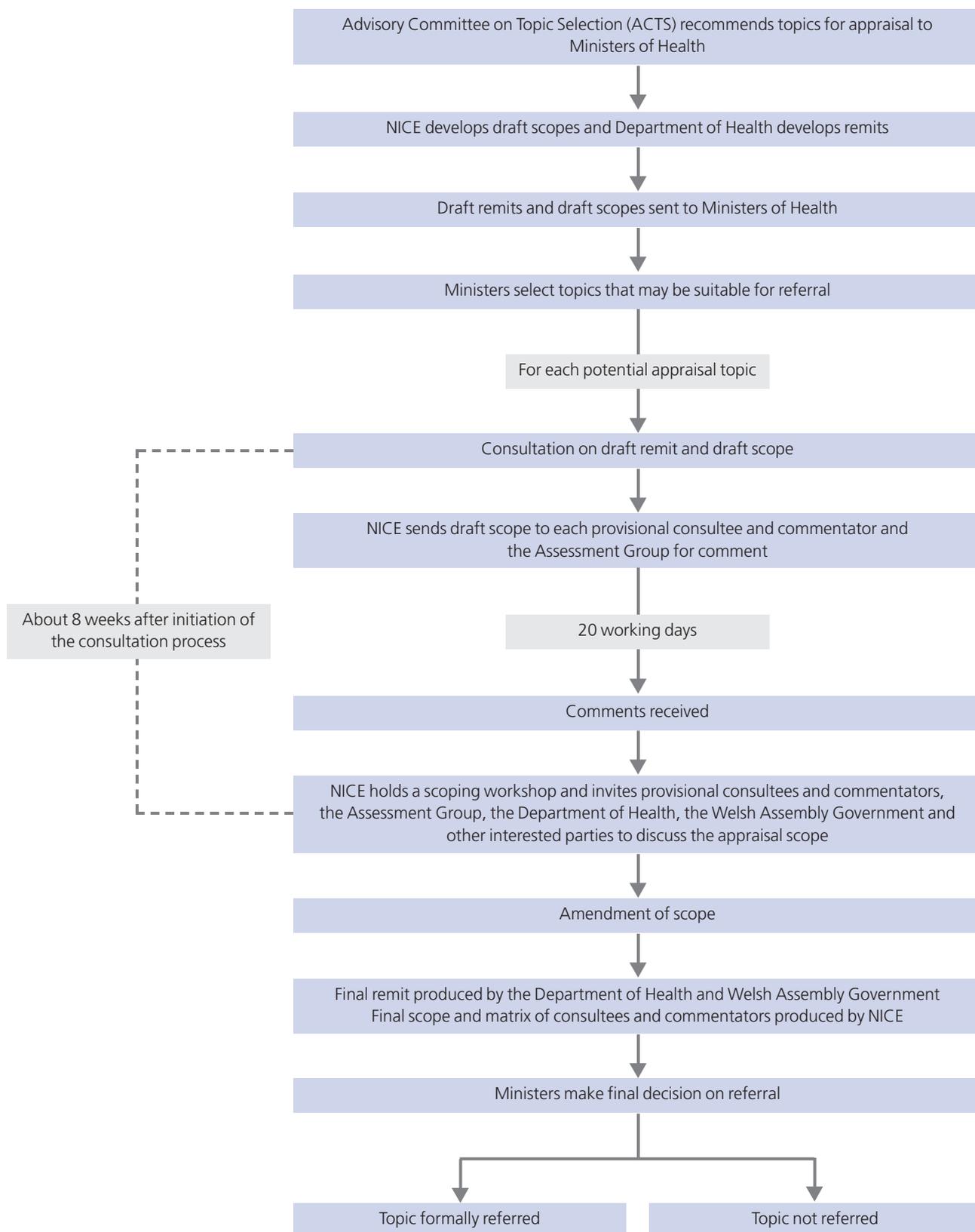
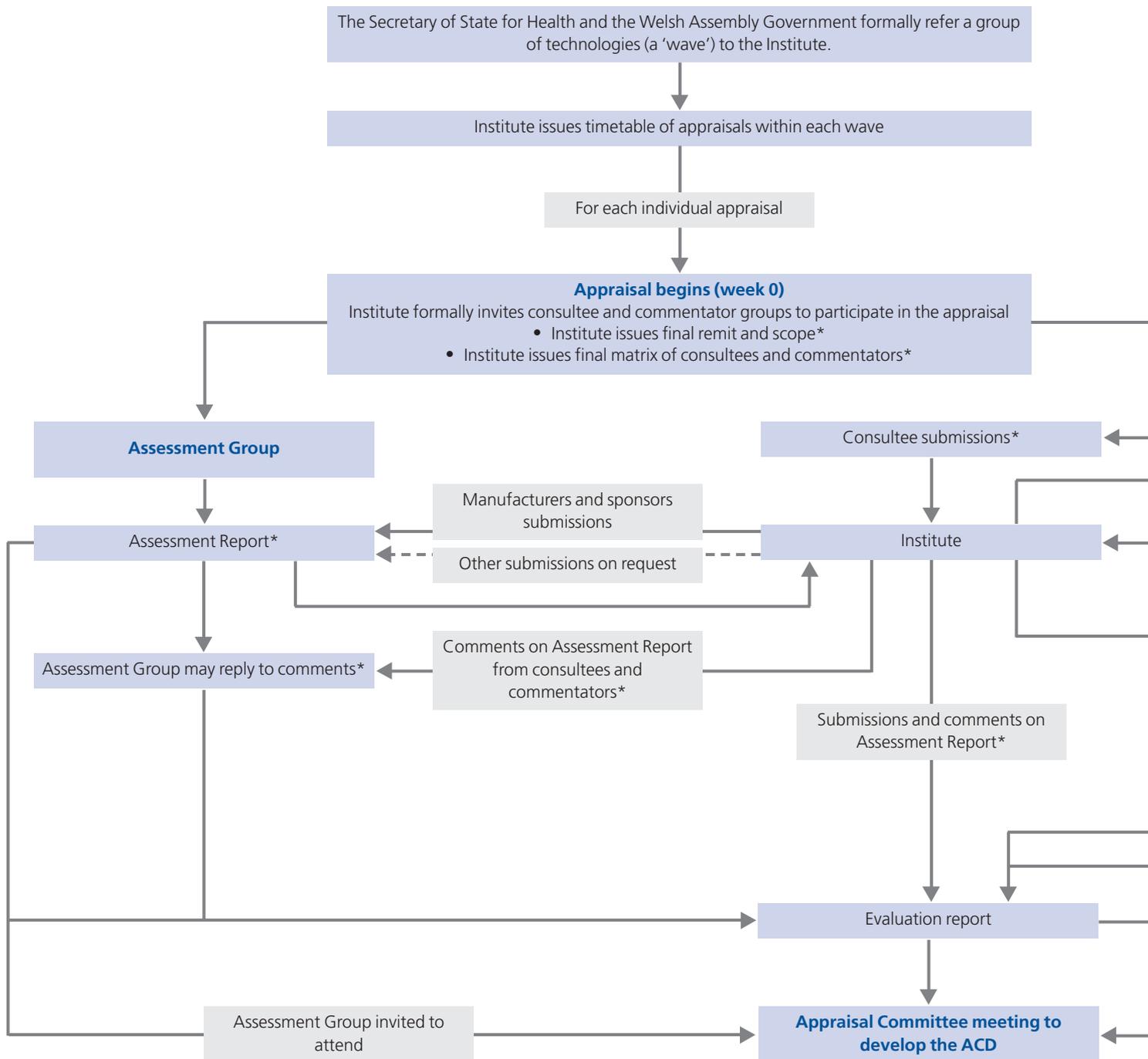


Figure 2 Summary of the appraisal process to development of the Appraisal Consultation Document (ACD).



*Component of the Evaluation Report

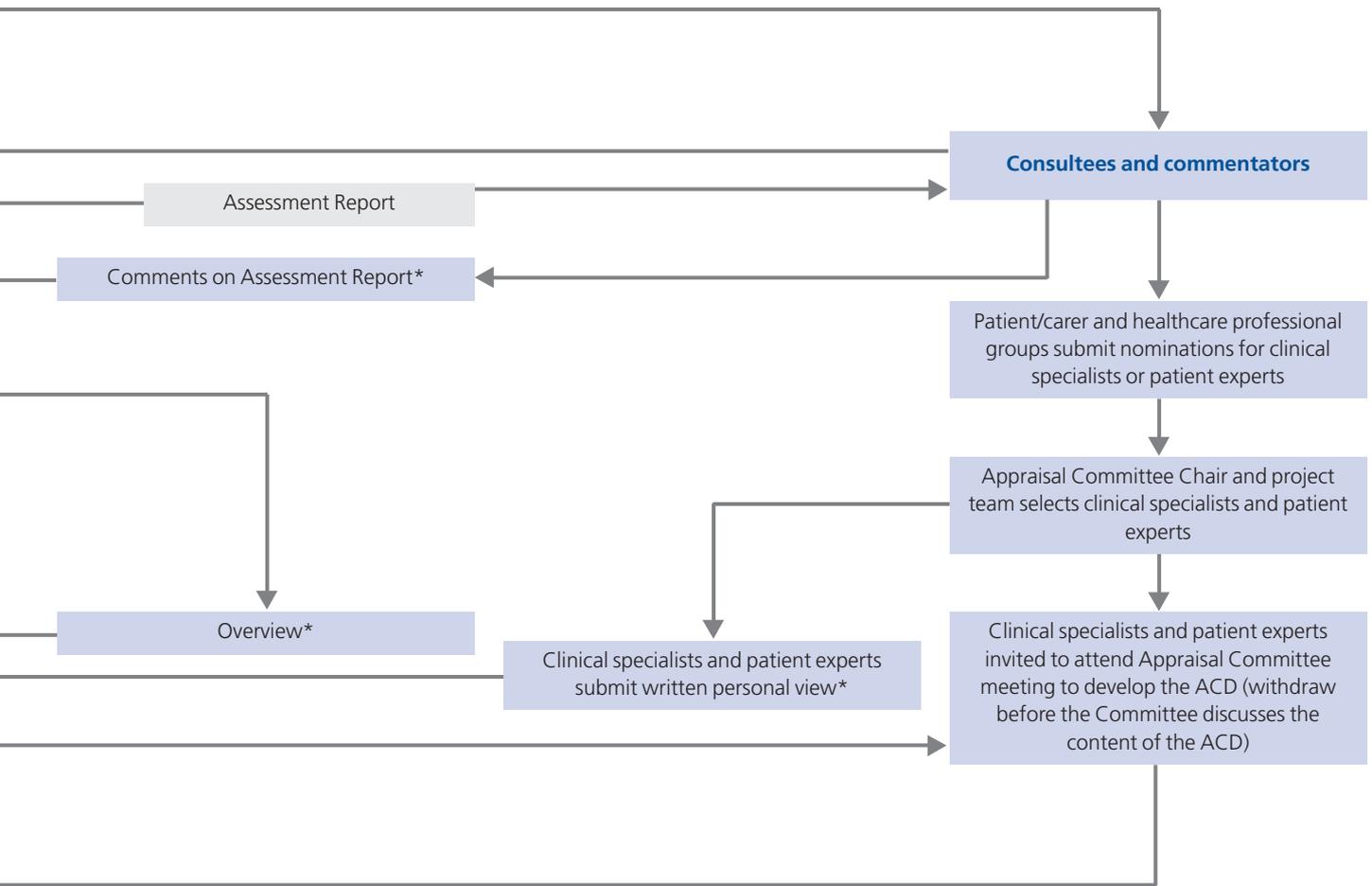
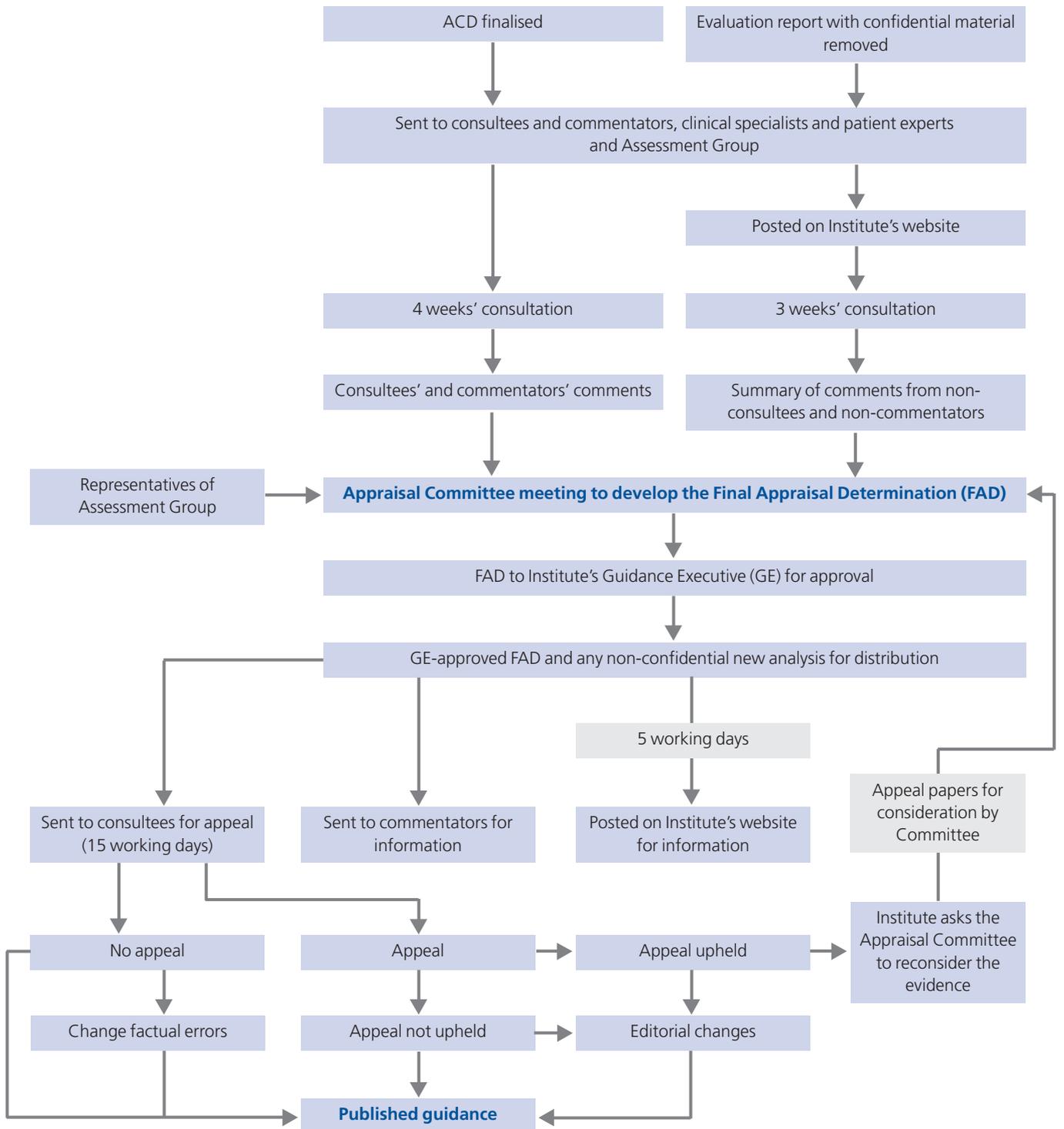


Figure 3 Summary of the appraisal process from consultation on the appraisal consultation document to publication of guidance.



2 Developing the scope

2.1 Introduction

- 2.1.1 Although the Department of Health and the Welsh Assembly Government provide the Institute with a remit for the appraisal, it is important to define in detail what the appraisal will and will not examine. This process is called 'scoping' and it is an important step because it determines the shape of future work.
- 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, comparators) as clearly as possible and sets the boundaries for the work undertaken by the Assessment Group and the Appraisal Committee.
- 2.1.3 The Institute undertakes an initial scoping exercise by conducting a preliminary search of the literature and working with an Assessment Group. Potential consultees, commentators and clinical specialists are then consulted on the draft scope and they are also invited to a scoping workshop to discuss their views. Discussion at the scoping workshop should ensure that all relevant issues have been considered and that the focus and boundaries of the appraisal have been clearly defined. The final scope for the appraisal is produced following the scoping workshop. The Assessment Group uses this scope to develop its assessment protocol.
- 2.1.4 The parameters of clinical and cost effectiveness that are defined in the scope include:
- the clinical problem and the population(s) and any relevant subgroups for whom treatment with the technology is being appraised
 - the technology and the setting for its use (for example, hospital [inpatient and outpatient], community)
 - the relevant comparator technologies (and the setting for their use)
 - the principal health outcome measures appropriate for the analysis
 - the measures of costs to be assessed
 - the time horizon over which benefits and costs will be assessed
 - other considerations, for example, identification of patient subgroups for whom the technology might potentially be particularly clinically and cost effective
 - special considerations and issues that are likely to affect the appraisal
 - the extent of the evidence.

2.2 Components of the scope

2.2.1 The clinical problem and defining the patient population(s)

- 2.2.1.1 The scope gives a clear definition of the spectrum of disease (or other clinical problem) relevant to the new technology. Where possible, the scope also specifies the population who may be treated within this spectrum (including its age and sex distribution, and co-morbidities). The scope will normally reflect:
- demographic characteristics (age, sex, ethnic or socio-economic group) and biological disease differences (for example, distinguishing between stable and unstable angina or type 1 and type 2 diabetes)
 - different severities of disease
 - the degree to which harmful effects of the new technology may affect different groups (for example, pregnant women or people with serious co-morbidity)
 - the capacity of different patient subgroups to benefit from the technology.

2.2.2 The technology and its treatment setting

- 2.2.2.1 Information is required about the development status of the technology and the current range of comparator technologies and their licensed uses. The circumstances of use are carefully specified – particularly where these differ from the circumstances in which alternative treatments for the same patient group might be used.

2.2.3 The comparator technologies

- 2.2.3.1 Comparator technologies are specified as precisely as the technology being appraised. There are frequently several potential comparator technologies, as, for example, practice is not necessarily consistent across England or Wales, and between the UK and elsewhere. All relevant comparators are identified, with consideration given to current practice and the natural history of the condition without suitable treatment. Although best alternative care is the essential comparator, treatments representing routine UK care are also important where they differ from best alternative care. Sometimes both technology and comparator form part of a treatment sequence.

2.2.4 The health outcome measures

- 2.2.4.1 As far as possible, principal measures of health outcome are identified as early as possible. For the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant; that is, they measure health effects and adverse effects that are important to patients. The most suitable outcome measures for the evaluation of cost effectiveness will normally be those that are clinically relevant.

2.2.5 The measures of costs

- 2.2.5.1 An identification of the potential direct and indirect resource costs for the NHS and personal social services (PSS) that would be expected from the introduction of the technology is presented.

2.2.6 The time horizon over which benefits and costs are assessed

- 2.2.6.1 The time span used in the appraisal usually reflects the period over which the main differences between technologies from the point of view of both their likely health effects and use of healthcare resources are expected to be experienced, taking into account the limitations of supporting evidence.

2.2.7 Special considerations and other issues likely to impact upon the appraisal

- 2.2.7.1 Where appropriate, the scope also includes brief details of other considerations that could form part of the appraisal. This may include related policy developments such as clinical guidelines or the National Service Frameworks, details of specific patient subgroups or service settings either of particular interest or to be excluded from consideration, highlighting of issues regarding the available evidence base (for example, emerging key trials) and information on the timing of regulatory approval of the technologies.

2.3 The scoping workshop

- 2.3.1 After consultees and commentators have submitted their comments on the draft scope, a meeting ('scoping workshop') is held to which the Assessment Group, all provisional consultees and commentators, the Department of Health, the Welsh Assembly Government and other interested parties are invited. This workshop is chaired by a senior member of the appraisals team or an Executive Director of the Institute. The workshop aims to generate discussion on the scope of the appraisal from different perspectives in order both to produce an appropriate final scope of the appraisal and to lead to the development of a protocol that will be used by the Assessment Group if the topic is formally referred to the Institute.
- 2.3.2 During the workshop, interested parties contribute their opinions regarding the appropriate format for the appraisal and give their views on important issues to be considered. Discussions also identify key questions to be included within the appraisal's scope in order to define the relevant issues to be considered and, in particular, to address the following:

- map the clinical problem and relevant clinical pathways
 - identify current best treatments (if known)
 - identify comparator technologies
 - identify key health outcomes, including quality of life
 - identify key clinical and economic studies
 - consider the potential structure for models developed to assess cost effectiveness.
- 2.3.3 Further information relating to the consultee workshop is included in the Institute's *Guide to the Technology Appraisal Process*.

3 Evidence for assessment and appraisal

3.1 Introduction

- 3.1.1 Consideration of a comprehensive and high-quality evidence base is fundamental to the appraisal process. Evidence on a number of aspects of care, of various types and from multiple sources, may be relevant to the appraisal considerations. 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 the analysis and their interpretation are of the highest standard and are transparent to scrutiny.
- 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 and outcomes
 - ▶ complete (all relevant evidence must be identified)
 - ▶ inclusive of all study design information (including the type of study, the circumstances of its undertaking and the selection of outcomes and costs) and inclusive of all intended-to-treat patients
 - ▶ fit for purpose (contributing to an overall assessment of the clinical benefit and quality of life, preferably in such units that allow comparison of the benefits from different technologies and between different patient groups).
- 3.1.3 Similarly, 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, and the presentation of explicit criteria by which studies are included and excluded). Models should also:
- ▶ be replicable
 - ▶ have face validity (that is, be plausible)
 - ▶ be open to external scrutiny.

3.2 Evidence for relative treatment effects

3.2.1 Introduction

- 3.2.1.1 The treatment effect of a technology can, in essence, be summarised as the difference between the health state or quality of life that would be experienced on average by patients receiving the technology and the health state or quality of life of the same group were they to receive alternative care.
- 3.2.1.2 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 that have inclusion and exclusion criteria that have been defined a priori. The different types of study design can therefore be ranked according to a hierarchy that describes their relative validity for estimating relative treatment effect. Hierarchies typically grade studies as follows: from level 1 (RCTs), through level 2 (controlled observational studies, for example, cohort studies, case–control studies), and level 3 (observational studies without control groups, for example, case series), to level 4 (expert opinion based on pathophysiology, bench research or consensus views).
- 3.2.1.3 Studies lower in the hierarchy are more prone to bias including publication, retrieval, selection, performance, measurement and attrition biases. However, it is important to recognise that (even as regards the analysis of relative treatment effects) RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore, good-quality observational studies will often be needed to supplement the RCT data. In addition, the value of evidence from anywhere in the hierarchy will depend on its quality and relevance.

- 3.2.1.4 In some appraisals, there will also be pre-existing, well-conducted, systematic reviews and meta-analyses, which may be considered in parallel with the primary evidence. If congruent with the appraisal scope, up to date and well conducted, such reviews could be considered at the top of the hierarchy.

3.2.2 Randomised controlled trials

- 3.2.2.1 RCTs are designed to minimise potential external influences in order to isolate the effects of a single variable in a precisely defined patient group. The outcome of the trial should theoretically 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 ranked first in the hierarchy of evidence for measures of relative treatment effect.
- 3.2.2.2 The Institute has a strong preference for evidence from ‘head-to-head’ RCTs that directly compare the technology and the appropriate comparator. Wherever such evidence is available and includes relevant outcome evidence, this is preferred over other study designs. Where no head-to-head trials are available, consideration is given to indirect comparisons, subject to careful and fully described analysis and interpretation.
- 3.2.2.3 The relevance of the RCT evidence to the appraisal depends on both the external and internal validity of each trial. Internal validity concerns the quality of the data for the trial’s particular circumstances. The data quality depends on features of the design and conduct of a trial, including blinding, the method of randomisation and the completeness of follow-up. Other important considerations are the size of the trial (and therefore its precision), the selection of outcomes (and therefore its relevance) and analysis by intention to treat (in order not to misrepresent the effectiveness of a technology with a high patient drop-out rate). External validity concerns 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.
- 3.2.2.4 In some circumstances, little or no RCT evidence may be available and it may have limited external validity, or be of uncertain quality.

3.2.3 Non-RCT evidence

- 3.2.3.1 The problems of confounding, lack of blinding, incomplete follow-up and frequently 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 may be needed to supplement what is available from RCTs to estimate relative treatment effect over longer time horizons than RCTs. In the absence of valid RCT evidence, evidence from the highest available level of study design will be considered with reference to the inherent limitations of the specific design.
- 3.2.3.2 The methods used to synthesise non-RCT data are evolving and complex, requiring caution in the interpretation of the results obtained.
- 3.2.3.3 In considering cost effectiveness, evidence that is usually required from sources other than RCTs includes:
- ▶ long-term outcomes including mortality
 - ▶ intermediate-term side effects and long-term adverse (or unanticipated beneficial) effects.
- 3.2.3.4 Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. Where possible, the use of more than one independent source of such indirect evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.
- 3.2.3.5 Whatever the sources of evidence available on a particular technology and patient group, they will be integrated into an independent systematic review with explicit, valid and replicable methods (see section 5.4.1).

3.3 Evidence for cost effectiveness

- 3.3.1 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' health-related quality of life (HRQL) and the valuation of those impacts to reflect the preferences of the general population. For costs, evidence requirements include quantifying the effect of the technologies on resource use in terms of physical units (for example, days in hospital, 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.

- 3.3.2 Evidence on cost effectiveness may be obtained from original analyses but also includes the findings of a systematic review of existing published economics literature.

3.4 Evidence for other appraisal considerations

3.4.1 Introduction

- 3.4.1.1 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, are relevant to these areas.

3.4.2 Acceptability, appropriateness and preference

- 3.4.2.1 Potentially, a health technology may have a substantial treatment effect and be cost effective, though it may not be considered to be an acceptable or appropriate technology (compared with alternative technologies) by patients, carers or healthcare professionals. Individuals or groups may prefer particular health technologies, for example, because of the frequency or nature of adverse events, the route or frequency of administration, or the physical design or appearance of the technology. In addition, they may be concerned about the ethics of using a particular technology.
- 3.4.2.2 These are important considerations for an appraisal, because they influence judgements on the usefulness of technologies and the extent of choice between them. Relevant evidence on these considerations can come in various forms, be based on quantitative or qualitative measurements and originate from a range of sources that have different intrinsic methodological strengths. 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.

3.4.3 Feasibility and impact

- 3.4.3.1 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 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.

3.4.4 Equity

- 3.4.4.1 The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence on equity 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.

4 Suppliers of evidence, commentary and analysis

The Institute will normally be supplied with evidence from the following groups:

- ▶ an independent academic health technology assessment group (the 'Assessment Group')
- ▶ manufacturers and sponsors of technologies
- ▶ patient/carer groups
- ▶ healthcare professionals
- ▶ clinical specialists and patient experts.

Detailed information for individual groups participating in an appraisal that wish to submit written or oral evidence is provided in the additional documents listed in section 1.1 and is available on the Institute's website.

4.1 Health technology assessment

4.1.1 The Assessment Group

- 4.1.1.1 The Assessment Group comprises a panel of independent, academic experts from one of a number of academic centres that 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 and produce an Assessment Report.

4.1.2 The Assessment Report

- 4.1.2.1 The Assessment Group develops an assessment protocol for the technology under appraisal. The protocol is derived from the scope of the appraisal, which is informed by the comments from organisations invited to attend the scoping workshop during the development of the scope.
- 4.1.2.2 The Assessment Group then prepares the Assessment Report, which is an independent synthesis of the evidence from published information and the submissions from manufacturers and sponsors regarding 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 submissions to the Institute.
- 4.1.2.3 The Assessment Group additionally consults clinical and methodological experts, and patient groups, in gathering of evidence for the Assessment Report.
- 4.1.2.4 The Assessment Report is not an exhaustive review of all the information on a given technology, but is a focused review of the evidence pertinent to the defined scope within the context of current clinical practice and based upon the protocol. There is no preset level of cut-off 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.
- 4.1.2.5 The Assessment Report may include a de novo assessment of cost effectiveness, including an economic model.
- 4.1.2.6 The Assessment Report 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. The Assessment Report is the responsibility of the authors, namely the Assessment Group, who do not propose recommendations on the use of the technology for the NHS, the final responsibility for which rests with the Institute.

4.2 Manufacturers and sponsors

Submissions are invited from manufacturers and sponsors of the technology or technologies being appraised.

4.2.1 Evidence submitted to NICE

- 4.2.1.1 A full systematic review is undertaken by the Assessment Group and is issued for consultation before the Appraisal Committee meeting to develop the Appraisal Consultation Document (ACD). This gives consultees and commentators an early opportunity to highlight any major issues they wish to raise about either the methods of the review or the study selection. The consultees and commentators have a further opportunity to comment on the Assessment Report in the period after the ACD is issued and before the Appraisal Committee meeting to develop the Final Appraisal Determination (FAD) (see the *Guide to the Technology Appraisal Process*).
- 4.2.1.2 Manufacturers and sponsors 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 registry evidence. It also includes relevant study evidence to which they have privileged access and which is not in the public domain. In particular, where technologies are undergoing appraisal in the period immediately before the expected date of regulatory approval, care should be taken that sufficient detail of the clinical trial evidence is made available to allow the Institute to fulfil the appraisal according to the defined scope.
- 4.2.1.3 For cohort studies and case series, a full report of baseline characteristics and the best equivalent evidence on the best care currently available for patients is needed.
- 4.2.1.4 At the earliest opportunity, ideally the scoping workshop, manufacturers are requested to make available details of the studies they intend to include in their submissions. Where there is extensive unpublished information, the Assessment Group may request the study reports before the submission date.
- 4.2.1.5 If the manufacturer and product sponsors include any estimates of effects in their submission, they must be explicit about the sources of all parameters used, including details of any searches they have undertaken for relevant studies, showing how and when the searches were done and how the retrieved records were assessed for relevance. The submission must also include details of all eligible studies that were identified and, if any eligible studies were not used to calculate the estimate of effect, details must be given of the reason for their exclusion. Where a meta-analysis has been conducted it should use accepted methods and be reported appropriately.

4.2.2 Summary of requirements for submissions by manufacturers and sponsors

- 4.2.2.1 Submissions should normally include the following.
- ▶ A complete list of all studies concerning the health technology under appraisal sponsored by manufacturers or sponsors or known to them (the Institute or the Assessment Group may request further information on studies included in the list).
 - ▶ An executive summary of not more than five pages.
 - ▶ A main submission of not more than 50 written pages. The main submission should, as a minimum, include sections on the following.
 - The aims of treatment and current approved indications for the technology.
 - An assessment of clinical effectiveness, containing a synthesis of clinical effectiveness evidence.
 - 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 analysis contained and referenced in the main submission. Documentation contained in the appendix for data and analysis not used in the main submission will not be accepted.
 - An appendix containing excluded evidence with the rationale for exclusion.
 - An electronic copy of the model used in the cost-effectiveness analysis.
- 4.2.2.2 Further information on the content of manufacturer and sponsor submissions is available in the Institute's document *Contributing to a Technology Appraisal: A Guide for Manufacturers and Sponsors*.

4.2.3 Unpublished and part-published evidence

- 4.2.3.1 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 only in abstract form or for which selected information has been reported. Because such information may be systematically different from the published evidence, it must be critically appraised and sensitivity analysis conducted to examine the effects of its incorporation or exclusion.

4.2.4 Evidence submitted in confidence

- 4.2.4.1 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 all 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.

4.3 Patient/carer groups

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).

4.3.1 Evidence submitted to NICE

- 4.3.1.1 Patient evidence refers to any information originating from patients and/or carers that may inform the appraisal of the technology.
- 4.3.1.2 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 evidence as the appraisal progresses.
 - Patient evidence can identify the limitations in the published research literature – in particular, the failure to capture the true concerns of individual patients related to quality of life over and above measurements using standardised instruments (such as questionnaires) developed using psychometric techniques.
- 4.3.1.3 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 both majority views and, where applicable, 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. 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.

4.3.1.4 Examples of issues for which patient evidence may provide important information include patient and carer perspectives on:

- the effectiveness of the technology (that is, how patients and carers assess and value the technology both in its own right and compared with other treatment options)
- the appropriateness of the technology (that is, is it appropriate for all patients or only for certain subgroups of patients with the condition?)
- the acceptability of the technology (that is, what factors influence patients' willingness to use a given technology – for example, adverse effects – and issues for patients' families or carers that might influence the uptake of a given technology)
- the impact of a health technology on factors that matter most to patients including physical or psychological symptoms, disability, function, long-term outlook, quality of life and lifestyle
- equity issues (that is, the perspectives of specific groups or subgroups of patients who may be advantaged or disadvantaged in terms of access to the technology).

4.3.2 Dimensions of patient experience

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

- experience of disease diagnosis and of 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.

4.3.2.2 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
- the difference the technology could make to:
 - the physical well being of patients (for example, symptoms, pain, mobility, disability)
 - lifestyles and the choices that matter to patients and carers (for example, impact on daily activities, work, hobbies, social life, relationships)
 - the psychological health of patients/carers (for example, mood, anxiety, distress)
 - the emotional health of patients/carers (for example, well being, impact on relationships)
 - the balance between quality of life and length of life
 - the various treatment choices that matter to patients and carers
 - the impact on the lives of family members and carers
- costs to the patient (financial and other) associated with the technology (including time, transport costs, carer costs).

4.4 Healthcare professionals

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.

4.4.1 Evidence submitted to NICE

- 4.4.1.1 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 importantly 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.
- 4.4.1.2 The written submissions provide a unique contribution outlining the professional view of the place of the technology in current clinical practice. 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, other healthcare professionals)
 - ▶ the current best alternative treatments, particularly where 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 evidence used in the systematic review prepared by the Assessment Group and to enable potential sources of bias to be determined)
 - ▶ evidence from registries and nationally co-ordinated 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 'off licence'
 - ▶ the impact of possible guidance on delivery of the service
 - ▶ the impact of possible guidance on the education and training requirements of NHS staff.

4.5 Clinical specialists and patient experts

- 4.5.1 During the Institute's scoping process, consultees and commentators are asked to nominate individuals to act as expert witnesses to the Appraisal Committee and give oral evidence.

4.5.2 The clinical specialist and patient experts

- 4.5.2.1 Two groups of experts – clinical specialists and patient experts – attend the Committee meeting to help in the discussion of the technology being appraised. No members of either group will have any personal financial involvement with the manufacturers or sponsors of the technology.
- ▶ **Clinical specialists** are selected on the basis of specialist expertise and personal knowledge of the use of the technology and other treatments for the condition. They may provide a range of differing perspectives of the use of the technology within the context of current clinical practice.
 - ▶ **Patient experts** have experience of the use of the technology and the condition either personally or as part of a representative group. Their evidence provides:
 - an individual view of the risks and benefits of the technology based on personal experience as a patient or carer
 - an understanding of the wider range of patient or carer views.

4.5.3 Format of the evidence

- 4.5.3.1 Although the clinical specialists and patient experts provide different types of evidence, there is often significant overlap.
- 4.5.3.2 The experts attending the Committee meeting are asked to submit, in advance, a brief written personal view of the role of the technology and its use in the NHS, as well as to provide oral evidence during the meeting. The purpose of the oral evidence provided by the experts is to enhance the evidence that is provided in the written submissions from consultees (described above), rather than to cover similar ground. During the open part of the meeting, clinical specialists and patient experts are encouraged to interact fully in the debate with the Committee, including both 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 ACD.
- 4.5.3.3 The oral views 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 staffing or equipment in NHS units, special requirements within the community for patients and carers (for example, travel to hospital for treatment), and 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 testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
 - ▶ Identifying how the introduction of the technology may impact on the education and training requirements of NHS staff.
 - ▶ 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 6.2.1)
 - issues raised by the Chair and other Committee members
 - issues raised by other experts.

5 Clinical and cost effectiveness and NHS impact

5.1 Introduction

This chapter 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.

The chapter is divided into nine sections:

- ▶ Guiding principles
- ▶ Framework for estimating clinical and cost effectiveness
- ▶ Synthesising evidence on outcomes
- ▶ Valuing health effects
- ▶ Evidence on costs
- ▶ Discounting
- ▶ Modelling methods
- ▶ Presentation of data and results
- ▶ Impact on the NHS.

5.2 Guiding principles

5.2.1 Clinical and cost effectiveness

- 5.2.1.1 In order 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 between submissions is needed to allow comparison between appraisals of different technologies and over time.
 - ▶ All relevant comparators for the technology being appraised need to be included in the analysis.
 - ▶ All relevant evidence needs to be assembled systematically and synthesised in a transparent and reproducible manner.
 - ▶ The costs that are most relevant are those of the NHS and the PSS.
 - ▶ Measures of health-related benefits used should be comparable, to promote consistency between appraisals and to allow comparison with the benefits from other technologies that may be displaced if technologies are 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 cost effectiveness needs to be explored.

5.2.2 Synthesis and modelling

- 5.2.2.1 The process of assembling evidence for health technology assessment needs to be systematic. That is, evidence must be identified, quality assessed and, where 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.

- 5.2.2.2 It is necessary for clinical and cost effectiveness to be considered over an appropriate time horizon, to be relevant to UK practice and patients, and to compare all relevant treatment options for the relevant patient groups. It will be necessary, therefore, to construct an analytical framework within which to synthesise the available evidence in order to estimate clinical and cost effectiveness relevant to the clinical decision-making context. This framework will usually require the development of a model. This may be a decision analytic model using aggregated data or a statistical model using patient-level data. Further details of modelling methods are provided in section 5.8.

5.2.3 Requirements for evidence

- 5.2.3.1 The requirements for evidence of effectiveness include the quantification of the effect of the technologies on the course of the disease, the effect of the technologies on patients' HRQL and the valuation of those effects in a manner that reflects the preferences of the general population.
- 5.2.3.2 Data are required to quantify the effect of the technologies on use of resources in terms of physical units (for example, days in hospital, visits to a GP) and valuing those effects in monetary terms using appropriate prices and unit costs.
- 5.2.3.3 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 for 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.

5.2.4 Analysis of uncertainty

- 5.2.4.1 It is important for the Appraisal Committee to know about the uncertainty associated with clinical and cost effectiveness information. This requires the appropriate use of rigorous methods to quantify the implications of parameter and methodological uncertainty for the results of an analysis. 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 5.9.3 and 5.9.4.

5.3 Framework for estimating clinical and cost effectiveness

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

5.3.1 The concept of the reference case

- 5.3.1.1 *The Institute has to make decisions across different technologies and disease areas. It is, therefore, important that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a consistent approach. To facilitate 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 where one or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case.*
- 5.3.1.2 There is considerable debate about the most appropriate methods to be used for some aspects of health technology assessment. This uncertainty relates to choices that are essentially value judgements – for example, which perspective to adopt and 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 classifying 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. The key elements of the analysis in the reference case are summarised in Box 5.1 below.

Box 5.1 Summary of reference case

Element of health technology assessment	Reference case	Section providing details
Defining the decision problem	The scope developed by the Institute	5.3.2
Comparator	Alternative therapies routinely used in the NHS	5.3.2
Perspective on costs	NHS and PSS	5.3.3
Perspective on outcomes	All health effects on individuals	5.3.3
Type of economic evaluation	Cost-effectiveness analysis	5.3.4
Synthesis of evidence on outcomes	Based on a systematic review	5.4.1
Measure of health benefits	Quality-adjusted life years (QALYs)	5.5
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	5.5
Method of preference elicitation for health state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	5.5
Source of preference data	Representative sample of the public	5.5
Discount rate	An annual rate of 3.5% on both costs and health effects	5.7.2
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.9.7

5.3.1.3 It is recognised that, in some instances, data required to present reference case results are not available. Similarly, 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.

5.3.1.4 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 even if they themselves do not provide a full reference case analysis. This is particularly important where 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 economic analysis undertaken by the Assessment Group.

5.3.2 Defining the decision problem

5.3.2.1 *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). These characteristics should be consistent with the Institute's scope for the appraisal.

- 5.3.2.2 The main technology of interest, the comparator(s) and the relevant patient group(s) will be defined in the scope developed by the Institute (see chapter 2).

5.3.3 Perspective

- 5.3.3.1 *For the reference case, the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analyses should be presented in addition to the reference case analysis.*
- 5.3.3.2 The reference case perspective on outcomes is consistent with an objective of maximising health gain from available resources. Some features of healthcare delivery that are often referred to as 'process characteristics' may ultimately have health consequences – for example, the length of waiting lists for elective surgery. When there are significant characteristics of healthcare technologies that have a value to individuals 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.
- 5.3.3.3 The Institute works in a specific context; in particular, it does not influence the budget that is set for the NHS. Hence, the appropriate objective of the Institute is to offer guidance that represents an efficient use of limited NHS and PSS resources. For these pragmatic reasons, the appropriate reference case perspective on costs is that of the NHS and PSS. In non-reference case analyses, significant resource costs imposed outside the NHS may also be considered and in offering guidance the Institute may take account of these costs. The resource costs that come under this heading could include direct costs on patients or carers (for example, travel costs) or costs to other public sector organisations, but will not normally include productivity costs.

5.3.4 Type of economic evaluation

- 5.3.4.1 *For the reference case, cost-effectiveness analysis is the appropriate 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 quality-adjusted life years (QALYs).*
- 5.3.4.2 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 understood. 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 a non-reference case analysis.
- 5.3.4.3 Despite the role of cost per QALY in the reference case, the Institute recognises that other forms of cost-effectiveness analysis and cost–benefit analysis may have a role to play, as non-reference case analyses in specific situations. For example, cost–benefit analysis may be particularly useful when non-health consequences are important in an evaluation. In such cases, willingness-to-pay methods may be used to value all consequences in monetary terms. Where such methods are used they should be fully described and the uncertainty in the results fully explored.

5.3.5 Time horizon

- 5.3.5.1 *The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.*
- 5.3.5.2 Many technologies have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic disease, for example, ischaemic heart disease, diabetes

and many types of cancer. In such instances, a lifetime time horizon for clinical and cost effectiveness is appropriate. Such a time horizon is also required in order to quantify the implications of any differential mortality effect between alternative technologies. For a lifetime time horizon, extrapolation modelling is often necessary. The modelling framework needs to be based on a comparison of several alternative scenarios reflecting different assumptions about future treatment effects (see section 5.8 on modelling). Such assumptions should include both the limiting assumption of no further benefit as well as more optimistic assumptions.

- 5.3.5.3 A time horizon shorter than lifetime could be justified when there is no differential mortality effect between options, and differential costs and HRQL relate to a relatively short period – for example, in the case of an acute infection. Resolving uncertainty around the time horizon used in the modelling, especially that related to the duration of the clinical trials, is a critical component of the work of the Appraisal Committee.

5.4 Synthesising evidence on outcomes

The objective of the analysis of clinical effectiveness is to produce an unbiased estimate of the mean clinical effectiveness of the technologies being compared. The analysis of clinical effectiveness should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes and comparison with relevant comparators. The analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty and data from all relevant studies.

5.4.1 Systematic review

- 5.4.1.1 All health effects should be identified and quantified, with all data sources clearly described. As a reference case, all evidence on outcomes should be obtained from a systematic review, which can be defined as the systematic location, appraisal and synthesis of evidence in order to obtain a reliable overview.
- 5.4.1.2 Assessments of diagnostic techniques should follow the general principles of systematic reviews for other healthcare technologies as set out in this document. However, it is recognised that the specifics of, for example, the meta-analysis of studies of the sensitivity and specificity of diagnostic tests are quite different from reviews of the effects of therapeutic interventions. This is an area of active methodological research. The findings of such research will be reflected in future updates of this document. Until then, assessments of diagnostic techniques will be required to use a recognised method of evidence synthesis and provide a satisfactory justification for any novel approaches.

Relevant studies

- 5.4.1.3 For estimates of relative treatment effect, it is accepted that the conclusions of the systematic review will be most valid if they are based on evidence from head-to-head RCTs; however, it is recognised that such evidence may not be available. In such circumstances, the implications of potential selection bias resulting from the use of indirect trial comparisons and non-RCT evidence should be assessed in an analysis of uncertainty.
- 5.4.1.4 Trial data may not be sufficient to quantify baseline health effects and allow an estimate of the effectiveness of the technology being appraised. Thus, quantifying the baseline health effects of existing treatments on the disease natural history separately from the relative effects of the new technology is often a useful way of estimating absolute health outcomes. This approach is also useful to adjust the absolute treatment effects observed in randomised trials, which include a range of patient subgroups or treatment locations, to the specific subgroups of interest in an appraisal and to clinical practice in England and Wales. The methods used to identify and critically appraise sources of data for these estimates should be stated and justified.

Study selection and data extraction

- 5.4.1.5 Once the search strategy has been developed and literature searching undertaken, a list of possible primary studies will be compiled. Each study must be assessed to determine whether it meets the inclusion criteria of the review. The validity of the decision process is increased if more than one reviewer assesses all records retrieved by the search strategy and agreement between reviewers is measured.

- 5.4.1.6 A systematic review is performed retrospectively and thus may be regarded as an observational study. Therefore, it is open to bias and should be conducted according to a previously prepared protocol. The protocol formalises the decisions made at the design stage, thereby reducing the risk of bias and ensuring that the review is reproducible. A log of ineligible studies should be maintained with the rationale for exclusion to allow assessment of the robustness of the literature search and study selection processes.

Critical appraisal

- 5.4.1.7 The validity of the results of an individual study will depend on the robustness of its overall design and execution. Therefore, each study meeting the criteria for inclusion should be subjected to critical appraisal. This information forms the basis of the systematic review. It is also important to critically appraise unpublished and part-published evidence to examine the effects of its incorporation or exclusion.

Treatment effect modifiers

- 5.4.1.8 Many factors can potentially affect the overall estimate of health effects obtained from a study and may explain apparent differences in outcomes between studies. Common examples are 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 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 area.

5.4.2 Meta-analysis

- 5.4.2.1 *Synthesis of outcome data through meta-analysis is appropriate provided there is sufficient relevant and valid data that use measures of outcome that are comparable. Where such data are not available, the analysis may have to be restricted to a qualitative overview that critically appraises individual studies and presents their results. Forrest plots are a useful tool to illustrate the individual study population results. The characteristics and limitations of the data (that is, population, intervention, setting, sample size and validity of the evidence) need to be fully reported.*
- 5.4.2.2 Before any statistical pooling is carried out, an assessment of the degree of, and the reasons for, heterogeneity in the study results should be undertaken – that is, variability in the effects between studies that may suggest that individual studies reflect different study circumstances. Statistical heterogeneity of study results can be addressed using a random (as opposed to fixed) effects model. Known clinical heterogeneity (for example, patient characteristics, or intervention dose or frequency) can be managed by judicious use of methods such as subgroup analyses and meta-regression. For methodological heterogeneity (for example, where different trials are of different quality) the results of sensitivity analyses (varying the studies in the meta-analysis) should be reported. If the risk of an event substantially differs among the control groups of the studies included in a meta-analysis, an assessment of whether the relative risk is constant over different baseline risks should be undertaken. This is especially important when the relative risk is to be used within 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.
- 5.4.2.3 Forrest plots should include lines for studies that are believed to contain eligible data even if the data are missing from the analysis in the published study. An estimate of the proportion of eligible data that are missing (because some studies will not include all relevant outcomes) will be needed for each analysis.
- 5.4.2.4 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. Where the Institute is appraising a number of related technologies within a single appraisal, both separate and combined analysis of the benefits of the individual technologies should be undertaken.

5.5 Valuing health effects

- 5.5.1 *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, a standardised and validated generic (non-disease-specific) instrument is required to quantify the effects of technologies in terms*

of HRQL for patients. The value of changes in patients' HRQL (that is, utilities) should be based on public preferences elicited using a choice-based method. Evidence should be presented to indicate that any data taken from the literature have been identified systematically.

- 5.5.2 To calculate QALYs for any technology, it is necessary to use a classification system to describe patients' HRQL over time. To allow comparisons across technologies, the Institute requires that health states should be measured in patients using a generic and validated classification system for which reliable UK population preference values, elicited using a choice-based method such as the time trade-off or standard gamble (but not rating scale), are available.
- 5.5.3 It is well established that different classification systems do not give consistent utility values to the same health states and hence 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, the Institute would ideally wish that all appraisals used the same system. Currently, the most appropriate choice in the UK appears to be the EQ-5D. While it is widely used and simple to incorporate into studies, the EQ-5D may not be appropriate in all circumstances. Given the evolving state of the art in this area, the Institute believes it would be inappropriate to require the use of the EQ-5D to the exclusion of any other methods that meet its underlying criteria. Those submitting data should provide reasons for their choice of instrument. They should also indicate whether they have any evidence that will help the Committee to understand to what extent, and for what reason, their choice of instrument will have impacted on the valuation of the QALYs gained.
- 5.5.4 Additional (non-reference case) analyses may be submitted where patients' HRQL has been measured using disease-specific instruments if these can be justified. Similarly, analyses incorporating utility values based on patients' (rather than public) preferences may be submitted if they can be justified and they markedly alter the results compared with the reference case.

5.6 Evidence on costs

5.6.1 NHS and PSS costs

- 5.6.1.1 *For the reference case, costs should relate to resources that are under the control of the NHS and PSS where 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. Where the actual price paid for a resource may differ from the public list price (for example, pharmaceuticals, medical devices), the public list price should be used. Sensitivity analysis should assess the implications of variations from this price. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.*
- 5.6.1.2 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, even 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.
- 5.6.1.3 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. Where cost data are taken from literature, the methods used to identify the sources should be defined. Where several alternative sources are available, a justification for the costs chosen should be provided. Where appropriate, sensitivity analysis should be used to assess the implications for results of using alternative data sources.
- 5.6.1.4 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.

5.6.2 Non-NHS and non-PSS costs

- 5.6.2.1 *Although not part of the reference case, there will be occasions where non-NHS/PSS costs will be differentially affected by the technologies under comparison. In these situations, the Institute*

should be made aware of the implications of taking a broader perspective on costs for the decision about cost effectiveness. 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/IPSS costs.

5.7 Discounting

- 5.7.1 *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, sensitivity analysis should vary the rate between 0% and 6%.*
- 5.7.2 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 annual rate of 3.5%, for both costs and health effects, is based on the recommendations of the UK Treasury.

5.8 Modelling methods

- 5.8.1 *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. Probabilistic sensitivity analysis should be conducted on models to reflect the combined implications of uncertainty in parameters.*
- 5.8.2 As described in section 5.2.2, modelling provides an important framework for synthesising available evidence and generating estimates of clinical and cost effectiveness relevant to the Appraisal Committee's decision-making process. Situations where modelling is likely to be required include those where:
- ▶ 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.
- 5.8.3 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 and data inputs should be clearly documented and justified. This is particularly important in the case of modelling to extrapolate costs and health benefits over an extended time horizon. In such circumstances alternative time horizon scenarios should be considered in order to compare the implications of different assumptions for the results. Scenarios might include that 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.
- 5.8.4 It is important for models to quantify the decision uncertainty associated with a technology – that is, the probability that a different decision would be reached if we were able to ascertain the true cost effectiveness of each technology before making the decision. The uncertainty associated with parameters can simultaneously be reflected in the results of the model by the use of probabilistic sensitivity analysis. Furthermore, in non-linear decision models, probabilistic methods provide the only reliable means of estimating mean costs and outcomes. In some circumstances the computational methods required to implement an appropriate model structure may limit the feasibility of conducting probabilistic sensitivity analysis. In these circumstances, the use of model structures which limit the feasibility of probabilistic sensitivity analysis should be clearly specified and justified.

5.9 Presentation of data and results

5.9.1 Presenting data

- 5.9.1.1 *All data 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 defined and justified.*
- 5.9.1.2 As much detail as possible on the data used in an analysis should be provided. The distributions chosen for probabilistic sensitivity analysis are not arbitrary, and therefore distributions for parameters should be chosen to appropriately represent the available evidence on the parameter of interest, and their use should be justified.

5.9.2 Presenting expected cost-effectiveness results

- 5.9.2.1 *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. Incremental cost-effectiveness ratios should be calculated as appropriate.*
- 5.9.2.2 Standard decision rules should be followed in combining costs and QALYs. These should reflect any situation where dominance or extended dominance exists. Incremental cost-effectiveness ratios (ICERs) reported must be the ratio of expected cost to expected QALY. Given that most models consist of non-linear combinations of parameters, probabilistic sensitivity analysis should be used to generate expected mean results, as this may not be achieved with models based on point estimates of parameter values.

5.9.3 Dealing with parameter uncertainty in cost-effectiveness analysis

- 5.9.3.1 *All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis should be used to translate the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared. The most appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.*
- 5.9.3.2 The use of univariate, best/worst case or scenario-based sensitivity analysis to quantify the effect of parameter uncertainty in an analysis cannot incorporate the uncertainty in more than two or three parameters simultaneously. The use of probabilistic sensitivity analysis (or, where appropriate, stochastic analysis of patient-level data) allows complete characterisation of the uncertainty associated with all input parameters. This can then be reflected in terms of decision uncertainty in the cost effectiveness of the options – that is, the probability that a given technology is more cost effective than its comparator(s) if the data and model structure are accepted as valid. The most appropriate ways of presenting uncertainty are confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves. When patient-level data are available to inform one or more parameters of the model, then statistical analysis of those data can be used to express uncertainty in those inputs. Within a probabilistic analysis it is also helpful to present the contribution of the uncertainty in each parameter to overall decision uncertainty. This can be achieved using expected-value-of-information methods.

5.9.4 Dealing with other forms of uncertainty

- 5.9.4.1 Sensitivity analysis should be used to deal with sources of uncertainty other than that related to the precision of the parameter estimates. This will include uncertainty about the choice of studies to include in a meta-analysis, and the structural assumptions made in a model. Each alternative analysis should present separate (probabilistic) results. Analyses using alternative methods to the reference case should be presented separately from those relating to structure and data.
- 5.9.4.2 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 formally examined using sensitivity analysis.

- 5.9.4.3 Common examples of this type of sensitivity would be:
- ▶ where there are doubts about the quality or relevance of a particular study in a meta-analysis, in which case the analysis could be re-run excluding this study
 - ▶ where there is uncertainty about the most appropriate assumption to use for extrapolation of costs and outcomes beyond trial follow-up
 - ▶ where there is variability between hospitals in the cost of a particular resource or service, or the acquisition price of a particular technology.
- 5.9.4.4 Uncertainty about the appropriateness of the methods used in the reference case can also be dealt with using sensitivity analysis, but these analyses must be presented separately.

5.9.5 Presenting analysis of clinical and cost effectiveness for patient subgroups

- 5.9.5.1 *For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be reflected in the analysis by the provision of separate estimates of clinical and cost effectiveness for each relevant subgroup of patients. The characteristics of patients in the subgroup should be clearly defined and care should be taken to justify the clinical basis for the subgroup differences. The uncertainty around estimates of parameters specific to the subgroup should be fully reflected in the analysis.*
- 5.9.5.2 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 clinical justification and, where appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Ad hoc data mining in search of significant subgroup effects should be avoided. Care should be taken to specify how subgroup analyses were undertaken, including the choice of scale on which effect modification is defined. The 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.
- 5.9.5.3 An intention-to-treat (ITT) analysis (where data for all participants are analysed regardless of whether or not they dropped out of the study, crossed over to another treatment or received an alternative intervention) is required to estimate clinical effectiveness because ITT analysis preserves the randomisation of the trial population. However, a particular instance of subgroup analysis that may also be useful is the analysis of per-protocol populations. The per-protocol population comprises individuals who completed the trial according to the pre-specified trial protocol. A per-protocol population can be a pragmatically valid subgroup when such a population would be successfully selected for treatment in the normal care setting.

5.9.6 Identifying future research needs from the evidence

- 5.9.6.1 *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.*
- 5.9.6.2 Part of the analysis of uncertainty is to identify the parameter uncertainty 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 and where that research should be focused.

5.9.7 Reflecting equity considerations in cost-effectiveness analysis

- 5.9.7.1 *In the reference case, an additional QALY should receive the same weight regardless of the other characteristics of the individuals receiving the health benefit.*
- 5.9.7.2 The estimation of QALYs as defined in the reference case implies a particular position regarding the comparison of health gained between individuals. Thus, 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. This position reflects the absence of consensus regarding whether these or other characteristics of individuals should result in differential weights being attached to QALYs gained. Research is currently being undertaken to inform this position for future updates of this document.

5.10 Impact on NHS

5.10.1 Implementation of NICE guidance

- 5.10.1.1 *Information on the net impact on the NHS (and PSS where appropriate) of the implementation of the health technology is required. Ultimately this information supports the Department of Health, Welsh Assembly Government and local NHS staff when planning the implementation of NICE appraisal guidance in the NHS in England and Wales.*
- 5.10.1.2 As outlined in more detail below, where 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, patient or service base (for example, per 100,000 population, per average primary care trust or per ward).

5.10.2 Implementation/uptake and population health impact

- 5.10.2.1 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.

5.10.3 Resource impact

- 5.10.3.1 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, 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, residential home places).
- 5.10.3.2 Any likely constraints on the resources required to support the implementation of the appraised technology should be highlighted, and comment made on the impact of this on the implementation time scale.

5.10.4 Costs

- 5.10.4.1 Estimates of net NHS (and PSS where appropriate) costs of the expected resource impact are required to allow effective national and local financial planning. The costs should be disaggregated by appropriate generic organisational (for example, NHS, PSS, hospital, primary care) and budgetary categories (for example, drugs, staffing, consumables, capital), where possible, to the same level and detail as adopted in resource unit information. Where 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.
- 5.10.4.2 Where the impact of implementation of the technology could have substantial resources implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored.

6 The appraisal of the evidence

6.1 Introduction

- 6.1.1 The purpose of this section is to explain how the Appraisal Committee appraises the evidence and how it makes the judgements that lead to its final conclusions.
- 6.1.2 The Appraisal Committee is an independent advisory body that 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 where 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 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 seen to be consistent across appraisals and that the views of consultees in the appraisal are taken into account.
- 6.1.4 The language and style used in the documents produced during an appraisal are governed by the following principles.
- ▶ The need for clarity and transparency to ensure that readers understand how the Appraisal Committee has come to its conclusions. Therefore, of particular importance is the 'Considerations' section of the guidance document, which summarises the various issues that have been debated and the rationale for the conclusions drawn.
 - ▶ The need to ensure that the text of the documents does not simply reiterate the factual information that can be found in the Evaluation/Assessment Reports, which are published alongside the guidance on the Institute's website. This requires careful judgement so that enough information and justification is given to enable the reader to understand what evidence the Appraisal Committee considered and, if appropriate, who provided that evidence.
- 6.1.5 The Appraisal Committee is not empowered to alter the Direction from the Secretary of State for Health and Welsh Assembly Government 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. The Committee's discretion to do so 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. The Institute will advise the Secretary of State and Welsh Assembly Government if it considers that the Direction should be varied.
- 6.1.6 The Appraisal Committee is also not normally expected to make recommendations regarding the use of a drug outside its current licensed indications, as published in the manufacturer's Summary of Product Characteristics. However, the availability of evidence relating to such 'off licence' use is not precluded from consideration during the assessment phase 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.
- 6.1.7 If evidence is forthcoming during the appraisal that leads the Appraisal Committee to question the original remit or scope, then it may do one of the following.
- ▶ Advise the Institute that the guidance document should contain sufficient information to fully clarify the limits of the current appraisal and encourage a widening or change of the scope for the appraisal review.
 - ▶ Suggest to the Institute that the appraisal should be suspended until further analysis of the new evidence has been undertaken to fully inform the Committee's deliberations.
- 6.1.8 The Committee is not able to make recommendations on the pricing of technologies to the NHS.
- 6.1.9 The remainder of this chapter describes the sequence of the discussions that take place at the

Appraisal Committee's meetings to develop an ACD and a FAD 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 meeting to develop the ACD

6.2.1 Lead team presentation

- 6.2.1.1 Two members of the Appraisal Committee (the 'lead team') make a brief presentation to the other members to introduce the topic of the appraisal. The presentation usually has the following format:
- ▶ overview of the condition for which the technology is indicated, including the epidemiology and pathophysiology relevant to the Appraisal Committee's considerations
 - ▶ overview of the technology and its place in the pathway of care for the condition and relevant alternative treatments/comparators
 - ▶ overview of the evidence of clinical effectiveness
 - ▶ overview of the evidence of cost effectiveness and, where appropriate, clarification and critique of the economic models received
 - ▶ identification of issues of importance for consideration by the Appraisal Committee to facilitate the discussion.
- 6.2.1.2 The presentation does not pre-empt the Committee's debate or the formulation of the guidance.

6.2.2 Role of the clinical specialists and patient experts

- 6.2.2.1 The invited clinical specialists and patient experts are selected from the nominations received from formal consultees, as described in the *Guide to the Technology Appraisal Process*. The clinical specialist nominees will be expected to have appropriate clinical experience of the circumstances surrounding the use of the technology being appraised. The patient/carer nominees represent the views of people who have used the technology. The clinical specialist and patient experts are:
- ▶ present throughout the discussion of the technology and are encouraged to interact fully in the debate with the Committee, including both responding to and posing questions
 - ▶ not expected to make additional presentations to the Committee
 - ▶ asked to withdraw for the final part of the meeting when the Committee discusses the content of the ACD.

6.2.3 The role of the Assessment Group

- 6.2.3.1 Members of the independent Assessment Group attend the meeting of the Appraisal Committee to develop the ACD. This allows the Committee to clarify aspects of the assessment covered in the written documentation. The Assessment Group is not involved in the drafting of the ACD and therefore has no direct input into this process.
- 6.2.3.2 If there are any outstanding issues following the meeting, the Committee, through the Institute, will seek clarification from the clinical specialists and patient experts and the Assessment Group.

6.2.4 Functions of the Chair

- 6.2.4.1 The functions of the Chair of the Appraisal Committee are:
- ▶ to highlight general considerations associated with the appraisal and identify key issues including those raised in the lead team presentation and during the discussion with the experts
 - ▶ to guide the Appraisal Committee in discussion regarding the importance of issues raised; in particular, the need to:
 - consider the factors listed in the Directions of the Secretary of State for Health and the Welsh Assembly Government (for details see the *Guide to The Technology Appraisal Process*)
 - keep within the remit and scope of the appraisal topic
 - consider the balance of probabilities when coming to conclusions

- ensure that the Committee takes account of the views expressed by the clinical specialists and patient experts.

6.2.5 Appraising clinical effectiveness

- 6.2.5.1 The Appraisal Committee has the discretion to take full account of the various kinds of clinical studies that have been carried out and is not expected to restrict itself to consideration of certain categories of evidence only.
- 6.2.5.2 This requires the Appraisal Committee to consider the full range of the hierarchy of evidence from RCTs to observational and qualitative evidence related to the experiences of patients and carers who have used the technology being appraised.
- 6.2.5.3 The importance given to these various kinds of evidence need not be restricted to the formal rules of the evidence hierarchy and depends on the overall balance and quality of the evidence from different sources, and the suitability of a particular type of evidence to address the issues under consideration. However, in general, greater importance is given to evidence derived from high-quality studies with methodology designed to minimise bias.
- 6.2.5.4 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 Assessment Group
 - the written submissions of the consultees
 - the views expressed by the clinical specialists, particularly their experience of the use of the technology in clinical practice including the extent and nature of 'off licence' use
 - the views of the patient experts 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
 - ▶ consideration of possible differential effectiveness or greater risk of adverse events in different subgroups 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.
- 6.2.5.5 Whether all or some of the above factors are taken into account in making judgements about the evidence of clinical effectiveness is a matter for the Committee's discretion. The Committee should also take into account advice from the Institute, which is partly informed by the work of its Citizens Council, on the appropriate approach to making scientific and social value judgements.

6.2.6 Appraising cost effectiveness

- 6.2.6.1 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.
- 6.2.6.2 The Appraisal Committee does not consider the affordability of the new technology but does take account of how its advice may enable the more efficient use of available healthcare resources.
- 6.2.6.3 The Appraisal Committee takes account of how the cost effectiveness of the technology being appraised relates to other interventions/technologies currently being applied in the NHS, including those that have been the subject of previous appraisals.
- 6.2.6.4 The Committee also has to make judgements on the appropriateness of comparator technologies as perceived by all NHS stakeholders, which is crucial to the weighting given to the cost-effectiveness evidence. This may be particularly relevant when considering the input from patient and carer organisations and their assessment of quality of life during treatment.

- 6.2.6.5 Where the evidence on clinical effectiveness used to estimate cost effectiveness has serious limitations and/or where a variety of assumptions have been necessary in the cost-effectiveness modelling, the additional uncertainty this generates will be taken into account in decision-making. For the most part, the Appraisal Committee is likely to give greater weighting to evidence on cost effectiveness that is underpinned by the best-quality clinical data than to evidence that is dependent to a large extent on theoretical modelling alone.
- 6.2.6.6 The Committee's judgements on cost effectiveness are influenced by the following factors:
- ▶ strength of the supporting clinical effectiveness evidence
 - ▶ the robustness of the structure and the plausibility of the assumptions made in the economic models
 - ▶ the Committee's preferred modelling approach, taking into account all of the economic evidence submitted and the critique of the manufacturers' models by the Assessment Group
 - ▶ the range and plausibility of the ICERs generated by the models reviewed.
- 6.2.6.7 The Appraisal Committee does not use a fixed 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 is that of the opportunity cost of programmes displaced by new, more costly technologies. However, estimating this threshold would require complete information about the costs and QALYs from all competing healthcare programmes and the Committee does not have this information. Furthermore, the threshold will change over time as the budget for healthcare changes. Although the use of a threshold is inappropriate, comparisons of the most plausible ICER of a particular technology compared with other programmes that are currently funded are possible and are a legitimate reference for the Committee. Such comparisons are helpful when the technology has an ICER that is lower than programmes that are widely regarded as cost effective, substantially higher than other currently funded programmes or higher than programmes previously rejected as not cost effective by the Committee.
- 6.2.6.8 The Appraisal Committee has been given discretion when determining cost effectiveness to take into account those factors it considers most appropriate to each appraisal. In doing so, it makes reference, selectively, to the factors listed in the Directions of Secretary of State for Health and the Welsh Assembly Government:
- ▶ the broad clinical priorities of the Secretary of State for Health and the Welsh Assembly Government (for example, as set out in *National Priorities and Planning Framework 2003–2006* and in National Service Frameworks, or any specific guidance on individual referrals)
 - ▶ the degree of clinical need of the patients with the condition under consideration
 - ▶ the broad balance of benefits and costs
 - ▶ any guidance from the Secretary of State for Health and the Welsh Assembly Government on the resources likely to be available
 - ▶ the effective use of available resources.
- 6.2.6.9 The Institute also takes into account the longer-term interests of the NHS in encouraging innovation in technologies that will benefit patients.
- 6.2.6.10 Below a most plausible ICER of £20,000/QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate. Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:
- ▶ the degree of uncertainty surrounding the calculation of ICERs
 - ▶ the innovative nature of the technology
 - ▶ the particular features of the condition and population receiving the technology
 - ▶ where appropriate, the wider societal costs and benefits.
- 6.2.6.11 Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong. 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.

- 6.2.6.12 The Committee has a strong preference for expressing health gains in terms of QALYs. In circumstances where the health gain is expressed in terms of life-years gained, the range of most plausible ICERs that are acceptable will be substantially lower than those described above. The exact adjustment that the Committee considers should be made to take account of the differences between QALYs and life-years gained are guided by reference to the population norms for HRQL for the affected population, and generally lower than this for a sick population.

6.2.7 Provisional decision

- 6.2.7.1 In coming to its provisional decision the Appraisal Committee will derive its recommendations directly from the evidence base and the views expressed by clinical specialists and patient experts at the Committee meeting. The Committee will attempt to resolve uncertainties as far as possible. However, if there remains significant uncertainty about either the clinical effectiveness evidence or the provisional assessment of the cost effectiveness of the technology, the Appraisal Committee may request additional information or suggest that further research is undertaken before even a provisional decision is made.
- 6.2.7.2 The Appraisal Committee will consider carefully who benefits most from the technology and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential benefit or risk of adverse events.
- 6.2.7.3 The Appraisal Committee, under the direction of the Chair, will endeavour to reach a consensus view on the preliminary recommendations for the ACD. If a consensus cannot be reached then, exceptionally, a vote may be taken among members present at the meeting.
- 6.2.7.4 Before calling for a vote, the Chair of the Appraisal Committee will consider whether deferring the topic for further consideration at the next meeting is likely to achieve a consensus decision. Only when this is unlikely is a vote taken. The decision after anonymous voting will be carried on a simple majority, with the Chair of the Appraisal Committee having a casting vote.

6.2.8 Preparation of the ACD

- 6.2.8.1 A consensus view on the Committee's preliminary recommendations on the use of the technology is reached during the Committee meeting. The Institute's appraisals team, in consultation with the Committee Chair and the Appraisal Committee, then prepares the content of the ACD.
- 6.2.8.2 The ACD goes through a number of drafting stages with consultation with members of the Appraisal Committee before a final version is agreed and sent out for the official consultation to consultees and placed on the Institute's website.
- 6.2.8.3 Formulating the 'Appraisal Committee's Preliminary Recommendations' and 'Considerations' sections of the ACD represents an important component of the Appraisal Committee's work at this stage. The Considerations section identifies the key evidence considered 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 been used in order to resolve areas of conflict.

6.3 Appraisal Committee meeting to consider the FAD

6.3.1 Review of consultation comments

- 6.3.1.1 Another meeting is held to review the results of the consultation on the ACD. The Committee is principally interested in the comments from consultees, commentators and the website consultation on the ACD within the context of the evidence base reviewed at the meeting to develop the ACD. The comments received on the key issues identified at the first meeting are carefully reviewed.

- 6.3.1.2 At this stage it is important to separate the submission of any new data from the general comment and opinion received on the ACD. Deciding whether new data are important is a significant component of the work of both the Appraisal Committee and the Institute's appraisal team at the second meeting. New data will generally only be accepted if they are likely to materially affect the provisional recommendations in the ACD, and only by prior agreement with the Appraisal Programme Director.
- 6.3.1.3 Under these circumstances new data or additional analysis of the original evidence can be reviewed at this stage but, if considered substantial, might lead the Committee to conclude, on the advice of the Appraisal Programme Director, the Chair of the Appraisal Committee and the Executive Lead, that it is necessary to re-formulate and re-issue an ACD for a further round of consultation rather than issue a FAD.
- 6.3.1.4 Examples of data that might lead the Committee to re-issue an ACD include:
- ▶ new trial evidence (published or unpublished) that was not included in the Assessment Report and which substantially adds to or alters the Appraisal Committee's original view of the evidence base
 - ▶ new analysis of an existing or re-worked economic model leading to substantial re-evaluation of the cost effectiveness of the technology
 - ▶ consultee comment that identifies key evidence that was missed in the original Assessment Report and that may have a substantial impact on the Appraisal Committee's deliberations
 - ▶ changes in the licensed indications of the technology.

6.3.2 Consideration of the Appraisal Committee's preliminary recommendations

- 6.3.2.1 The Appraisal Committee at this stage 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, 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).

6.3.3 Preparation of the FAD

- 6.3.3.1 A consensus is arrived at on the nature and importance of the comments from consultation and whether changes to the ACD are needed. The appraisals team, in consultation with the Committee Chair and the Appraisal Committee, then prepares the content of the FAD in which the 'Appraisal Committee's preliminary recommendations' become 'Guidance'.
- 6.3.3.2 The FAD undergoes a number of drafting stages involving consultation with the Appraisal Committee before a final version is agreed.
- 6.3.3.3 As is the case with the ACD, the final content of the 'Considerations' section of the FAD is modified to clarify the key evidence considered by the Appraisal Committee and its view of this evidence. It clearly describes the Appraisal Committee's thoughts on each aspect of the guidance. It highlights particularly the areas of contention that have arisen during the Appraisal Committee discussions of the evidence and details in general terms the written and oral inputs that the Appraisal Committee has used in order to resolve areas of conflict.

6.4 Final guidance

- 6.4.1 The final review of the FAD and approval for distribution to consultees 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.
- 6.4.2 If an appeal is required and some or all of the appellants' points have been upheld, the Committee may be required to review the appraisal at a further meeting. Under these circumstances the Committee may require further evidence from consultees, clinical specialists, patient experts and the Assessment Group.

APPENDIX A Steering Group and Working Parties

Steering Group

Andrew Dillon (Chair)
Chief Executive, NICE

David Barnett (Chair, Methodology Working Party)
Chair, Appraisals Committee

Carole Longson (Chair, Process Working Party)
Appraisal Programme Director, NICE

Methodology Working Party

David Barnett (Chair)
Chair, Appraisals Committee

Ron Akehurst
Dean and Professor of Health Economics, School of Health & Related Research, University of Sheffield

Chris McCabe
Senior Lecturer in Health Economics, University of Sheffield

Tony Culyer
Non-Executive Director, NICE

Marcia Kelson
Director, Patient Involvement Unit

Carole Longson
Appraisal Programme Director, NICE

David Murray
Technical Team Leader, NICE

Mark Sculpher
Professor of Health Economics, University of York

Andrew Stevens
Professor of Public Health, University of Birmingham

Kent Woods
Chief Executive, Medicines and Healthcare products Regulatory Agency

APPENDIX B Task groups

Clinical effectiveness

Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

Keith Abrams

Professor of Medical Statistics, University of Leicester

Mike Clarke

Nursing Collaborating Centre

Sarah Garner

Technical Advisor, NICE

Gill Gyte

National Childbirth Trust/Cochrane Collaboration

Philip Home

Professor of Diabetes Medicine, University of Newcastle Upon Tyne

Peter Littlejohns

Clinical Director, NICE

Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology Assessment

Jackie Napier

Specialist Care Medical Director, Schering Healthcare

Janet Robertson

Technical Advisor, NICE

Economics

Mark Sculpher (Chair)

Professor of Health Economics, University of York

John Brazier

Professor of Health Economics, University of Sheffield

Andrew Briggs

Public Health Career Scientist, Health Economics Research Centre, Department of Public Health, University of Oxford

Martin Buxton

Academic Director of Health Economics, Brunel University

Ruth Carlyle

Information Materials Programme Manager, Macmillan Cancer Relief

Karl Claxton

Senior Lecturer in Economics, University of York

Francoise Cluzeau

Guidelines Technical Advisor, NICE

Michael Donaghy

Clinical Neurologist, Radcliffe Infirmary, Oxford

Dogan Fidan

Health Technology Analyst, NICE

Alastair Fischer
Health Technology Analyst, NICE

Nick Wells
Senior Director, Outcomes Research, Pfizer

Patient evidence

Marcia Kelson (Chair)
Director, Patient Involvement Unit

Iain Chalmers (comments on documents)
Project Co-ordinator, James Lind Initiative

Eleanor Donegan
Health Technology Analyst, NICE

Rahana Mohammed
Policy & Campaigns Manager, Arthritis Care

James Partridge
Chief Executive, Changing Faces

Anne-Toni Rodgers
Corporate Affairs Director, NICE

Peter Sharplin
Manager of Health Economics, Aventis Pharma

Sophie Staniszewska
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Karen Thompson
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Technology assessment

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Stirling Bryan
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Director, National Collaborating Centre for Health Technology Assessment

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Suzy Paisley
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Seren Phillips
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Cathryn Thomas
Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Norman Waugh
Professor of Public Health Medicine, University of Aberdeen

APPENDIX C Glossary

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 adheres to the health advice agreed with healthcare professionals. May also be referred to as 'compliance'.

Aggregated data

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

Appraisal Committee

Standing advisory committees of the Institute. Members are drawn from the NHS, patient/carer organisations, relevant academic disciplines and the pharmaceutical and medical devices industries.

Appraisal Programme Director

The Appraisal Programme Director (APD) is responsible for the delivery of the appraisal programme. In addition to, and in conjunction with, the Executive Lead the APD is responsible for signing off consultation documents at various stages of an individual appraisal. The APD is also responsible for ensuring that appraisals are conducted in accordance with the published appraisal process and methodology.

Assessment Group

An independent academic group commissioned by the NHS Research and Development Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee.

Assessment protocol

Written instructions for the conduct and analysis of the assessment of a technology.

Assessment Report

In technology appraisals, a critical review of the clinical and cost effectiveness of a health technology/technologies. 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

The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.

Bias

Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.

Blinding (masking)

Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.

Case-control study

Comparative observational study in which the investigator selects individuals 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.

Case series

Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.

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.

Class (of drugs in NICE appraisal)

A group of drugs with the same or similar mechanism of action which 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 systematic review of care against explicit criteria and the implementation of change.

Clinical effectiveness

The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical efficacy

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

Clinical specialist

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

Cochrane Library

A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.

Cohort study

A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Commentator

Organisations that engage in the appraisal process but that are not asked to prepare a submission dossier, and that receive the Final Appraisal Determination (FAD) for information only, without 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 where appropriate.

Commercial in confidence

See 'In confidence material'.

Co-morbidity

Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.

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 as a result 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 one would trade off for a given quality improvement is independent of the amount of remaining life.

Consultation

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

Consultee

Organisations that accept an invitation to participate in the appraisal. Consultees can participate in the consultation on the draft scope, the Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations representing patient/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 peoples' observed or stated preferences using, for example, the willingness-to-pay approach.

Cost-effectiveness acceptability curves

A graph that plots the willingness to pay per extra unit of effect of an intervention on the x axis against the probability (chance) that the intervention will be cost effective on the y 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, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model

An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the 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 an evaluation, which relates specifically to the decision(s) that the evaluation is designed to inform.

Discounting

Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.

Dominance

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

Effectiveness

See 'Clinical effectiveness'.

Efficacy

See 'Clinical efficacy'.

Epidemiological study

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

Equity

Fair distribution of resources or benefits.

Evaluation report

In technology appraisals, the written evidence considered by the Appraisal Committee.

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).

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 for a given treatment alternative is higher than that of the next, more effective, alternative.

External validity

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

Extrapolation

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

Forrest plot

A common way of presenting the results of a meta-analysis. The estimates of treatment effects, along with their standard errors, are plotted on the same axis. From this plot, an idea of the distribution of the estimates can be gained.

Generalisability

The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true 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 'Utility'.

Health-related quality of life (HRQL)

A combination of an individual's physical, mental and social well-being; 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.

Healthy-years equivalent

A measure of health-related quality of life 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 QALY because not only is it based on the individuals' preferences for the duration of life, but also on the individuals' preferences for the states of health.

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' as 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 difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Indication (specific)

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

Intention-to-treat analysis (ITT analysis)

An analysis of the results of a clinical study 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 (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See '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 protecting and promoting 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 summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

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 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

The progression of a disease when untreated.

Observational study

Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies 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 may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.

Patient expert

Acts as expert witness to the Appraisal Committee. Patient experts have experience of the use of 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.

Per-protocol analysis

Analysis of individuals who completed the trial according to the pre-specified trial protocol.

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

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

Product licence

An authorisation from the 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 reduce sources of bias.

Randomised controlled trial (RCT)

A comparative study in which participants 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).

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 means 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 in order 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.

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.

Standard gamble

A method used to measure utility (for example, health states) where the individual is asked to make a trade-off between having a chronic disease (the state being valued) for a certain period of time, and a gamble with good health for the same period and death. The chances of ending up in good health are varied until the individual is indifferent between the certain and uncertain choices.

Synthesis of evidence

A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order 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 pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Technical Lead

An appraisals team member who has responsibility for the technical aspects of the appraisal including liaising with the Assessment Group, scoping the appraisal, preparing drafts of consultation documents and advising the Appraisal Committee on technical aspects of the appraisal. There may be more than one Technical Lead for an appraisal.

Technology

See 'Health technology'.

Technology assessment

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

Time horizon

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

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 choices of intervention available.

Treatment sequence

The intervention being evaluated and the comparator are used sequentially in the management of a condition.

Utility

A measure of the strength of an individual'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.

Willingness-to-pay

Individuals are asked the maximum, in monetary terms, they are willing to give up (from surplus income) to acquire the benefits of the intervention.



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