

National Institute for Clinical Excellence
Guide to the Methods of Technology
Appraisal

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Foreword

The National Institute for Clinical Excellence (NICE) 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 as formally requested by the Department of Health (DH) 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 should be used as 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.

Accompanying this methodological guidance document is a companion document describing the Institute's appraisal process (*Guide to the Technology Appraisal Process*).

This document should be seen as an aid to thought during the process of submission. It will therefore require interpretation in the context of each specific technology. It is indicative of 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 prior agreement of the Appraisal Programme Director.

The Institute is aware that many who are not expert in technology appraisal will read this document. Although a glossary of terms referring to the methods of technology appraisal and systematic reviews has not been included, two useful glossaries are the US Panel Guidelines (Gold MR *et al.*) and Culyer AJ, "A glossary of the more common terms encountered in health economics".

Because the methodology of technology appraisal is developing rapidly, there remain several 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 to adopt a consistent approach regarding cost-effectiveness analysis. For this reason the Institute has decided to adopt a 'reference case' approach, designed to be the most appropriate for the Appraisal Committee's purpose.

The Institute would like to encourage those with the appropriate skills to participate in the further development of the methods of technology appraisal. Innovative approaches to aspects of technology appraisal that are 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 first discussed and agreed with the Appraisal Programme Director.

Those preparing submissions may discuss the perspective and presentation of their evidence with the Appraisal Programme Director and/or the Technical Lead for an individual appraisal prior to making their submissions. However, there are limits to the extent to which the Institute's staff can engage in discussions about submissions. Opportunity is provided at the beginning of the appraisal process to discuss with Institute staff and the Assessment Group matters regarding methodology about which there might be doubt.

The Institute is itself a sponsor of research into the methods of technology appraisal and would welcome suggestions for both primary and secondary research that might lead to improvements in methods and make subsequent editions of this document more helpful. Any such suggestions ought to be made in the first instance to the Appraisal Programme Director.

The Institute is aware that there exists a national shortage of the skills required for technology appraisal. Manufacturers and sponsors of technologies who lack the relevant methodological skills in-house are urged to 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 which forms the basis of it.

List of abbreviations

CBA	Cost-benefit analysis
DH	Department of Health
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

The Institute issues guidance on technologies that have successfully completed the regulatory or quality assurance procedures required to obtain a marketing authorisation. The safety, clinical efficacy and quality of technologies is therefore taken as a given; the methods described here are focused on the Institute's objectives, which are to establish the clinical and cost effectiveness of the technologies it is asked to appraise.

1.1 Health technologies and their selection

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 are as follows:

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

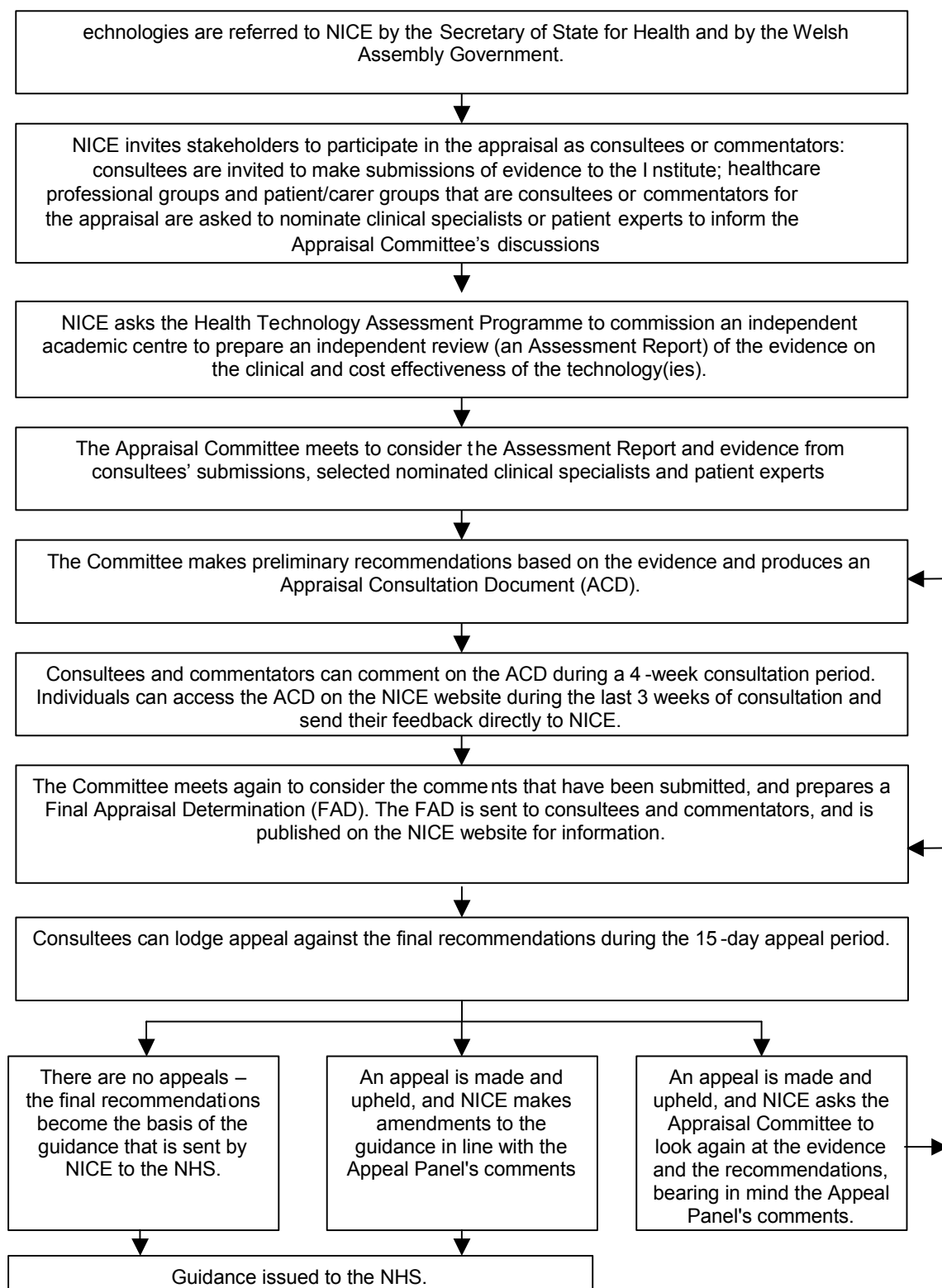
The Institute provides guidance to the NHS on the use of selected new and established health technologies. The purpose of the appraisal carried out by the Institute is as described in the directions of the Secretary of State for Health and the Welsh Assembly Government: that is, to appraise the clinical benefits and the costs of those interventions notified by the Secretary of State for Health and the Welsh Assembly Government and to make recommendations.

The Department of Health and the Welsh Assembly Government select technologies for appraisal based on one or more of the following criteria.

- Is the technology likely to result in a significant health benefit, taken across the NHS as a whole, if given to all patients for whom it is indicated?

- Is the technology likely to result in a significant impact on other health-related Government policies (for example, reduction in health inequalities)?
- Is the technology likely to have a significant impact on NHS resources (financial or other) if given to all patients for whom it is indicated?
- Is the Institute likely to be able to add value by issuing national guidance? For instance, 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?

1.2 Summary of the appraisal process



What is technology appraisal?

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

- scoping
- assessment
- appraisal.

1.3.1 Scoping

The Institute scopes the specific questions to be addressed for each technology appraisal. This defines the issues of interest (for example, population, comparators) as clearly as possible. Consultees and commentators are consulted during the scoping process.

Through the consultation process, the Institute develops a final scope that describes the boundaries of the appraisal and the parameters that are to be investigated. The scope captures the therapeutic aims of the technology, for example, life extension, benefit for a specific group or enhanced tolerance. Scoping identifies issues of relevance to people involved in the provision or consumption of healthcare that may involve the technology and the questions that should be answered. The scope is further developed into a protocol for technology assessment.

1.3.2 Assessment

Assessment is a systematic and independent evaluation of all the relevant evidence available with the aim of producing a best estimate of the clinical and cost effectiveness of the technology for a specific indication. It normally has two mutually dependent components: a systematic review of the evidence and an economic evaluation. Health technology assessment aims to support appraisal decisions on the key questions identified during the scoping stage. The assessment process requires an understanding of the appraisal question and the context within which it is to be addressed, covering, for example, the description of care as currently delivered, the comparators and appropriate dimensions of comparison. 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

Appraisal is a consideration of the outputs of the assessment process within the context of additional information supplied by consultees and commentators. The Appraisal Committee translates the evidence available in the Assessment Report and elsewhere into an appraisal decision, applying judgements on the importance of a range of factors that may vary from appraisal to appraisal. While there is a boundary between assessment and appraisal, it is recognised that the division is not perfect and judgement about, for example, choice of outcome measures to be investigated influences the appraisal process.

1.4 Guiding principle

In general, technologies can be considered clinically effective if they confer a net health benefit 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 health implications for the wider group of patients in the NHS are considered alongside the effects for those patients directly benefiting from the technology of interest.

1.5 The methods of technology appraisal

The purpose of this document is to provide an overview of the principles and methodologies of assessment and appraisal within the context of NICE appraisal processes. The aims are to introduce the concepts underlying each stage of the appraisal process and to describe in principle what is required of participants considering the submission of evidence to NICE. Within this document, the roles of participants in the NICE appraisal process are described and the methodologies underlying each stage of the process (scoping, assessment, appraisal) are summarised.

The Institute's appraisal process relies on information and input from a number of sources, including the Assessment Group, manufacturers and sponsors, healthcare professionals and patient/carer representatives. This document describes the methodology of technology appraisal and is the foundation for detailed documents addressing issues of relevance to each group. Detailed information for individual groups participating in an appraisal is provided in the following documents.

- *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*
- *Contributing to a Technology Appraisal: A Guide for Clinical Specialists and Patient Experts.*

2 Defining the scope of the appraisal

The Institute scopes the questions to be addressed for each technology appraisal. This defines the issues of interest (for example, population, comparators) as clearly as possible. Consultees and commentators are consulted during the scoping process and are invited to a workshop to help define the final scope that describes the boundaries of the appraisal and the parameters that are to be investigated. The Assessment Group further develops the scope into an assessment protocol.

The clinical and cost effectiveness parameters that are defined in the scope include:

- the clinical problem and the patient population(s) for whom treatment is being assessed
- the technology and its treatment setting (for example, hospital [inpatient and outpatient], community)
- the comparator technologies (and their treatment setting)
- the outcome measures to be assessed (that is, health and other outcomes)
- the measures of costs to be assessed
- the time horizon over which benefits and costs are assessed
- other considerations (for example, identification of patient subgroups for whom the technology is particularly clinically/cost effective).

2.1 Components of the scope

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

A clear definition of the spectrum of disease (or other clinical problem) relevant to the new technology is required. The patient groups within this spectrum (including their age and sex distribution, and co-morbidities) need to be specified. These would normally reflect demographic characteristics (age, sex, ethnic or socio-economic group), biological disease differences (phenotypes and genotypes; for example, distinguishing between stable and unstable angina or type I and type II diabetes), different elements of the

spectrum of severity of disease, the degree to which harmful effects of the new technology may affect different patient groups (for example, pregnancy and serious co-morbidity), and the capacity to benefit different patient subgroups.

2.1.2 The technology and its treatment setting

This includes information on the development status of the technology, current range of applications, potential future uses and licensed applications for pharmaceuticals. The circumstances of use must be carefully specified – particularly where these differ from the circumstances in which alternative treatments for the same patient group might be used.

2.1.3 The comparator technologies

Comparator technologies are specified as precisely as the technology being appraised. There are frequently a number of potential comparator technologies, as practice is not necessarily consistent across England and Wales and between the UK and elsewhere. Comparison is with all relevant comparators, with consideration given to current practice and the natural history of the condition without treatment. Although best alternative care is the essential comparator, technologies representing typical UK care are also necessary where they may differ. Natural history, best supportive care or some other alternative treatment may also provide helpful comparators. Sometimes both intervention and comparator will be a treatment sequence.

2.1.4 The health outcome measures

As far as possible, principal measures of outcome are identified as early as possible. For the valid analysis of clinical effectiveness the principal outcome(s) should be clinically relevant; that is, they should measure health effects that are important to patients. The clinically relevant outcomes should be amenable to cost-effectiveness analysis.

2.1.5 The measures of costs

An outline of the potential direct and indirect resource and cost implications for the NHS (and Personal Social Services) that the introduction of the technology would be expected to bring.

2.1.6 The time horizon over which benefits and costs are assessed

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

2.2 The consultee workshop

Proposed appraisal topics identified by the Department of Health and the Welsh Assembly Government and approved by Ministers of Health for consultation are discussed at a consultee workshop, which takes place before topics are formally referred to the Institute. The workshop aims to bring together discussion on the scope of the appraisal from different perspectives in order to produce an appropriate final scope of the appraisal and an assessment protocol should the topic be formally referred to the Institute.

During the workshop, consultees and commentators contribute their opinions regarding the appropriate format for the appraisal and give their views on important issues to be considered. Discussions at the consultee workshop capture key questions to be included within the appraisal's scope in order to define the relevant issues to be addressed and in particular to help:

- 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.

Further information relating to consultee workshop is included in the Institute's *Guide to the Technology Appraisal Process*.

3 Evidence for assessment and appraisal

3.1 Introduction

Consideration of an inclusive and high-quality evidence-base is fundamental to the appraisal process. Evidence on a number of dimensions, of various types and from multiple sources may be relevant to varying degrees 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, the analyses and their interpretation are of the highest standard and are transparent to scrutiny.

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)
- properly reported, inclusive of all contextual 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 render comparable the benefits from different interventions, and to different patient groups).

Similarly, the analyses and modelling should be methodologically sound and, in particular, minimise biases (for example, through the use of evidence from randomised trials to estimate relative treatment effects, and the presentation of explicit criteria by which studies are included and excluded). They should also be replicable, have face validity (that is, be plausible), and should be open to external scrutiny.

3.2 Evidence for relative treatment effects

The treatment effect of a technology can, in essence, be summarised as the difference in health state or quality of life that would be experienced by patients receiving the technology and the health state or quality of life of the same group were they to receive alternative care.

The primary research methods and designs that are used to measure the treatment effect can be broadly categorised into observational or experimental studies. The most reliable evidence about the relative treatment effects of an intervention emerges from experimental studies with high internal and external validity that have a priori defined inclusion and exclusion criteria. The different types of study design can therefore be ranked according to a hierarchy of evidence that describes their relative validity for relative treatment effect (see Box).

Hierarchy of study designs for relative treatment effects

Level 1	Randomised controlled trials
Level 2	Quasi-experimental studies (for example, trials without randomisation)
Level 3	Controlled observational studies (cohort studies, case-control studies)
Level 4	Observational studies without control groups (case series)
Level 5	Expert opinion based on pathophysiology, bench research or consensus

Studies at the bottom of the hierarchy are more prone to sources of bias including publication, retrieval, selection, performance, measurement and attrition biases. However, for cost-effectiveness modelling, it may be quite appropriate to use observational evidence for parameters other than relative treatment effect (see Chapter 5).

In some appraisals there will also be pre-existing, well-conducted, systematic reviews, which may be considered in parallel with the primary evidence.

3.2.1 Randomised controlled trials

Randomised controlled trials (RCTs) are designed to minimise potential external influences in order to isolate the effects of a single variable, namely the intervention, 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 intervention relative to those that are

associated with the control. RCTs are therefore first in the hierarchy of evidence for measures of relative treatment effect.

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 to be preferred over other study designs; and, where appropriate, double-blind RCTs are to be preferred over open RCTs. Where no head-to-head trials are available, consideration will be given to indirect comparisons subject to careful and fully described analysis.

Aspects that affect the validity of RCTs include blinding, the means of randomisation (for example, concealed allocation), and the completeness of follow-up. Other factors include the numbers of people randomised, the patient groups considered, the outcomes measured, and the time span of observation.

In some circumstances the available RCT evidence may be limited (and limited in terms of external validity), be of uncertain quality, or be absent altogether.

3.2.2 Non RCT evidence

The problems of confounding lack of blinding, incomplete follow-up and frequent lack of a clear denominator and endpoint will usually be much worse in non-randomised studies; but in some circumstances, evidence from these studies may be needed to supplement what is available from RCTs to estimate relative treatment effect. Therefore, 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 (see Box, page 19). The design of the study will be formally evaluated using a recognised, evaluated quality checklist.

Furthermore, in order to understand certain elements vital to the overall evaluation of clinical and cost effectiveness, it will almost always be necessary to go beyond RCT evidence. Such elements might include:

- long-term outcomes including mortality
- intermediate-term side effects and long-term adverse (or unanticipated beneficial) effects
- evidence allowing the translation of trial outcomes into quality-of-life measures.

Inferences about relative treatment effect 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 will be examined to gain some assurance of the validity of any conclusions drawn from it.

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

The evidence requirements for economic evaluations include the quantification of the effect of the interventions 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 in such a way as to reflect individuals' preferences. On the cost side, evidence requirements include quantifying the effect of the interventions 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. For example, while randomised trial evidence should be identified to estimate the relative treatment effect of interventions, such evidence may not be necessary to quantify these effects in terms of HRQL and costs.

Furthermore, there are always likely to be imperfections in the evidence base available for economic evaluation. For example, small sample sizes may

result in some parameters being estimated with a low degree of precision, and evidence on effectiveness might come from outside the UK 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 taken about the use of new technologies – such evidence limitations cannot be used to justify foregoing formal economic evaluation. Rather, studies should use the evidence available, be explicit about evidence limitations and any attempts to overcome these, and quantify as fully as possible the implications of the evidence limitations for the uncertainty in the results of the analysis.

3.4 Evidence for other appraisal considerations

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

3.4.1 Acceptability, appropriateness and preference

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 intervention (as compared to alternative technologies) by patients, carers or professionals. As a result, individuals or groups may hold preferences for alternative health technologies, for instance related to the frequency or nature of adverse effects, administration route of a medicine (for example, daily vs. weekly, oral vs. injection), or the physical design/appearance of a device, or have ethical concerns. These are important considerations for an appraisal, which influence judgements on the availability of technologies and the extent of choice between them.

Evidence on these dimensions may take a number of forms, be based on quantitative or qualitative measurements, and originate from a range of sources with varied intrinsic methodological strengths. These include (listed in suggested evidence hierarchy – strongest first):

- literature reviews
- adverse effect/adherence/continuation data collected in research studies
- patient surveys, for example, of adverse effects or preferences
- testimonies from clinical specialists and patients, ideally synthesised

3.4.2 Feasibility and impact

Similarly, clinically effective and cost-effective health technologies may require additional consideration of the organisational issues which impact on patients and carers or those providing care. Such factors may affect the feasibility of a technology's implementation (for example, location or availability of specialist services) or the size of their implementation impact (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.

3.4.3 Equity

The effects of a health technology may deliver benefits differentially across the population. For instance, this may mean that different groups, such as age groups, genders, ethnicities or socio-economic groups could gain more than others. In light of the health needs of such groups in question, these differences may be considered to be unfair or unethical forms of disadvantage.

Again, evidence on equity may take a variety of forms and originate from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and investigation 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 wishing to submit written or verbal evidence is provided in the additional documents listed in Section 1.5.

4.1 Health technology assessment

4.1.1 The Assessment Group

The Assessment Group comprises a panel of independent, academic experts commissioned by the NHS Health Technology Assessment Programme through the NCCHTA to critically review available evidence concerning a technology under appraisal. The Assessment Group forms an independent view of the evidence based on published information and submissions from manufacturers and sponsors. The Assessment Group consults in their gathering of evidence and synthesises available evidence in their report.

4.1.2 The Assessment Report

The Assessment Group prepares an Assessment Report for the technology under appraisal; this is the most important, but not the only, source of information for the Appraisal Committee in their decision-making process.

The Assessment Report is a critical review of the clinical and cost effectiveness of the technology under appraisal. It normally includes a systematic review, following recognised guidelines, of the effectiveness evidence relevant to the defined questions. It is not to be considered 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 derived 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 each element for the interpretation of outcomes in question. The Assessment Report draws on submissions from manufacturers and sponsors. The extent to which the Assessment Group uses submitted evidence depends on how closely it fits with the criteria defined in the appraisal protocol.

The Assessment Report is the responsibility of the authors producing it. It is not expected to provide the final conclusions on the appropriate use of a technology within the NHS, but it is used by the Appraisal Committee as an important part of the evidence that informs its consideration of the technology under appraisal.

4.2 Manufacturers and sponsors

4.2.1 Evidence submitted to NICE

Manufacturers and sponsors must identify all evidence pertinent to the appraisal. They must supply a list of all studies sponsored by them or known to them. This should include all clinical trials as well as follow-up studies and registry evidence. They must also supply relevant study evidence to which they have privileged access, which is not in the public domain. In particular, care should be taken where technologies are being appraised prior to licensing; manufacturers must ensure that sufficient clinical trial evidence is made available to allow NICE to fulfil their appraisal according to the defined scope.

Where evidence from cohort and case series is supplied, it is essential that a full list of all such studies known to the manufacturer be provided. It must be accompanied by a full report of baseline characteristics and the best equivalent evidence on best comparator care.

At the earliest opportunity, manufacturers are requested to make available details of which studies they will be including in their submissions. Where there is extensive unpublished information, the Assessment Group may request the study reports prior to the submission date.

Manufacturers and sponsors are not routinely required to submit a full systematic review as this is undertaken by the Assessment Group and is issued for consultation prior to the first Appraisal Committee meeting. This gives consultees and commentators the opportunity to address any issues with either the methodology or the study selection. However, 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 will have used accepted methodology and have been appropriately reported.

Manufacturer submissions must include an executive summary of a maximum of five pages, and the total report must not be more than 50 pages, including appendices (see Section 4.2.2).

The results of RCTs should be reported using the CONSORT statement as a guide (www.consort-statement.org).

4.2.2 Summary of requirements for manufacturers and sponsors' NICE submissions

Submissions would normally include:

- 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 submission of 50 written pages, including appendices (there may, however, be special circumstances, for example, very complex appraisals or where the evidence base is very extensive, where, with the prior agreement of NICE, the main part of the industry submission would exceed 50 pages)
- a synthesis of clinical effectiveness evidence and 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 requirements
- an electronic copy of the model used in the analysis.

The information should be easily accessible and user friendly. Manufacturers and sponsors are strongly encouraged to include any information that the Assessment Group and Appraisal Committee might need (for example, detailed descriptions of any economic model and how it should be used).

4.2.3 Unpublished and part-published evidence

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 evidence from unpublished clinical trials and additional evidence from trials that have either only been published in abstract form or for which only selected information has been reported. In recognition that such information may be systematically different from the published evidence, it is critically appraised and sensitivity analysis is conducted to examine the effects of its incorporation or exclusion. The Institute takes steps to ensure that unpublished evidence is made available without selection, including searches of prospective trial registers and communication with consultees and other researchers.

4.2.4 Commercial in confidence evidence

Under exceptional circumstances unpublished evidence is accepted under agreement of confidentiality; for example, if it 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, the Institute considers it highly desirable that evidence pivotal to the Committee's decisions should be available publicly. At a minimum, the evidence should be available to all consultees and commentators. Consultees and commentators 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

Patient evidence refers to any information originating from patients and/or carers that is able to inform the appraisal of the technology.

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 evidence coverage within 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 standardized instruments (questionnaires) developed using psychometric techniques.

For the purpose of informing its technology appraisals, the Institute is looking for a concise and balanced overview that reflects the full range of patient and carer perspectives, including both majority views and, where applicable, potentially important views that may be held by a minority of patients only. The Institute is interested in capturing a range of patient and carer views on, and experiences of, living with the condition, the impact of a technology on a patient's condition, symptoms, physical, social, psychological and emotional state, as well as what it might be like living without the technology. Patient evidence should be presented as a synthesis of information, balancing positive and negative views, rather than a series of individual testimonials.

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 to 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 and quality of life and lifestyle
- equity issues (that is, the perspectives of specific groups or subgroups of patients who may be disadvantaged in terms access to the technology).

4.3.2 Dimensions of patient experience

Patient experience of treatment and therapy can be classified under broad headings that reflect different stages, each of which can be subdivided into different elements of patient experience:

- experience of disease diagnosis and of the varieties of therapy 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 therapy with the technology
- changes induced by the effects of the technology itself
- experience of disease progression with or without therapy.

Within each of the stages 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 (symptoms, pain, mobility, disability)
 - lifestyles and the choices that matter to patients and carers (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, productivity 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

4.4.1 Evidence submitted to NICE

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-registration studies, which often relates to efficacy and safety rather than 'real world' clinical effectiveness.

The written submissions provide a unique contribution on 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 base-line risk of the condition and capacity to benefit from different subgroups
- identification of appropriate outcome measures and the appropriate use of surrogates
- the relative importance of side effects/adverse reactions and the clinical benefits
- the particular circumstances in which treatment is delivered including:
 - the need for co-treatments
 - the settings in which treatment is delivered (for example, primary versus secondary care, the requirement for specialist clinics)
 - the requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)
- the currently considered 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'
- impact of possible guidance on delivery of the service
- impact of possible guidance on the needs for education and training of NHS staff.

4.5 *Clinical specialists and patient experts*

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 verbal evidence.

4.5.1 The clinical specialist and patient expert witnesses

Two groups of experts – clinical specialists and patients experts – attend the Committee meeting to help in the discussion of the technology being appraised. Neither group should normally have any overriding conflicts of interest.

- *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 should, if at all possible, provide a range of differing perspectives. They provide a view of the technology within the context of current clinical practice, with insights not typically available in the published literature.
- *Patient experts* have experience of the use of the technology and the condition either personally or as part of a representative group. They provide evidence on:
 - an individual view based on the risks and benefits of the technology from personal experience as a patient or carer
 - an understanding of the wider range of patient or carer views.

4.5.2 Format of the evidence

The kind of evidence provided by the experts varies between the clinical specialists and the patients, but there is often a significant degree of overlap between them.

The experts attending the Committee meeting are asked to provide, in advance, a brief written personal perspective of the use of the technology as well as verbal evidence during the meeting.

The verbal evidence provided by the experts should not simply cover similar ground to that which is provided in the written submissions from consultees as above, but should aim to enhance this. Experts should interact directly with the Committee during the live discussion of the technology.

The experts' verbal views can usefully inform the debate in a variety of ways, such as:

- identifying important variations in clinical practice in both the management of the condition in general and specifically 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 the needs of extra staffing or equipment in NHS units, special requirements within the community for patients and carers (for example, travel to hospital for treatment), issues of improved compliance and acceptability.
- giving personal perspectives on the use of the technology and the difficulties encountered. This should include 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 commencing and stopping use of the technology, most typically applied to pharmaceuticals. 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 needs for education and training for NHS staff
- responding to queries that arise from:
 - the lead team presentation (the lead team being two Committee members who present to the rest of the Committee on the topic, 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 the evidence relating to the technologies and their comparators to estimate their clinical and cost effectiveness. These two estimates are, individually, key inputs into the decision-making of the Appraisal Committee. It should also be emphasised that they are interdependent because the comprehensive, transparent reproducible synthesis of all relevant evidence on health effects is a necessary pre-condition for high-quality cost-effectiveness analysis in health technology assessment. In defining these methods, the Institute seeks to promote high quality analysis and to encourage consistency in analytical approaches, while acknowledging the methodological uncertainty in the area and the need for the flexibility to report studies in alternative ways to reflect particular circumstances.

The chapter is divided into 9 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
- NHS impact

5.2 Guiding principles

5.2.1 Clinical and cost effectiveness

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 some important features.

- There is a need for comparability between submissions, between appraisals of different technologies and over time, and therefore a comparative 'reference case' needs to be defined.
- All relevant and feasible alternative interventions for the patient group of interest need to be compared.
- 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 Personal Social Services (PSS).
- Measures of health-related benefits used need to be comparable, not only to help achieve consistency on decisions between submissions (as mentioned above) but also to allow direct comparability with the benefits from other technologies that may be displaced if interventions are adopted that impose additional costs on the health service.
- The time horizon should be sufficiently long to reflect important cost and benefit differences between the technologies under comparison.
- The uncertainty surrounding the estimates of cost-effectiveness needs to be appropriately characterised and clearly quantified.

5.2.2 Synthesis and modelling

The process of assembling evidence for health technology assessment needs to be systematic. That is, evidence needs to be identified, quality assessed and, where appropriate, pooled using explicit criteria and justifiable and reproducible methods. These principles apply to all parameters 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 longitudinal cohort studies for parameters relating to natural history,

randomised trials for relative treatment effects and cross-sectional surveys for resource use and costs. There is also a need for clinical and cost effectiveness to be expressed over an appropriate time horizon, to be relevant to UK practice and patients and to compare all relevant management options for the relevant patient groups. There will, therefore, be a need for an analytical framework within which to synthesise available evidence and to estimate clinical and cost effectiveness relevant to the 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

The evidence requirements for effectiveness include the quantification of the effect of the interventions under comparison on the course of the disease, the impact of those effects on patients' health-related quality of life (HRQL) and the valuation of those impacts in a manner that reflects individuals' preferences.

On the cost side, data requirements include quantifying the effect of the interventions 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. For example, while randomised trial evidence should be identified to estimate the relative treatment effect of interventions, such data may not be necessary, or even appropriate, to quantify these effects in terms of HRQL and costs.

There are always likely to be imperfections 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 and evidence on effectiveness might come from outside the UK 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 taken about the use of new technologies, and therefore data limitations cannot

be used to justify foregoing the process of estimating clinical and cost effectiveness. Rather, studies should use the evidence available, be explicit about data limitations, any attempts to overcome these, and quantify as fully as possible the implications of the data limitations for the uncertainty in the results of the analysis.

5.2.4 Analysis of uncertainty

Decisions about the clinical and cost effectiveness of health technologies have to be taken despite data limitations. However, it is important for the Appraisal Committee to know about the uncertainty associated with their decisions. This requires the use of rigorous methods to quantify the implications of parameter uncertainty, heterogeneity and methodological uncertainty for the results of an analysis. This quantification of decision uncertainty should then feed into subsequent decisions about 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. In some sections, the position statement is set out in italics at the beginning. This is followed by explanation and justification.

5.3.1 The concept of the reference case

There remains considerable debate about the most appropriate methodology for some aspects of health technology assessment. In part, this uncertainty relates to choices that are essentially value judgements – for example, which perspective to adopt and whose preferences to use to value 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.

However, the Institute has to make decisions across different technologies and disease areas, and over time. It is, therefore, important that the methods used to estimate clinical and cost effectiveness to inform the Appraisal Committee adopt a consistent approach. To facilitate this, for those methods

subject to uncertainty, a reference case will be defined 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 ideally include a set of results generated using these reference case methods. This does not preclude additional sets of results 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. The key elements of the analysis described in this chapter are summarised in the table below.

Table 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
Perspective on costs	NHS and Personal Social Services	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 <i>generic</i> instrument	5.5
Method of preference elicitation for health state valuation	Choice-based method (for example, time trade-off; standard gamble)	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
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.9.7

It is recognised that, in some instances, data required to present reference case results will not be available. In these cases, any non-reference-case data that are substituted should be clearly specified and the likely implications of

this data limitation should, as far as possible, be quantified in the analysis of uncertainty. The Appraisal Committee will then make a judgement regarding the weight it attaches to the results of a non-reference-case analysis.

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 role for consultees is particularly important where they 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

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

The main technology of interest and the relevant patient group(s) will be defined in the scope developed by the Institute.

5.3.3 Perspective

For the reference case, the perspective on outcomes should be all health effects whether on patients or other individuals. 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 of an analysis, these analyses should be separately presented.

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. However, when there are significant characteristics of healthcare technologies that have a value to individuals that is independent of

any resulting health implication, these should be noted and, if possible, their value estimated. These characteristics include the convenience with which healthcare is provided and the level of information available for patients. The methods for valuing such effects should be clearly specified and the generalisability of the results assessed.

The Institute works in a specific policy context; in particular, it does not influence the budget that is set for the NHS. Hence, the appropriate policy 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 should be that of the NHS and PSS. However, in offering guidance, the Institute will consider significant resource costs imposed outside the NHS. These costs might be direct costs on patients or carers (for example, travel costs), costs to other public sector organisations or productivity costs.

5.3.4 Type of economic evaluation

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).

The focus on cost-effectiveness analysis is justified by the more extensive use and publication of these methods compared with cost-benefit analysis (CBA), 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 reflecting both mortality and HRQL effects. It is recognised that alternative measures exist (for example, the healthy-year equivalent) that require fewer assumptions about individuals' health preferences, but relatively few economic evaluations have used these methods and their strengths and weaknesses are less 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 alternative measures presented as a non-reference-case analysis.

Despite the role of cost per QALY in the reference case, the Institute recognises that other forms of cost-effectiveness analysis and CBA may have a role to play, as additional analyses. CBA 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 fully described and the uncertainty in the results fully explored.

5.3.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the options under evaluation.

Many interventions have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic disease, which would include ischaemic heart disease, diabetes and many forms of cancer. In such instances, a lifetime time horizon for clinical and cost effectiveness is most appropriate. Such a time horizon is also required in order to quantify the implications of any differential mortality effect between options on mean survival duration. For a lifetime time horizon, extrapolation modelling is often necessary, which should be based on a comparison of several alternative scenarios reflecting different assumptions about future treatment effects (see Section 5.8 on modelling). 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. Uncertainty around the time horizon used in the modelling, especially that related to the availability of underpinning trial evidence, will be critically assessed.

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 appraisal

technology intervention. It should reflect the full range of typical patients as closely as possible, normal clinical circumstances, clinically relevant outcomes and comparison to 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

All health effects should be identified and quantified, with all data sources clearly described. As a reference case, all evidence on outcomes should be attained through the process of systematic reviewing that can be defined as the systematic location, appraisal and synthesis of evidence in order to obtain a reliable overview.

5.4.1.1 Relevant studies

Although, 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, it is recognised that such evidence may not be available. In such circumstances, the implications of potential selection bias resulting from the use of non-trial evidence should be assessed in the analysis of uncertainty.

Separately quantifying the baseline health effects of existing treatments or the disease natural history from the relative effects of a new intervention 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 the appraisal and to practice in England and Wales. Trial data may not be necessary to quantify baseline health effects. However, the methods used to identify and critically appraise sources of data for these estimates should still be stated and justified.

5.4.1.2 Study selection and data extraction

Once the search strategy has been undertaken and a list of possible primary studies has been compiled, each study must be assessed as to 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 their concordance measured. In addition, a log of ineligible studies should be maintained with the rationale for exclusion, as this allows external assessment of the literature search and study selection processes.

As the systematic review is performed retrospectively and is essentially observational, it is open to many sources of bias and therefore should be conducted according to a previously prepared protocol. This formalises the decisions made at the design stage, thereby reducing the risk of bias and ensuring that the review is reproducible.

5.4.1.3 *Critical appraisal*

The validity of the results of an individual study will depend on the robustness of the overall design and execution. Therefore, each individual study should be separately subjected to critical appraisal. This information must be incorporated into the systematic review. Unpublished and part-published evidence should be critically appraised, and sensitivity analysis conducted to examine the effects of its incorporation or exclusion.

5.4.1.4 *Effect modifiers*

Many factors can potentially have an impact on the overall estimate of health effect obtained from a primary study and may explain apparent between-study differences in outcomes. Common examples are characteristics of patients such as age or sex, severity of disease, choice and measurement of outcomes, care setting, additional routine care and, because techniques change, the year of the study. Such effect modifiers should be identified prior to data analysis, either by a thorough review of the subject area or contact with experts.

5.4.2 *Meta-analysis*

Synthesis of outcome data through meta-analysis is appropriate unless precluded by insufficient relevant and valid data that use comparable measures of outcome. Where such data are not available, the analysis should be restricted to a qualitative overview that critically appraises individual

studies and presents their results. However, even in such circumstances, to aid interpretation, Forest plots that illustrate the individual study population results are desirable. The characteristics and limitations of the data (population, intervention, setting, sample size and validity of the evidence) should all be made completely explicit.

Prior to any statistical pooling, an assessment of the degree of heterogeneity in the study results should be undertaken – that is, variability in the effects between studies that may suggest that the study results are dependent on certain study characteristics, such as treatment dose or the comparator used. Statistical heterogeneity of study results can be explored using a random (as opposed to fixed) effects model. Clinical heterogeneity (for example, patient characteristics, intervention dose, frequency) can be managed by judicious use of subgroup analyses and meta-regression methods while having regard to the uncertainty in results. For methodological heterogeneity, the results of sensitivity analyses should be reported both with respect to the studies included (for example, high- and low-quality trials or published and unpublished studies) and methods used for formal synthesis.

If the risk of an event varies 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.

Forest plots should include lines for studies that are believed to contain eligible data missing from the analysis. An estimate of the proportion of eligible data that are missing (because some studies will not include all relevant outcomes) should be given for each analysis.

Where the Institute is appraising a number of interventions and there is good reason to believe that they form a class, the calculated benefits from one member of the assumed class will be attributed to other members. Evidence

will be sought to verify such attributions from both pharmacological data and indirect comparative evidence

The need to assess and have reliable estimates of the effectiveness of diagnostic techniques is recognised. Such assessments should follow the general principles of systematic reviews 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 interventions. This is an area of active (and much needed) 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 and provide a satisfactory justification for any novel approaches.

5.5 Valuing health effects

For cost-effectiveness analysis, the value of health effects should be expressed in terms of QALYs over the appropriate time horizon. For the reference case, a standardised and validated generic (non-disease-specific) instrument is required to classify the effects of interventions in terms of HRQL. Health-state values should be based on public preferences elicited using a choice-based method. Evidence should be presented to indicate that any valuation data taken from the literature have been identified systematically.

To calculate QALYs for any intervention, it is necessary to use a classification system for health states to describe patients' HRQL over time. The Institute requires that health states should be defined in generic terms (to allow comparisons across technologies) using a standardised and validated preference-based measure for which reliable UK population preference values, elicited using a choice-based method such as the time trade-off or standard gamble, are available. However, it is well established that different systems do not give entirely consistent valuations to the same health-state changes and hence results from the use of different systems can only be compared with caution. 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 obvious

contender in the UK is the EQ-5D. Whilst it is widely used and simple to incorporate in studies it 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 currently, or may in the future, meet its underlying criteria. Whatever the instrument used, those submitting the data should give reasons for their choice of instrument. They should also indicate whether they have any evidence that will help the Committee understand to what extent, and for what reason, their choice of instrument will have impacted on the valuation of the QALYs gained.

Additional (non-reference-case) analyses may be submitted using disease-specific-health-state descriptions if these can be justified. Similarly, analyses incorporating health-state values based on patients' preferences may be submitted if they can be justified and they markedly alter the results compared to the reference case.

5.6 Evidence on costs

5.6.1 NHS and PSS costs

For the reference case, costs should relate to all resources that are under the control of the NHS and PSS where differential effects between the interventions under comparison are possible. These resources should be valued using the prices faced by the NHS and PSS. Where the actual price paid for a resource may differ from the 'list' price in the public domain (for example, pharmaceuticals, medical devices), the public list price should be used, with sensitivity analysis to assess the implications of variations from this price. Evidence should be presented to indicate that resource use and cost data taken from the literature have been identified systematically.

Given the cost perspective in the reference case, it is appropriate for the financial costs facing the NHS/PSS to be used as the basis of costing, although 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 studies. Although a

complete list of published unit costs for all services and resources does not exist, useful sources are publicly available. The methods of systematic review for cost data are not as well defined as for evidence 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, their strengths and weaknesses should be described and 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.

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 PSS costs

If important differential impacts are likely between the interventions on non-NHS and PSS direct costs, these should be quantified separately from NHS/PSS costs, and overall results presented as a non-reference-case analysis. Direct costs (for example, patients' travel costs) should be calculated using market prices. Patients' time costs should be calculated using the time-cost-valuation methods described in UK Treasury guidance. The time costs of informal carers or voluntary workers should be valued using the cost of replacement with an appropriate paid worker. Productivity costs should be estimated with full details of methods and assumptions, and careful attention should be paid to avoid double counting with the valuation of health effects in the QALY.

Although not part of the reference case, it is recognised that there will be occasions where non-NHS/PSS costs will be differentially affected by the interventions 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. Identifying a single approach to the valuation of productivity costs is particularly difficult given the complexities regarding double-counting with

QALYs and the role of friction costs. For this reason, this guidance is not prescriptive on how productivity costs should be valued, but full details and justification of methods is necessary. In all cases, these costs should be reported separately from NHS/PSS costs.

5.7 Discounting

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%.

The need to discount to a present value is widely accepted in economic appraisal, 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

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. Models should be probabilistic to reflect the combined implications of uncertainty in all parameters.

As described in Section 5.2.2, modelling provides an important framework for synthesising available evidence and generating clinical- and cost-effectiveness estimates relevant to the analytical framework required for the Appraisal Committee's decision-making. Situations where modelling is likely to be required include those where: trial patients do not match typical patients on whom the technology is likely to be used in the NHS; intermediate measures of outcomes are used rather than effect on HRQL and survival; relevant comparators have not been used; trials do not include evidence on relevant subgroups; and extrapolation is necessary beyond trial follow-up.

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 a long-term time horizon where a range of alternative scenarios is likely to be necessary in order to compare the implications of different assumptions for results. These scenarios might include the assumptions that, beyond primary follow-up, experimental and control groups have identical conditional effects (for example, survival curves run parallel); and that, beyond primary follow-up, the patients on experimental treatment return to the control-group prognosis (for example, survival curves become identical).

It is important for models to quantify the decision uncertainty associated with a technology – that is, if the decision represents the most cost-effective use of resources, the probability that the decision is wrong. The only way that the full uncertainty associated with all parameters can simultaneously be reflected in the results of the model is through the use of probabilistic modelling. Furthermore, in most decision models (which are non-linear), probabilistic methods provide the only reliable means of estimating mean costs and outcomes. When patient-level data are available, stochastic methods using the variability observed in the data should be used to express uncertainty in the cost-effectiveness results.

5.9 Presentation of data and results

5.9.1 Presenting data

All data used to estimate clinical and effectiveness should be presented clearly in tabular form including 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.

As much detail as possible should be provided on the data used in an analysis. The distributions to be used for probabilistic analysis are not arbitrary; rather, there are some standard distributions for particular parameters such as beta distributions for probabilities and gamma distributions for costs.

5.9.2 Presenting expected (mean) cost-effectiveness results

The mean of each component of cost and mean total costs should be presented; mean QALYs for each option compared in the analysis should also be detailed. Incremental cost-effectiveness ratios should be calculated as appropriate.

Standard decision rules should be followed in combining costs and QALYs. These should reflect any situation where dominance or extended dominance exists. Given that most models consist of non-linear combinations of parameters, probabilistic models should be used to generate an unbiased estimate of 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

All parameters used in the analysis will be estimated with a degree of imprecision. Probabilistic modelling 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 measures of uncertainty are cost-effectiveness acceptability curves.

The use of standard sensitivity analysis to quantify the effect of parameter uncertainty in an analysis is partial as it is difficult to incorporate the uncertainty in more than two or three parameters simultaneously. The use of probabilistic decision models (or stochastic analysis of patient-level data) will allow 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, conditional on accepting the data and model structure as valid, the probability that a given intervention is more cost effective than its comparator(s). Decision uncertainty can be shown using

cost-effectiveness acceptability curves that indicate this probability for a range of threshold values that the NHS is willing to pay for an additional QALY.

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 elasticities and expected-value-of-information methods.

5.9.4 Dealing with other forms of uncertainty

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.

Section 5.9.3 deals with the joint effect of the uncertainty in all parameters for overall decision uncertainty in cost-effectiveness analysis, but this is conditional on factors such as a model's structure and data inputs being considered appropriate. These characteristics are also subject to uncertainty, the importance of which can be assessed using sensitivity analysis. A common example 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 without the study results. Another example relates to the alternative assumptions used to extrapolate costs and outcomes beyond trial follow-up. Alternative analyses could also be presented where there is variability between hospitals in the cost of a particular resource or service, or the acquisition price of a particular technology. Uncertainty about the appropriateness of the methods used in the reference case can also be dealt with using sensitivity analysis, but these non-reference-case analyses must be presented separately.

5.9.5 Presenting clinical- and cost-effectiveness analysis for patient subgroups

For many technologies, the capacity to benefit from treatment will vary 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 defining the subgroup should be clearly defined and care should be taken to justify the clinical basis for the subgroup differences. The uncertainty around subgroup-specific parameter estimates should be fully reflected in the analysis.

Given the Institute's focus on maximising health gain from limited resources, it is important to consider the potential for clinical and cost effectiveness to vary by identifiable characteristics of the potential patient population. Typically, it is the capacity to benefit from treatment that will vary between patients, but this may also impact on the subsequent cost of care. There should always be a clear clinical justification for the observed subgroup effect. In particular, ad hoc data mining in search of significant subgroup effects should be avoided. Care should be taken to specify how subgroup estimates 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 patient characteristics associated with the subgroups presented should be clearly identified in order that the Appraisal Committee can judge the appropriateness of the analysis for decision-making.

Generally, intention-to-treat (ITT) analysis, which considers the available data from all patients who were randomised into an RCT, regardless of whether they completed the study, is preferred in the estimate of clinical effectiveness because it preserves the randomisation of the trial population. However, a particular instance of subgroup analysis that may be useful is the analysis of per-protocol populations. The per-protocol population comprises individuals who actually 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 reality.

5.9.6 Identifying future research needs

Candidate topics for future research should be identified which should be based on the results of the analysis of uncertainty.

Part of the analysis of uncertainty is to identify the parameter uncertainty to which the results of an analysis are 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 models 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

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

The estimation of QALYs as defined in the reference case implies a particular position regarding the inter-personal comparison of health gained – namely, that 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 exists in the absence of a clear 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 NHS impact

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.

This information does not form part of the Appraisal Committee's consideration on the availability of a technology in the NHS, but is added to the ACD following the first Committee meeting by the Institute for consultee comment.

As outlined in more detail below, where possible, the information 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 PCT or per ward). It should also be consistent with that provided in other analyses submitted to the Institute, such as that on cost effectiveness.

5.10.1 Implementation/uptake and population health impact

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/life-years gained) in a given population should be calculated. These should take account of the condition's epidemiology and the appropriate levels of access to diagnosis and treatment in the NHS, and highlight any key assumptions or uncertainties.

5.10.2 Resource impact

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

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.

5.10.3 Financial costs

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 as detail as adopted in resource unit information. Supplied costs should 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.

Where the cost of knock-on resources is substantial, the impact on submitted evidence on cost effectiveness should be explored (see Section 5.9.3).

6 The appraisal of the evidence

6.1 Introduction

The purpose of this section is to explain how the Appraisal Committee appraises the evidence presented to it and how it makes the judgments on this evidence that lead to its final conclusions.

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 has the responsibility for the dissemination of the final guidance to the NHS.

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.

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 judgment so that enough information is given to enable the reader to understand what evidence the Appraisal Committee considered and, if appropriate, who provided that evidence.

The Appraisal Committee is not empowered to alter the Secretary of State for Health's directions on the implementation of the Institute's guidance. This includes the mandatory requirement placed upon Health Commissioners to make funds available for implementation of the Institute's guidance within 3 months of publication. However, the Appraisal Committee may consider circumstances in which these requirements should be altered (such as the availability of supporting staff or other technologies) and make additional recommendations to the Institute regarding these. It is then for the Institute to consider if this should be referred to the Secretary of State for further action.

The Appraisal Committee is not able to make recommendations regarding the use of a drug outside its current licensed indications, as published in the manufacturer's Summary of Product Characteristics. The availability of evidence relating to such 'off licence' use is, however, 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 drugs (for example, medical devices), the Appraisal Committee's recommendations are based solely on the evidence that it receives regarding clinical and cost effectiveness. However, evidence of acceptable quality of manufacturing processes such as the CE mark will be required.

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.

The Committee is not able to make recommendations on the pricing of technologies to the NHS other than indicating the relevance of price to the cost-effectiveness calculations, where appropriate.

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

6.2 *First Committee meeting*

6.2.1 Lead team presentation

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 clinical-effectiveness evidence
- overview of the cost-effectiveness evidence 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.

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

The invited experts are selected from the nominations received from official 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 are able to represent the views of people with the condition. 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 Committee's deliberations when decisions regarding the content of the ACD are formulated in draft.

6.2.3 The role of the Assessment Group

Members of the independent Assessment Group attend the first meeting of the Appraisal Committee. This allows the Committee to probe aspects of the assessment that they feel have not been covered sufficiently 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.

If there are any outstanding issues following the meeting, the Committee, through the Institute, will seek clarification from the experts and the Assessment Group.

6.2.4 Functions of the Chair

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 Secretary of State for Health and the Welsh Assembly Government (for details see the Institute’s 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
- - consider the importance of different views amongst the clinical specialists and patient experts.

6.2.5 Appraising clinical effectiveness

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.

This requires the Appraisal Committee to consider the full range of the hierarchy of evidence from randomised controlled trials to observational and qualitative evidence related to the experiences of patients and carers with the technology being appraised.

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.

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 with 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 sub groups of patients
- the risks (adverse effects) and benefits of the technology as seen from the patients perspective
- the position of the technology in the overall pathway of care and what alternative treatments are available.

The Appraisal Committee has considerable discretion when making judgments on the evidence of clinical effectiveness to take all or some of the above factors into account. In addition, they may also consider issues that are reported by the Institute's Citizens Council.

6.2.6 Appraising cost effectiveness

The Institute operates on the basis that its determination of cost effectiveness has to take account of the overall resources available to the NHS. Therefore, decisions on the cost effectiveness of a new technology must include judgments on the implications for other healthcare programmes that may be displaced by the adoption of the new intervention.

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.

The Appraisal Committee has discretion to take 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.

The Committee also has to make judgments 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.

Where the evidence on clinical effectiveness used to estimate cost effectiveness is characterised by 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 that which is dependent to a large extent on theoretical modelling alone.

The Committee's judgments on cost effectiveness take account of the following factors:

- consideration of the submitted economic models including their structure, plausibility of their assumptions, and the evidence inputs and outputs
- the Committee's preferred modelling approach, taking account of the critique of the manufacturers' models by the Assessment Group
- identification and resolution of uncertainty which includes:
 - identification of an acceptable point estimate for cost effectiveness
 - review of the uncertainty in cost effectiveness (for example, by the use of cost-effectiveness acceptability curves).

The Appraisal Committee does not use a fixed incremental cost-effectiveness 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 interventions. Estimating this threshold would require complete information about the costs and QALYs from all competing healthcare programmes. These information requirements are beyond what is currently available in any healthcare system. 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 incremental cost-effectiveness ratio (ICER) of a particular technology compared to 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.

The Appraisal Committee has been given discretion to take those factors it considers most appropriate to each appraisal into account when determining cost effectiveness. 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 (for details see the Institute's Guide to The Technology Appraisal Process) and it will also take account of the advice that the Institute receives from its Citizens Council.

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 such as the degree of uncertainty surrounding the calculation of ICERs, the innovative nature of the technology and the particular features of the condition and population receiving the intervention. 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.

6.2.7 Provisional decision

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. If, however, there remains significant uncertainty in 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.

The Appraisal Committee will consider carefully who benefits most from the technology and if there are subgroups of individuals for whom the effectiveness evidence suggests differential benefit or risk of adverse events.

The Appraisal Committee, under the direction of the Chair, will endeavour to reach a consensus view on the content of the guidance for the ACD. If a consensus cannot be reached then, exceptionally, a vote may be taken amongst members present at the meeting.

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 where this is unlikely is a vote taken. The decision after a vote is taken will be carried on a simple majority, with the Chair of the Appraisal Committee having a casting vote.

6.2.8 Preparation of the Appraisal Consultation Document (ACD)

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.

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.

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 their 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 inputs, both written and verbal, that have been used in order to resolve areas of conflict.

6.3 *Second Committee meeting*

6.3.1 Review of consultation comments

The second meeting is held to review the results of the consultation on the ACD. As such, the Committee is principally interested in the consultee, commentator and web comments on the ACD within the context of the evidence base reviewed at the first meeting. The comments received from consultees, commentators or via the web on the key issues identified at the first meeting are carefully reviewed.

At this stage it is important to separate the submission of new data (if any) from general comment and opinion 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.

Submission of new data or additional analysis of the original evidence can be reviewed at this stage but, if considered substantial, this might lead the Committee to conclude that it is necessary to re-formulate and re-issue an ACD for a further round of consultation rather than issue a Final Appraisal Determination (FAD).

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

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
- their 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 DH regarding the application of implementation criteria agreed with the DH
- 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

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'.

The FAD undergoes a number of drafting stages involving consultation with the Appraisal Committee before a final version is agreed and sent out for consultation with consultees and placed on the Institute's website.

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 their 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 inputs both written and verbal that the Appraisal Committee has used in order to resolve areas of conflict.

Appendix A Steering Group and Working Party

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 of School of Health & Related Research, 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	Director, NHS Health Technology Assessment Programme

Appendix B Task Groups

Clinical Effectiveness

Andrew Stevens (Chair)	Professor of Public Health, University of Birmingham
Keith Abrams	Dept of Epidemiology & Public Health, University of Leicester
Mike Clarke	Nursing Collaborating Centre
Sarah Garner	Health Technology Analyst NICE
Gill Gyte	NCT/Cochrane Collaborative
Philip Home	Professor of Diabetes Medicine, University of Newcastle
Peter Littlejohns	Clinical Director, NICE
Ruairidh Milne	Senior Lecturer, NCCHTA
Jackie Napier	Associate Medical Director, Schering Healthcare
Janet Robertson	Health Technology Analyst, NICE

Economics

Mark Sculpher (Chair)	Professor of Health Economics, University of York
John Brazier	Professor of Health Economics, University of Sheffield
Andy Briggs	Health Economics Research Centre, Oxford
Martin Buxton	Academic Director of Health Economics, Brunel University
Ruth Carlyle	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 for NICE, College of Health
Iain Chalmers (comments on documents)	Director, UK Cochrane Centre
Eleanor Donegan	Health Technology Analyst, NICE
Rahana Mohammed	Policy & Campaigns Manager, Arthritis Care
James Partridge (comments on documents)	Chief Executive, Changing Faces
Anne-Toni Rodgers	Corporate Affairs Director, NICE
Peter Sharplin	Manager of Health Economics, Aventis Pharma
Sophie Staniszewska	Senior Research Fellow, RCN Institute
Karen Thompson	Senior Policy Officer, Diabetes UK

Technology Assessment

Ron Akehurst (Chair)	Dean of School of Health and Related Research, Sheffield
Stirling Bryan	Professor of Health Economics, HSMC, Birmingham
Tom Dent	Director, Interventional Procedures Programme, NICE
Julia Earnshaw	Head of Evidence Planning and Outcomes Research, GSK
John Gabbay	Director, NCCHTA
Alec Miners	Health Technology Analyst, NICE
Suzy Paisley	Managing Director SchARR, Sheffield
Seren Phillips	Technical Team Leader, NICE
Cathryn Thomas	Senior Lecturer, University of Birmingham
Norman Waugh	Dept of Public Health, Aberdeen