



*National Institute for
Clinical Excellence*

Guidance for

Manufacturers

and Sponsors

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Issue date: June 2001

About the technology appraisal series

This document is one of a set of five, which describe the process the Institute uses to undertake technology appraisals and provide guidance to the organisations invited to contribute to these appraisals.

When a submission to the Institute is being considered or prepared, the statement of process should be read in conjunction with the guidance documents referred to below. All five documents are available on the Institute's website: www.nice.org.uk

Note: Documents 1, 2 and 5 replace the Institute's publication entitled *Appraisal of New and Existing Technologies: Interim Guidance for Manufacturers And Sponsors December 1999*.

Ordering information

These publications can be ordered by telephoning the NHS Response Line on 0870 1555 455 and quoting the relevant reference number below. The price is £10.50 each with a 10% discount for orders between 5 and 50 copies. Discounts for orders over 50 by application to NICE. The five technology appraisal documents are:

Title	Ref. No.
1. Guide to the Technology Appraisal Process	N0010
2. Guidance for Appellants	N0011
3. Guidance for Patient/Carer Groups	N0012
4. Guidance for Healthcare Professional Groups	N0013
5. Guidance for Manufacturers and Sponsors	N0014

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Foreword

In September 1999, the Institute published guidance on submissions by manufacturers and sponsors to its technology appraisal programme. This initial guidance was 'interim' and intended to be replaced in time by an updated and revised version. This first revision of the *Guidance* is issued following extensive consultation and discussion with members of the relevant disciplines and professions in the health care industries, universities, the Department of Health and the National Assembly for Wales and the wider NHS, and represents a consensus. The process of guidance revision is outlined in section 3 of this document.

The *Guidance* is designed to both assist manufacturers and sponsors to frame their submissions and help the Institute discharge its duty to the Secretary of State in identifying clinically effective and cost-effective technologies for the NHS, to remove unfairness in the availability of technologies in different localities and to minimise the possibility of further examples of unfairness or inequity being introduced.

The *Guidance* should be seen as an aid to thought during the process of submission rather than as a substitute for it. 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 their task. Substantive departures from this *Guidance* should therefore not be made without the prior agreement of the Appraisal Programme Director.

The Institute issues guidance on technologies which have successfully completed any regulatory or quality assurance procedures required to obtain a marketing licence. The safety, clinical efficacy and quality of technologies is therefore taken as a given and submissions should be focused on the Institute's objectives, which are to establish the clinical effectiveness and cost-effectiveness of the technologies which it is asked to appraise.

The Institute is aware that the *Guidance* will be read by many who are not themselves expert in technology appraisal or the writing of systematic reviews. It is neither a textbook of appraisals methodology (of which many exist), nor an inflexible template to be followed slavishly. A glossary of terms referring to the methods of technology appraisal and systematic reviews has not been included. Two such glossaries are the US Panel Guidelines (Gold MR et al) and Culyer, A J. "A glossary of the more common terms encountered in health economics". Because the methodology is itself developing rapidly, there remain several areas of controversy, where the *Guidance* suggests a flexible approach, or the adoption of more than one approach, and there are also aspects – of which the incorporation of equity considerations is the most conspicuous – which are as

yet relatively underdeveloped. Subsequent editions of the *Guidance* may give more specific advice on such matters. The Institute would like to encourage those with the appropriate skills working for manufacturers and sponsors to play a role in the further development of the methods of technology appraisal. Innovative approaches to aspects of technology appraisal which are presently undeveloped or where there is no agreed standard would therefore be welcome. Work of this sort should be first discussed and agreed with the Appraisal Programme Director.

Manufacturers and sponsors may discuss the scoping, perspective and presentation of their submissions with the Appraisal Programme Director and 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, so manufacturers and sponsors are urged to take the opportunity provided for a meeting with Institute staff and the assessment group at the beginning of the appraisal process to discuss outstanding matters about which there might be doubt.

The Institute is itself a sponsor of research into the methodology of technology appraisal and would welcome suggestions for both primary and secondary research which might lead to improvements in methods and make subsequent editions of this *Guidance* 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 and systematic reviews. Manufacturers and sponsors who lack the relevant skills in-house are urged to seek them elsewhere rather than attempt a submission 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.

Executive Summary

- The National Institute for Clinical Excellence provides guidance to the National Health Service (NHS) in England and Wales on the use of selected new and established technologies.
- The Institute undertakes appraisals of technologies as formally requested by the Department of Health (DH) and the National Assembly for Wales (NAW). Technologies are selected for appraisal on a number of criteria.
- The appraisal by the Institute encompasses the clinical effectiveness, cost-effectiveness and wider NHS implications of a technology. Manufacturers and sponsors of technologies are requested to submit all relevant data in relation to each of these issues.
- In September 1999, the Institute published an interim version of guidance to provide manufacturers and sponsors of technologies with a basis for preparing their submission. This more detailed statement of the Guidance for Manufacturers and Sponsors is intended to enhance the quality of submissions and encourage consistency of format and content.
- The revised Guidance has been developed through a process of literature review, invited consultation, general consultation, workshop discussion and review by a Steering Committee of academic and industry evaluation experts.
- The revised Guidance is based on the following principles:
 - (i) the best available data relevant to the problem are required;
 - (ii) data on final outcomes are preferred to intermediate (surrogate) outcomes;
 - (iii) data from controlled prospective studies carried out in a routine care situation are preferred;
 - (iv) all data and analysis should be presented transparently.
- It may be necessary to carry out an appraisal before the best quality outcome data are available. In these circumstances modelling is appropriate to adapt the best available data to the problem being addressed. Any such modelling must be carried out using accepted best practice and presented transparently so that the framework and assumptions are clear.
- Clear presentation of results and conclusions of all studies is essential to enable the Institute to carry out its appraisals. This applies to the clinical effectiveness, cost-effectiveness, NHS impact and equity elements of submissions.

Summary of Guidance

This section highlights paragraphs contained within the document.

2.3 Specific guidance

2.3.1 Perspective

The evaluation should be conducted from the perspective of the NHS and Personal Social Service (PSS) decision-maker. That is to say the benefits should include all clinical and health-related benefits valued from the perspective of society, and costing should include all use of NHS and PSS resources required to achieve those benefits.

2.4 Context of the evaluation

2.4.1 Problem definition

The nature and scope of the problem addressed in any evaluation should be clearly defined and with reference to the Institute's scope for the appraisal. This should include the clinical problem, the patient group being treated (e.g. age and sex distribution and co-morbidities), the comparators being evaluated and the treatment context (e.g. hospital, clinic, community). Manufacturers and sponsors should provide background information on the clinical problem to which their technology offers a solution. This should include estimates of patient numbers (incidence and prevalence) and recent trends in these figures.

2.4.2 Development of the technology

The development status of the technology, including the history of its development, the current range of applications and potential future uses, should be described.

2.4.3 Forms of analysis

The analysis should take the form of a cost-effectiveness analysis or cost-utility analysis depending on the nature of the clinical problem being addressed.

2.4.4 Time horizon

The time span of the analysis should cover the period over which the main health effects and health care resource use are expected to be experienced. This may require extrapolation beyond the period for which data from controlled clinical trials are available. The nature of any modelling used in the extrapolation should be fully explained and the sensitivity of the results to the method of extrapolation and the choice of time horizon should be thoroughly tested.

2.5 Comparisons

The choice of comparator will usually be determined by the scope for the appraisal by the Institute in its request for submissions. The main comparator should normally be the most frequently used intervention for the patient group in question.

The preferred form of outcome data for evaluation of health care technologies is long-term clinical effectiveness (morbidity and mortality) with self-assessment of health status by patients at each distinct stage of disease progression. This facilitates cost-effectiveness analysis and, when combined with data on social preferences between health states, can be used in cost-utility analysis. Modelling techniques may be used to adjust efficacy data to reflect what is expected in practice. The scientific basis of any modelling must be justified and the assumptions, data and processes made transparent and subjected to sensitivity analysis.

2.6 Outcome measurement

The settings, populations and methods by which outcomes and costs are measured in the original studies from which data are drawn should be described and the implications of generalising the data to the NHS in England and Wales explained.

2.7 Generalisability of study results

2.8.1 Reporting of results

The clear presentation of clinical trial data is important and the Institute recommends that manufacturers and sponsors should refer to published guides including the International Committee on Harmonisation (ICH) guidelines.

2.8 Presentation of clinical data

2.8.2 Format of reporting

The results for the principal outcomes of each study included in submissions should be reported individually, preferably in tabular form. Numerators and denominators of rates (and proportions) should be provided. Estimates should be expressed as appropriate central estimates with suitable interval assessments.

Graphical presentation should be used where it substantially assists in interpretation of the results. The relevant underlying data should be presented, if necessary in an appendix to the submission (see Appendix C).

2.8.3 Risk estimates

Results should be reported both as relative estimates and absolute estimates. The period over which the risk estimates have been calculated should be stated and these estimates should generally be annualised.

2.8.4 Sub-group analysis

Subgroup analysis is justified where there is a sound biological *a priori* rationale for doing so (e.g. 'high risk' patients) and where there is evidence that clinical effectiveness or cost-effectiveness may vary between such groups.

2.8.5 Interpretation of results

Manufacturers and sponsors of technologies should include the data on the clinical effectiveness of their product within a systematic review of evidence of the effectiveness of their product in the relevant patient group.

2.9 Valuation of outcomes

2.9.1 Utilities

When cost-utility analysis is undertaken the valuation of health gain must reflect the health state preferences indicated by the analytical perspectives. Given the perspective of the Institute (Section 2.3.1) the most relevant values are those of the general population of England and Wales.

2.9.2 Productivity

Impacts on social productivity may be assessed if considered sufficiently important in specific cases. The methods used to measure and value the productivity gains should be fully presented.

2.10 Resource use and costs

2.10.1 Resource use identification

The principal component of resource use from the Institute's perspective is direct provision of health and social care in association with the use of the technology. Models extrapolating the long-term outcomes of treatment from short-term clinical trials should include future health care resources consumed in managing the long-term sequelae of the disease under study (e.g. myocardial infarction after re-stenosis post-PTCA) but not those used for the treatment of unrelated conditions. Resources used by patients in obtaining treatment (e.g. time and travel) should be recorded separately.

2.10.2 Resource measurement

The resources used by each treatment approach must be presented separately, aggregated in natural units such as hospital days, number of consultations and volumes of drugs. The sources of the resource data must be clearly stated.

2.10.3 Resource costing

Total costs for each comparator should be calculated by applying standard unit values to the quantities of each type of resource. These unit costs should generally reflect the average cost of the resource to the NHS and PSS. The source of each unit cost should be cited.

2.11 Discounting

Future outcomes and costs must be discounted to reflect social time preferences and social opportunity costs of resources. The conventional view is that benefits and costs should be discounted at the same rate. The current recommendation of the DH and the NAW is that costs should be discounted at 6% per annum and benefits at 1½%. To maintain consistency with appraisals undertaken elsewhere within the NHS these values should be used in the base case analysis of evaluations in submissions to the Institute. Sensitivity analyses should also be carried out using, amongst others, the combinations 6% costs and 6% for outcomes, and 6% for costs and 0% outcomes.

2.12.1 Incremental comparisons

Incremental cost-effectiveness ratios and/or cost utility ratios should be presented, as well as total costs and outcomes for each comparator.

2.12.2

The results should also be presented in disaggregated form so that the nature and extent of differences between comparators are easily discernable. For example, mortality and quality of life data should be presented separately as well as in the form of utility measures such as QALYs.

2.12.3

Quantities of resources used and unit costs for each type of resource should be presented separately.

2.12.4 Uncertainty

Wherever possible the results of the economic comparisons should be subjected to sensitivity analysis testing. For example, when data are drawn exclusively from clinical trials, 95% confidence intervals can be calculated for cost-effectiveness ratios. When data are drawn from a variety of sources and used in a modelling framework, probabilistic sensitivity analysis is recommended in order to take account of the uncertainty around data values. Bayesian approaches which reflect effects of uncertainty would be acceptable, provided they are transparent.

2.13.1 Budget impact

Manufacturers and sponsors should provide an analysis of the likely budget impact on the NHS of the use of their technology. For new technologies, this should include estimates of the changing budget impact over a 3 to 5 year period as a result of varying diffusion rates and also an estimate of impact once diffusion has reached a 'steady state'.

2.13.2 Service impact

When a technology has requirements for specific health care resources, for example, specialist training for clinical personnel or availability of particular diagnostic services, these should be explained in general terms.

Manufacturers and sponsors should provide as much detail as possible on the probable clinical and social status of patients likely to benefit from the use of their technology. They should also provide information on any aspects of the technology which might lead to increased or reduced personal costs to patients and their carers and families.

2.12 Presentation of results

2.13 Wider NHS impact

2.14 Equity

1. Introduction

The National Institute for Clinical Excellence provides guidance to the National Health Service (NHS) on the use of selected new and established health technologies^{1,2}. The Institute's functions in this context are as set out in the Secretary of State's and the National Assembly for Wales' Directions³.

“to appraise the clinical benefits and the costs of those interventions notified by the Secretary of State and the National Assembly for Wales and to make recommendations”.

The Institute appraises the evidence of all the clinical benefits and costs of an intervention in the broadest sense. Clinical benefits include the impact on quality of life (e.g. relief of pain and disability) as well as likely effects on mortality. In the light of the evidence the Institute reaches a judgment as to whether, on balance, the intervention can be recommended as a cost-effective use of NHS resources in general, or for specific indications, or for defined subgroups of patients. The Appraisal Committee will consider the net impact on both costs and benefits of the intervention.

The Institute's appraisal process relies on information and input from a number of sources including manufacturers and sponsors. This document provides guidance on the form and format of the submission by manufacturers and sponsors. There are separate documents to assist professional and patient groups. All documents are available from the Institute's website (www.nice.nhs.uk).

1.1 The technology appraisal programme

The Institute undertakes appraisals of new and established technologies, as formally requested by the DH and the NAW, they include:

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

1 Department of Health. A First Class Service: Quality in the new NHS. Leeds; 1998

2 Department of Health. Faster Access to Modern Treatment: How NICE Appraisal will Work. Leeds; 1999

3 National Institute for Clinical Excellence. Framework Document. London; 2000

The DH and the NAW 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 (e.g. 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 Identification of products for appraisal

The appraisals by the Institute of both new and existing technologies encompass:

- their clinical effectiveness;
- their cost-effectiveness; and
- their wider NHS implications.

1.3 Summary of the appraisal process

Manufacturers and sponsors are requested to submit relevant data in relation to all of these issues. In summary, the Institute commissions a systematic review of the literature to produce an assessment report. This is usually undertaken by a university-based department, commissioned through the Health Technology Assessment arm of the NHS Research and Development Programme. Submissions from patient and professional organisations, executive summaries of the manufacturer(s) or sponsor(s) submissions, the written perspectives of the experts invited to attend the meeting of the Appraisal Committee and the comments made by the consultees [manufacturer(s)/sponsor(s), patient and professional groups, the Health Technology Board for Scotland and two health authorities] on the assessment report are added to the assessment report to form an Evaluation Report which is presented to the Institute's Appraisal Committee. When the Committee meets, its members consider the report together with comments invited from clinical experts and patient advocates.

The committee's first deliberations result in an Appraisal Consultation Document (ACD), which goes out for consultation to the formal consultees. It is posted on the Institute's website 5 working days later. The committee, at its second meeting, revises the ACD in light of the comments and produces a Final

Appraisal Determination (FAD). This is again released to the consultees and then posted on the Institute's website five working days later. The FAD is presented to the Institute, which then, subject to any appeal, releases it as guidance to the NHS. If any of the consultees feel that there are grounds to appeal to the Institute over the contents of the FAD then they have 15 working days to lodge an appeal. There are three grounds for appeal:

- The Institute has failed to act fairly and in accordance with its published procedures.
- The FAD is perverse in the light of the evidence submitted;
- The Institute has exceeded its powers.

If the appeal is upheld the Appraisal Committee may be asked to reconsider the FAD and the normal process follows. If the appeal is not upheld guidance is released to the NHS. The process of consultation and appeal are integral to the preparation of the Institute's guidance.

1.4 'Commercial in confidence' data

The Institute recognises the need for manufacturers and sponsors to submit data that are considered as 'commercial in confidence'. Such information should be clearly identifiable within a submission. In addition, a justification for the designation of data as 'commercial in confidence' and an explanation at the period over which such confidentiality should apply should be provided. Data that can be included as confidential include those which may influence share values or are intellectual property (i.e. data awaiting publication). Manufacturers and sponsors should mark as confidential only those sections of their submissions which are commercially sensitive. Submissions must contain an appendix which sets the elements of the report, which are commercial in confidence, referenced to the text.

The Institute undertakes to uphold the confidential nature of material during the ACD and FAD stages of consultation. However, as the Institute's final guidance document aims to provide an audit trail of the evidence base that underpins the guidance, the Institute may wish to discuss options for presenting key data in its documents.

2. Guidance

The Guidance attempts to be as specific and helpful as possible yet also to allow for flexibility and innovation. It is intended that the Guidance will encourage consistency of format and content of submissions to the Institute as well as improve the general quality of submissions over time.

2.1.1 Four principles

The guidance is governed by four underlying considerations:

- a) the best available data relevant to the problem under consideration are required;
- b) data on final clinical outcomes such as life years gained and changes in patient quality of life are preferred to intermediate clinical outcomes such as events avoided or changes in physiological measures such as LDL cholesterol or blood glucose levels;
- c) data from controlled, prospective studies carried out in a routine care environment are preferred to data from other types of study;
- d) all data and analysis should be presented transparently demonstrating the relevance of the data and approaches used.

2.1 Guiding principles

2.1.2 Hierarchy of evidence

There is general agreement in the literature that data from well-conducted randomised controlled trials are preferable to those from other study designs. Several authors have produced hierarchies of evidence quality from various types of study (see for example, NHS Centre for Reviews and Dissemination, 1996). The Institute is concerned with issues of clinical effectiveness and cost-effectiveness rather than clinical efficacy. The hierarchy of studies which can produce data on these issues may differ from the ranking of studies for testing hypotheses regarding clinical efficacy. Data quality expectations for all technologies will rise over time, but RCTs may continue to be inappropriate in some circumstances for practical and ethical reasons. Selection of data sources will often involve trade-offs between methodological rigour, relevance to the question under study, and the timing of an appraisal.

2.1.3 Data sources

The term “clinical effectiveness” encompasses benefits to patients for whom the technology is used. Such benefits may include reductions in morbidity and mortality and improved quality of life. The ideal source of effectiveness data is a prospective, randomised, controlled trial with a naturalistic design which imposes the minimum restriction on the normal decision-making processes of health care professionals and patients.

The design and quality of many clinical trials is determined by the regulatory requirements for the licensing of technologies. In the case of drugs, data are required on efficacy and safety, which are customarily measured in RCTs with homogeneous patient populations and strict experimental protocols for treatment delivery. In other technologies the expected standards do not require evidence from RCTs for licensing. In these circumstances, when appraising technologies the choice has been between taking good efficacy data from RCTs and modelling to estimate effectiveness, and using data on effectiveness from less rigorous studies. However, the design of efficacy trials can be made more relevant, for example, by the inclusion of usual care in comparisons, the use of final outcome measures as well as intermediate clinical endpoints and the collection of resource use data. Truly naturalistic trial designs may be possible only when a technology is in routine use, but much of the data required for technology appraisal can be obtained from more pragmatically designed registration trials. These data may still have to be supplemented from non-randomised sources and adjusted by modelling. The potential biases in any non-randomised sources must be fully explained and the nature and underlying assumptions of any models clearly presented.

2.1.4 Choice of outcome measures

The measures of clinical effectiveness should be appropriate for the condition and include final outcomes such as reduced mortality and improved quality of life. In studies relying on intermediate (surrogate) outcomes one of the following should be demonstrated: (i) a strong and consistent association between the intermediate outcome and final outcome; (ii) where the intermediate results are large, precise and lasting enough to be considered a possible basis for making a treatment decision.

Quality of life data are generally regarded as more relevant in the treatment of chronic illness, but their collection is desirable in most circumstances. Even when extended survival is the main clinical benefit of an acute treatment, the health state during survival may vary. Adverse events can affect quality of life seriously in acute and chronic treatments.

Where multiple outcomes are measured, data on all of them should be presented. The choice of a particular outcome measure as the basis of the cost-effectiveness analysis should be clearly justified.

For some technologies, for example in diagnostics, it has been customary to design trials to measure only diagnostic accuracy, rather than impact on final patient outcomes. The latter carries more weight. The points made above about the use of surrogate outcomes are particularly relevant for such technologies.

2.1.5 Use of modelling

For new technologies it may be necessary to carry out an appraisal before long-term outcome data are available. In these circumstances modelling from intermediate outcomes is appropriate and can be subjected to validation later when empirical data are collected. This should not, however, be used as a substitute for proper trial design and extended follow-up, when such constraints do not apply (Buxton et al, 1997).

Modelling may also be required in order to address the particular question under study. For example, there may be no RCTs directly comparing the technology being appraised with current usual treatment. Data may be available from studies carried out in different settings which may be adapted to the relevant setting through modelling. Data from observational studies may be the best available data to address the study question.

Modelling, like other analytical approaches, has its place in the assessment of a technology. What is important is that it is used appropriately and carried out to the highest standards. Several recent papers have addressed the issue of good practice in modelling for economic evaluation (see, for example, Halpern et al., 1998, Sculpher et al, 2000).

The guidance on particular aspects of evaluation is presented below. The guideline statement is set out in blue type at the head of each section. This is followed by an explanation and justification for the guidance given. Where necessary, source documents and key references are given in the text and listed at the end of this section.

2.3.1 Perspective

The evaluation should be conducted from the perspective of the NHS and Personal Social Services (PSS) decision-maker. That is to say the benefits should include all clinical and health-related benefits valued from the perspective of society, and costing should include all use of NHS and PSS resources required to achieve those benefits.

The selection of a study perspective has an important bearing on which costs and benefits are included in the analysis, and how they are valued. Most of the existing economic evaluation guidance documents from other jurisdictions recommend the use of a “societal perspective” for both costs and benefits, on the assumption that other perspectives can be assessed by selecting subsets of the overall costs and benefits. Because choice of perspective influences the valuation of costs and benefits as well as their scope, this transformation of analytical perspective is not as straightforward as is sometimes thought.

2.2 Format of guidance

2.3 Specific guidance

The choice of perspective recommended here reflects the objectives of the NHS in general, and the Institute in particular, in maximising the health gain from the use of NHS and PSS resources. Although health status impact should be assessed directly by patients, any valuation of health gains, for example utility measurements, should be from the viewpoint of society. Any wider health-related benefits, such as productivity gains from earlier return to work, which are not thought to be encompassed by measures of quality of life or utility, should be presented separately if they are thought to be an important element of the benefits. They should not be subtracted from the NHS and PSS resource costs.

The recommended perspective includes all resource use funded by NHS and PSS budgets (including any element of those budgets contributed by patients). Costs of any non-health resources, such as time and transport costs borne by patients and their families and carers in the course of receiving treatment should be presented separately where these differ significantly between comparators within the analysis. Data may also be presented separately on any major impacts on resource use in other parts of the public sector and their relevance to the appraisal explained.

2.4 Context of the evaluation

2.4.1 Problem definition

The nature and scope of the problem addressed in any evaluation should be clearly defined and referenced to the Institute's scope for the appraisal. This should include the clinical problem, the patient group being treated (e.g. age and sex distribution and co-morbidities), the comparators being evaluated and the treatment context (e.g. hospital, clinic, community). Manufacturers and sponsors should provide background information on the clinical problem to which their technology offers a solution. This should include estimates of patient numbers (incidence and prevalence) and recent trends in these figures.

As part its appraisal process the Institute will scope the specific question to be addressed for each technology appraisal. This will define the issues of interest (e.g. population, comparators) as clearly as possible. Manufacturers and sponsors will be consulted during this scoping process.

2.4.2 Development of the technology

The development status of the technology, including the history of its development, the current range of applications and potential future uses, should be described.

Manufacturers and sponsors will be best placed to provide this information on their technologies. It will assist in demonstrating the rationale for the study question which is being addressed.

2.4.3 Forms of analysis

The analysis should take the form of a cost-effectiveness analysis or cost-utility analysis depending on the nature of the clinical problem being addressed.

Whilst there is increasing application of contingent valuation methods in health economic evaluations, experience of the use of these methods in a cost-benefit framework is relatively limited in the health field. Clinical effectiveness measures are the most frequently used indicators of health gain. However, utilities can provide a comparative context for judging the relative value of health gain from interventions in different disease areas. If monetary measures of health benefits based on willingness-to-pay are presented, they should be accompanied by a clear explanation of their relevance to a decision on the allocation of NHS and PSS resources and be presented in addition to data on health effects or utilities.

Before equal effectiveness is assumed it must be demonstrated that: (i) there is no clinical meaningful effect via a trial adequately powered for that effect, and that the interpretation of 'clinically meaningful' is justified or (ii) a suitably high posterior probability of no clinically meaningful difference has been demonstrated. If such evidence for equivalence can be provided, a cost minimisation approach may be substituted for a cost-effectiveness or cost-utility approach.

2.4.4 Time horizon

The time span of the analysis should cover the period over which the main health effects and health care resource use are expected to be experienced. This may require extrapolation beyond the period for which data from controlled clinical trials are available. The nature of any modelling used in the extrapolation should be fully explained and the sensitivity of the results to the method of extrapolation and the choice of time horizon should be thoroughly tested.

In the choice of time horizon there may be a trade-off between the economically relevant period and the period for which reliable clinical and economic data are available. In general, evaluations should cover the most relevant period using final outcomes such as life years gained or QALYs gained, rather than being limited to truncated cost-effectiveness analysis based on surrogate clinical outcomes which are limited to the time scale of clinical trials.

2.5 Comparisons

The choice of comparator will usually be determined in the scope for the appraisal prepared by the Institute. The main comparator(s) should normally be the most frequently used intervention(s) for the patient group in question.

The absence of head-to-head comparisons is a common problem especially for new drugs when registration trials have been placebo-controlled. Many drug trials are international in scope and the comparator treatment in the control arm may not be the most relevant to the UK NHS. Modelled comparisons using the study arms of separate trials with a common comparator may be necessary. Particular attention must be paid to the similarities and differences in the patient groups in the different trials. There will often be a trade-off between internally valid RCTs which do not compare the relevant alternatives, and more relevant modelling studies which may be more subject to bias. Where it is the case that it is known that there is a more cost-effective treatment available than that in common use, it should also be considered as a comparator.

The relevant comparator for a class of technology (e.g. a drug) may be a procedure in another class of technology (e.g. surgery).

The greater the number of comparators the greater the likelihood of divergent standards of clinical and resource data available for each one. For example, there are unlikely to be directly comparative trials for all the treatment approaches. New drug treatments may have clinical efficacy data only from Phase III trials. Given the timescale of many trials from design to reporting, there will still be situations in which the relevant comparator changes before trials are completed. For the economic analysis to be relevant to NHS decision-makers it must address the current and likely future clinical practice patterns. If this requires modelling and the synthesis of data from a variety of sources then this should be done following recommended best practice, with transparency of model structure, assumptions and data sources.

2.6 Outcome measurement

The preferred form of outcome data for evaluation of health care technologies is long-term clinical effectiveness (morbidity and mortality) with self-assessment of health status by patients at each distinct stage of disease progression. This facilitates cost-effectiveness analysis and, when combined with data on social preferences between health states, can be used in cost-utility analysis. Modelling techniques may be used to adjust efficacy data to reflect what is expected in practice. The scientific basis of any modelling must be justified and the assumptions, data and processes made transparent and subjected to sensitivity analysis.

The availability of clinical effectiveness and patient outcome data is constrained by the development status of a technology. In many cases, particularly with new drugs, decisions on utilisation have to be made before prospective cost-effectiveness trials with a naturalistic design can be carried out. One solution is to use the best quality efficacy data from randomised controlled prospective studies as the outcome measure and subject the results to sensitivity analysis. Since efficacy rates in selected populations under research conditions are usually higher than effectiveness rates in more heterogeneous populations under routine service provision, efficacy data may over-estimate clinical benefits. If the outcome data on all the comparators are of this type, then choice between these options may not be biased. However, if there is a desire to compare the marginal “cost-effectiveness” of the chosen option with that of other health technologies for which actual effectiveness data is available there is a considerable risk of bias.

The balance of outcome data availability is likely to vary on a case-by-case basis, so that those making submissions must clearly explain the reasons for their choice of outcome measure.

The settings, populations and methods by which outcomes and costs are measured in the original studies from which data are drawn should be described and the implications of generalising the data to the NHS in England and Wales explained.

There may be issues of generalisability of the results of studies carried out within the UK (e.g. in specialist centres as opposed to general hospitals) and of international studies. It is essential to compare the characteristics of the study populations to those of the patient populations in whom the intervention is to be used. Any modelling to make data more relevant to the setting in which use of the intervention is proposed should be transparently presented.

2.8.1 Reporting of results

The clear presentation of clinical trial data is important and the Institute recommends that manufacturers and sponsors should refer to published guides including the International Conference on Harmonisation (ICH) guidelines.

This document is not intended to provide detailed guidance on the reporting of clinical trials, which is adequately covered elsewhere (see, for example, the ICH guidelines).

2.8.2 Format of reporting

The results for the principal outcomes of each study included in submissions should be reported individually, preferably in tabular form. Numerators and

2.7 Generalisability of study results

2.8 Presentation of clinical data

denominators of rates (and proportions) should be provided. Estimates should be expressed as appropriate central estimates with suitable interval assessments.

Graphical presentation should be used where it substantially assists in interpretation of the results. The relevant underlying data should be presented, if necessary in an appendix to the submission (see Appendix C).

2.8.3 Risk estimates

Results should be reported both as relative estimates and absolute estimates. The period over which the risk estimates have been calculated should be stated and these estimates should generally be annualised.

Absolute risk estimates are most useful for cost-effectiveness analysis. However, relative risk estimates are necessary when extrapolating clinical effectiveness from one population to another.

2.8.4 Sub-group analysis

Subgroup analysis is justified where there is a sound biological *a priori* rationale for doing so (e.g. high risk patients) and where there is evidence that clinical effectiveness or cost-effectiveness may vary between such groups.

The Institute is concerned with the maximisation of health benefits from the use of NHS and PSS resources. Analyses which help to target interventions on those patients likely to benefit most will assist in the achievement of the objective. Consequently, sub-group analyses will still be useful even when there is a significant difference in clinical outcomes or costs for the whole study population.

The credibility of subgroup analyses is improved if confined to the primary outcome and to a few predefined subgroups on the basis of biologically plausible hypotheses. Claiming a treatment difference in a sub-group when the overall treatment comparison is not significant is not warranted unless the evidence is statistically convincing and clinically sensible.

Statistical tests of interaction, assessing whether a treatment effect differs between subgroups, are required rather than inspection of subgroup p values, which may encourage inappropriate sub-group claims. The analysis should make corrections for multiple comparisons.

2.8.5 Interpretation of results

Manufacturers and sponsors of technologies should include the data on clinical effectiveness within a systematic review of evidence of the effectiveness of their product in the relevant patient group.

Manufacturers and sponsors of technologies are well-placed to conduct systematic reviews as they will be able to include all the evidence from published and unpublished trials of their products. The Institute may also commission an independent review but, if all manufacturers contribute a systematic review with comprehensive data on their own product, the final knowledge base will be more complete and reliable.

2.9.1 Utilities

When cost-utility analysis is undertaken the valuation of health gain must reflect the health state preferences indicated by the analytical perspectives. Given the perspective of the Institute (Section 2.3.1) the most relevant values are those of the general population of England and Wales.

The Institute's objective is to obtain maximum health benefits from the use of NHS and PSS resources, subject to equity and other considerations. No single utility measurement approach is prescribed but, whichever method used must provide a reasonable basis for the Institute to conclude that the utilities used reflect the preferences of the population of England and Wales. If utilities are used in modelling, care must be taken to ensure that the method of elicitation and the sample composition are compatible especially where utilities for different comparators are taken from different studies. Similar considerations apply with regard to sources of values if supplementary monetary measures of benefit are included.

2.9.2 Productivity

Impacts on social productivity may be assessed if considered sufficiently important in specific cases. The methods used to measure and value the productivity gains should be fully presented.

Changes in productivity, such as increased availability for work, may be a consequence of health gain resulting from the use of a technology. Any such monetary estimates of benefits should not be subtracted from the estimates of health care resource costs.

2.10.1 Resource use identification

The principal component of resource use from the Institute's perspective is direct provision of health and social care in association with the use of the technology. Models extrapolating the long-term outcomes of treatment from short-term clinical trials should include future health care resources consumed in managing the long-term sequelae of the disease under study (e.g. myocardial infarction

2.9 Valuation of outcomes

2.10 Resource use and costs

after re-stenosis post-PTCA) but not those used for the treatment of unrelated conditions. Resources used by patients in obtaining treatment (e.g. time and travel) should be recorded separately.

The above guidance follows closely the equivalent sections of existing guidance from other countries and reflects current practice in the majority of cost-effectiveness studies. In all evaluations the boundaries of measurement of resource consequences must be determined. The boundary has been drawn here to concentrate on those resources which are most relevant to the Institute's objectives and which are subject to the least uncertainty in measurement. Increased use of the resources of patients and their carers may replace NHS and PSS resources in some interventions. Where this is significant it would be inappropriate to exclude them from the efficiency calculation. Direct costs to patients will also be important in any equity assessment.

2.10.2 Resource measurement

The resources used by each treatment approach must be presented separately, aggregated in natural units such as hospital days, number of consultations and volumes of drugs. The sources of the resource data must be clearly stated.

This serves to clarify differences in treatment approaches and allows the effect of different resource prices and quantities to be tested. This is particularly important if trial data are being used in a modelling framework. When resource volumes are observed in controlled trials it is important to identify those aspects of service provision which are induced by the protocol (e.g. study visits and extra tests) as distinct from those needed in routine care. It is also important to correct for missing resource data resulting from variable periods of patient follow-up common in clinical trial design. Resource data from naturalistic trials are more relevant as they reflect the routine care situation. Resource data from registries and databases may reflect routine care but are often difficult to control for disease severity and patient outcome, unless the registry has been created for the express purpose of collecting resource and outcome data.

2.10.3 Resource costing

Total costs for each comparator should be calculated by applying standard unit values to the quantities of each type of resource. These unit costs should generally reflect the average cost of the resource to the NHS and PSS. The source of each unit cost should be cited.

In most appraisals it is satisfactory to use market prices, that is the prices actually paid for particular goods or services, to value resources. In some cases, usually involving buildings or capital equipment, the market price may not reflect the

true opportunity cost. For example, rents paid on a historical basis may not reflect the current market value of property and may need to be adjusted. In services using capital equipment, such as diagnostic imaging, the marginal cost of increased use will vary with the existing level of capacity utilisation. To make the results more generalisable it is preferable to use an average cost per test, recognising that the actual cost will vary according to local circumstances.

Future outcomes and costs must be discounted to reflect social time preferences and social opportunity costs of resources. The conventional view is that benefits and costs should be discounted at the same rate. The current recommendation of the DH and the NAW is that costs should be discounted at 6% per annum and benefits at 1½%. To maintain consistency with appraisals undertaken elsewhere within the NHS these values should be used in the base case analysis of evaluations in submissions to the Institute. Sensitivity analyses should also be carried out using, amongst others, the combinations 6% costs and 6% outcomes, and 6% costs and 0% outcomes.

The use of a 6% discount rate for costs reflects the current advice from the Treasury to the whole of the public sector. The Treasury is currently revising its investment appraisal guidance and this rate may change.

In all other countries the cost-effectiveness guidance recommends discounting of costs and outcomes at an equal rate. As social time preference and opportunity cost can vary between countries, the recommended rates vary (between 3% and 5%).

Differing views can be found in the health economics literature regarding the choice of discount rate. Most authors and textbooks (e.g. *Gold et al, 1996*) recommend equal rates for costs and effects. Other authors (e.g. *Parsonage and Neuberger, 1992*; and *Brouwer et al, 2000*) have argued that, although discounting of health outcomes may be appropriate, there is no reason why the appropriate rate should be equal to that for costs.

It is desirable for the purposes of consistency and comparability that all submissions to the Institute use the same approach to discounting. The effect of this guidance on the results of studies will be kept under review.

2.12.1 Incremental comparisons

Incremental cost-effectiveness ratios and/or cost utility ratios should be presented, as well as total costs and outcomes for each comparator.

2.11 Discounting

2.12 Presentation of results

These ratios and totals should reflect the perspective of the analysis, which will usually be as described in 2.3.1. In cases where costs borne by patients and carers are thought to be an important part of treatment costs, or where wider health related benefits such as productivity gains from earlier return to work are not thought to be encompassed by measures of quality of life or utility, a separate analysis with a broader cost perspective may be included. Caution should be exercised in the use of ratios calculated on different bases and a clear justification should be provided.

2.12.2

The results should also be presented in disaggregated form so that the nature and extent of differences between comparators are easily discernable. For example, mortality and quality of life data should be presented separately as well as in the form of utility measures such as QALYs.

2.12.3

Quantities of resources used and unit costs for each type of resource should be presented separately.

The cost-effectiveness or cost-utility analysis will draw on the outcome data already presented in the clinical effectiveness section of the submission. The presentation of outcome data used in the economic evaluation should not duplicate what has gone before but should indicate clearly where clinical data have been adapted for use in the economic evaluation, for example, when trial data have been extrapolated to provide long-term outcomes or efficacy data have been adjusted to reflect effectiveness. No single source of unit cost data is recommended. The Institute may in the future develop a standard cost manual for use in submissions.

2.12.4 Uncertainty

Wherever possible the results of the economic comparisons should be subjected to sensitivity testing. For example, when data are drawn exclusively from clinical trials, 95% confidence intervals can be calculated for cost-effectiveness ratios. When data are drawn from a variety of sources and used in a modelling framework, probabilistic sensitivity analysis is recommended in order to take account of the uncertainty around data values. Bayesian approaches which reflect effects of uncertainty would be acceptable, provided they are transparent.

Adequate sensitivity testing is essential for all aspects of studies which involve modelling. In all such instances the rationale for the model, the structure and assumptions should be clearly laid out. All the data sources must be justified and point estimate, ranges and distributions of values identified to test best case and worst-case scenarios.

Uncertainty surrounding the cost-effectiveness ratios can be presented using cost-effectiveness acceptability curves (*van Hout et al, 1994*).

2.13.1 Budget impact

Manufacturers and sponsors should provide an analysis of the likely budget impact on the NHS of the use of their technology. For new technologies, this should include estimates of the changing budget impact over a 3 to 5 year period as a result of varying diffusion rates, and also an estimate of impact once diffusion has reached a 'steady state'.

Where a technology is expected directly to replace an existing treatment, the budget savings from this should also be calculated. When a technology is already being used in the NHS, the net additional budget impact should be considered.

2.13.2 Service impact

When a technology has requirements for specific health care resources, for example, specialist training for clinical personnel or availability of particular diagnostic services, these should be explained in general terms.

These factors will have a budget impact and should be included in the budget impact and cost analysis. They may also impose physical constraints on the ability of NHS management to implement the new technology. Manufacturers and sponsors are likely to have the most detailed knowledge of the requirements of their technology, and provision of such information will improve the decision-making process for all concerned.

Manufacturers and sponsors should provide as much detail as possible on the probable clinical and social status of patients likely to benefit from the use of their technology. They should also provide information on any aspects of the technology which might lead to differences in personal costs to patients and their carers and families.

The Institute will be developing further guidance on the treatment of equity. In the meanwhile, manufacturers and sponsors should bear in mind the classic principles of horizontal equity (treating the same those who are the same in relevant respects) and vertical equity (treating appropriately differently those who are different in relevant respects). A "relevant respect" might be "capacity to benefit" from the technology in question but there may also be other "relevant respects", depending on the technology and the characteristics of the patient groups in question. Particular attention should be drawn to instances

2.13 Wider NHS impact

2.14 Equity

where the cost-effectiveness of a technology varies across groups according to age, sex, geographical location, social class, ethnicity, language, or educational attainment . It will help the Appraisal Committee if any such cost differentials were presented explicitly, with estimates of the additional costs of providing the technology to them. The list of groups here is not intended to be exhaustive and there may, on occasion, be other subgroups thought appropriate to be brought to the committee's attention. In some cases it may be helpful to attach a differential weight to the outcome measure for particular groups and, where this is done, a sensitivity analysis should also be performed to indicate the size of the weight required to achieve a cost-effectiveness of the technology that is similar to that for the main group of patients being considered. The Appraisal Committee will form a judgement in cases of technologies whose efficiency characteristics are relatively unfavourable compared with other technologies but where there may be significant matters of equity which might compensate.

References to Section 2

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Parsonage M, Neuberger H. Discounting and health benefits, *Health Economics* 1992;1:71-6.

Sculpher M, Fenwick E. Claxton K. Assessing quality in decision analytic cost-effectiveness models. *Pharmacoeconomics* 2000;17:461-77.

Appendix A

Composition of the Guidance Steering Committee

Prof. Tony Culyer

Department of Economics and Related Studies, University of York (Chair)
Vice Chairman of the Institute

Prof. Ron Akehurst

University of Sheffield. Member of the Institute's Appraisal Committee

Prof. David Barnett

Chairman of the Institute's Appraisal Committee

Dr. Sheila Bird

Medical Research Council. Member of the Institute's Appraisal Committee

Mr. Jim Brown

AstraZeneca Pharmaceuticals

Prof. Martin Buxton

Brunel University. Member of the Institute's Appraisal Committee

Mr. Andrew Dillon

Chief Executive, NICE

Prof. Mike Drummond

Centre for Health Economics, University of York. Member of the Institute's
Guidelines Advisory Committee

Prof. Stephen Evans

Medicines Control Agency.

Prof. Miranda Mugford

School of Health Policy and Practice, University of East Anglia

Prof. John Posnett

University of York/Smith and Nephew

Dr. François Schubert

Glaxo Wellcome Research and Development

Dr Rod Taylor

Head of Appraisals, NICE (until November 2000)

Prof. Alan Williams

Centre for Health Economics, University of York

The positions shown for each member of the Steering Committee were those held at the time the Committee was in existence.

Appendix B

Consultation exercise

The Institute wishes to acknowledge the contribution of the following individuals who contributed to the consultation process.

Jan Baker, Bristol-Myers Squibb Pharmaceuticals Ltd

Sheila Bird, Medical Research Council Biostatistics Unit, University of Cambridge

Andrew Briggs, Health Economics Research Centre, University of Oxford

Anita Burrell, Aventis Pharma Ltd

Amanda Burls, Department of Public Health and Epidemiology, University of Birmingham

Paul Catchpole, Roche Products Ltd

Jim Chilcott & Suzy Paisley, Rapid Reviews, SCHARR, University of Sheffield

Mike Clarke, UK Cochrane Centre

Charles Dobson, Department of Health

Alison Edwards, BASF Pharma Ltd

Diana Elbourne, Medical Statistics Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine

Alastair Fischer, NICE Appraisals Team

Paul Glasziou, Commonwealth Department of Health and Aged Care, Australia

Eddie Grey, SmithKline Beecham Ltd

Karen Jewitt, Novartis Pharmaceuticals UK Ltd

Trevor Jones, Association of the British Pharmaceutical Industry

Oliver Keene, Glaxo Wellcome UK Ltd

Denise Lievesley, Royal Statistical Society

Ruairidh Milne, Wessex Institute for Health Research and Development, University of Southampton

Angela Morley, AstraZeneca UK Ltd

James Raftery, University of Birmingham

Mark Sculpher, Centre for Health Economics, University of York

Jorgen Seldrup, International Society for Clinical Biostatistics

Debbie Stephenson, Eli Lilly and Company Ltd

Tom Stevens, AstraZeneca UK Ltd

Rod Taylor, Department of Public Health and Epidemiology University of Birmingham

George W Torrance, McMaster University, Canada and **D Feeny**, University of Alberta, Canada

Keith Tolley, Glaxo Wellcome UK

Paul Trueman, Johnson and Johnson Medical UK Ltd

Sara Twaddle, Stobhill Hospital, Glasgow

Jason Ward, **Carole Longson**, Evidence Research Unit and **Prof. Nick Freemantle**, Medicines Evaluation Group, Centre for Health Economics, University of York;

Harry Ward, Wolverhampton Health Authority

Char Weeks, Health Communication Network

Nick Bruce and **Nick Wells**, Pfizer Ltd

Appendix C

Standard form for reporting of manufacturers and sponsor's submissions

The reporting structure provides a format to ensure that submissions are reported adequately, transparently and in a consistent manner to facilitate their review and comparison.

All subjects mentioned in this standard reporting form should be dealt with in the report. If there is any departure, for example, if a subject is excluded, this needs to be explained and substantiated. Extending the report to include other subjects is allowed.

The main text should not exceed 50 pages of A4-format. All extra information should be added in the form of an appendix. The submission should be provided in an electronic format.

Standard structure for report

1. Executive summary

This section should include a structured summary of the introduction, methods, results, discussion and conclusions. A key aspect of this summary is a quantitative statement of the key main 'bottom line' results – clinical and cost effectiveness and NHS impact. This section should not exceed 3 A4 sheets.

2. Contents page

3. Declaration

A fundamental requirement of all submissions is that all relevant evidence relating to that technology appraisal be included. Submissions are required to include the following standard declaration: *'This submission contains all the relevant evidence in the [name of company] possession related to the appraisal of [technology].'*

4. Introduction

The following issues should be included in this section:

- Epidemiology (guideline 2.4.1)
- Development of technology (guideline 2.4.2)
- Problem definition (guideline 2.4.1)

5. Clinical effectiveness

The following issues should be included in this section:

- Presentation of methods
- Inclusion and exclusion criteria for studies used in the submission

-
- Forms of analysis (guideline 2.4.3)
 - Time horizon (guideline 2.4.4)
 - Comparisons (guideline 2.5)
 - Outcome measurement (guideline 2.6)
 - Presentation of results (guideline 2.12)
 - Presentation of clinical data (guideline 2.8)

6. Cost effectiveness

The following issues should be included in this section:

- Presentation of methods
- Forms of analysis (guideline 2.4.3)
- Perspective (guideline 2.3.1)
- Valuation of outcomes (guideline 2.9)
- Resource use & costs (guideline 2.10)
- Discounting (guideline 2.11)
- Presentation of results (guideline 2.12)
- Dealing with uncertainty (guideline 2.12.4)

7. Wider implications of the technology

The following issues should be included in this section

- Budget impact (guideline 2.13.1)
- Service impact (guideline 2.13.2)
- Consideration of equity (guideline 2.14)

8. Discussion

- Generalisability of study (guideline 2.7)

All results must be considered in the discussion. All limitations of the study should be considered and their impact on the results.

9. Conclusions

Should be supported by the results of the study

10. References

Should be reported in standard scientific convention

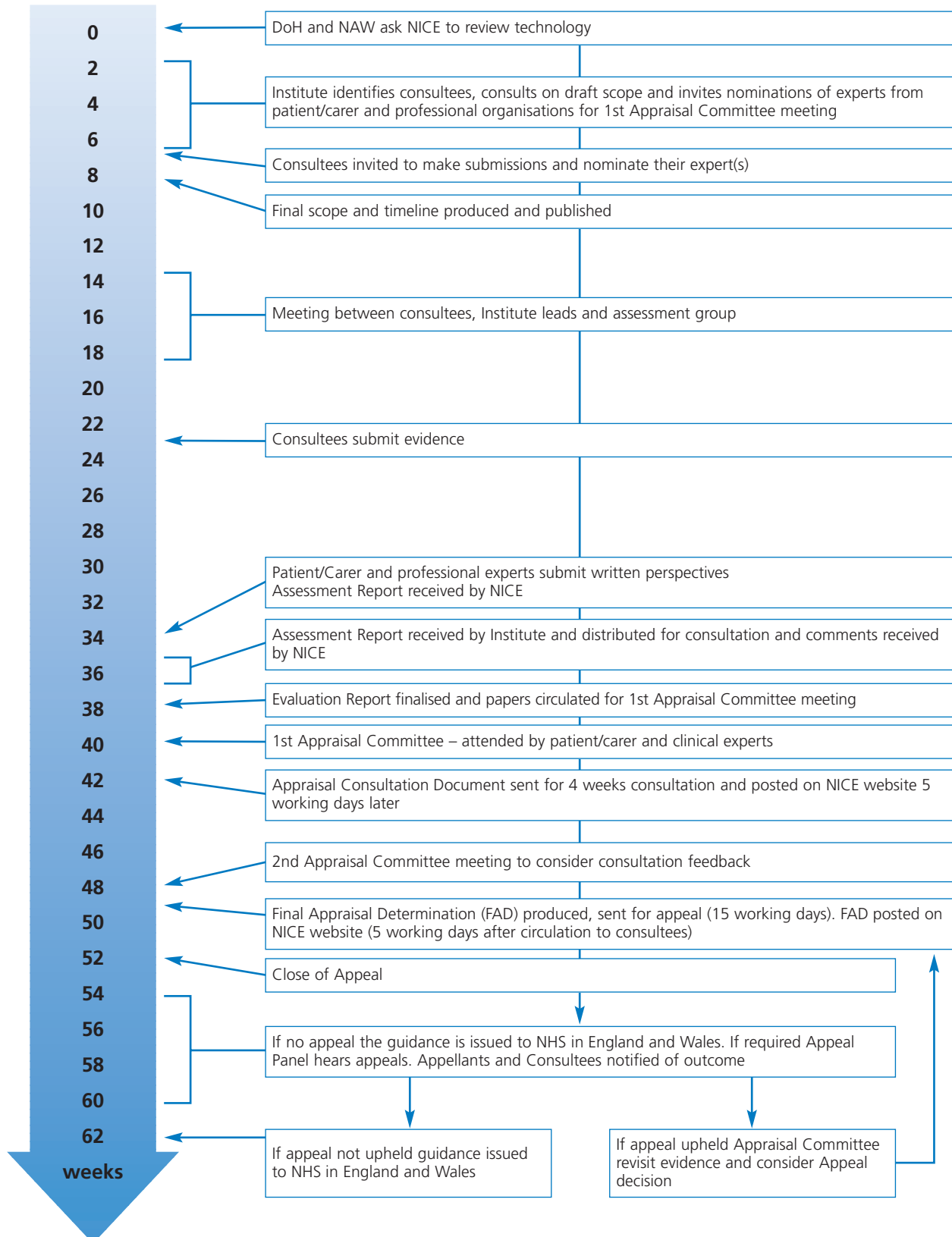
11. Appendices

The appendices should include:

- Study reports for any unpublished studies included within the submission
- Electronic copies of models used within submission
- Description of research studies currently underway or pending

Appendix D

Diagrammatic timeline for the appraisal process



The Technology Appraisals Process Series

1. Guide to the Technology Appraisal Process
2. Guidance for Appellants
3. Guidance for Patient/Carer Groups
4. Guidance for Healthcare Professional Groups
5. **Guidance for Manufacturers and Sponsors**



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