Introduction
This guidance has been prepared to assist manufacturers in the submission of a case to the Scottish Medicines Consortium. It is based upon guidance issued by Health Technology Board for Scotland but has been adapted in several minor respects to take account of the different needs of SMC. This guidance assumes the reader has basic familiarity with the concepts of economic evaluation.

The guidance should be read in conjunction with guidance for completion of other sections of the form. Following this guidance is not a guarantee of a positive SMC recommendation. However, failure to follow the guidance may be a reason for a negative recommendation, depending on the SMC’s view of the seriousness of the consequences.

The guidance consists of the following sections:
1. Choice of options to be included in economic evaluation
2. Perspective to be adopted
3. Time horizon of the evaluation
4. Choice of type of economic evaluation
5. Modelling costs and benefits
6. Resource use data
7. Health effects
8. Discounting future costs and benefits
9. Summarising results in economic evaluation
10. Handling uncertainty and variability in the data used
11. Equity implications

1. Choice of alternative option(s) against which drug should be compared
The optimal comparator is the technology that is most likely to be displaced in Scotland if the new technology were introduced. For some technologies, it may be appropriate to consider more than one comparator. For others, the comparator may relate to a “care package” that varies between locations. It is also important to distinguish between care packages in which the technology forms an additional element and care packages that are clear alternatives and would be displaced if the technology were adopted.
It is recognised that comparators used in clinical trials may not be those used in Scotland. In such circumstances some form of bridging assessment to an appropriate comparator and sensitivity analyses to assess the impact of assumptions about comparators and discussion of possible biases will be necessary.

2. Choice of Perspective
In principle, economic evaluation should aim to assess comprehensively the changes in health states and the associated cost changes that arise from the adoption of a technology. The main analysis should be focused on (i) those changes that affect the Scottish healthcare system, and (ii) patients and their families where these are thought to differ significantly between the options. An indication of the nature and likely magnitude of any excluded benefits and costs that would arise from adopting a wider societal perspective and the effect of including these in the cost effectiveness analysis, should also be provided, even where these are difficult to quantify. Every effort should be made to
reduce the risk of a partial and potentially misleading assessment of the balance of gains and losses.

3. Time Horizon
The time horizon adopted should be sufficient for the main health outcomes and resource use effects to be explored. The approach used to select a time horizon and the resulting issues that the time frame presents for any modelling of long term health outcomes and resource use should be explained, together with an account of the reasons for and effects of its adoption over its alternatives. If the model is sensitive to the choice of time frame or the approach used to extrapolate data over time then sensitivity analysis should be provided. Any steps taken to deal with censored and truncated data should be discussed.

4. Modelling costs and benefits
The specific aim of the modelling component of an economic evaluation needs to be clearly defined. Each stage of the modelling should be fully disclosed, with the source of all inputs clearly explained and assumptions justified. Modelling techniques should be described in sufficient detail and results should be fully reported to allow independent scrutiny of methods and replication of results. If the model uses data that are not the same as that used to evaluate clinical effectiveness, a clear explanation of the rationale for this and potential biases introduced should be provided.

5. Specific Types of Economic Evaluation
Economic evaluation encompasses cost-minimisation analysis, cost-effectiveness analysis and cost-utility analysis.
Cost-minimisation studies can be used if there is no clinically meaningful difference in the distribution of health effects between the alternative technologies. For pharmaceuticals, this would require well-designed equivalence trials for the evaluation of efficacy (effectiveness) (ICH E10: Choice of Control Group) and close comparability of other effects, which were not the subject of the equivalence analysis (e.g. secondary variables, side effects, compliance, etc.).
Where a single measure of health outcome can be justified (e.g. life years gained) standard cost-effectiveness analysis is appropriate. However, most studies examine a range of outcomes and require the application of the cost-utility approach for summation. Where this summation is invalid or misleading, a disaggregated presentation of gains and losses can be presented using cost-consequence analysis. The rationale for adopting a cost-consequence approach should be clearly explained, together with the attempts made to map patient outcomes to a principal aggregatable measure.
Under circumstances where a significant outcome of the technology relates to non-health outcomes and is unlikely to be captured within health state utilities (e.g. information and reassurance supplied by ante-natal screening) it may be appropriate to apply cost-benefit analysis.

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6. Resource Consequences

Full disclosure of methods used to identify, measure and value resource consequences and health effects is required for an informed critical review of the economic evaluation. Resource implications should ideally be identified, measured and valued within a Scottish context, or at least a UK setting. Submitted economic evaluations that are not set in Scotland should include a comment on the validity of using resource data from outside Scotland, to include referencing any relevant differences in the patient and healthcare environments.

The main analysis should present direct healthcare resource usage for the technology and its comparator(s) separately and in natural units, such as hospital days, volume of drugs or number of screenings, with data sources cited. Any resource use arising from clinical trials, as opposed to that in routine care, should be excluded from the analysis. When long-term effects are modelled, future resource use should include treatment of the condition under consideration but not resource use from treating unrelated conditions. Patient resource use in accessing treatment should also be included where felt to be significant, particularly where this differs between the technology and its comparator(s).

Other resource use may also be presented separately where differences arise between the technology and its comparator(s) e.g. direct non-healthcare resource use such as that by social and educational services, and productivity losses attributable to changes in health outcomes.

Total costs should be calculated for the technology and its comparator(s) by the application of standardised unit costs to resource use data. For most direct healthcare resource use, the actual price paid will be an acceptable estimate of opportunity cost. Staffing costs should include employers' costs such as superannuation, etc. Capital and building costs should also be annualised using current replacement costs, anticipated life-span and the discount rate (see below) and allocated using realistic capacity utilisation rates within the Scottish context.

There may be cases when the market price does not exist or where it is inappropriate to use: a shadow price reflecting the value in the next best use should be included and justified.

The date of the study or reference time period spanning the collection of cost, expenditure or price data used to value resource quantities should be clearly stated along with the local currency and price indices used to calculate current costs.

Any statistical transformations used in the analysis of cost data or models employed to assess count data (e.g. doctor visits, in-patient episodes) should be documented.

Any essential and specific healthcare resources necessary to implement and operate the technology should be separately identified.

7. Health Effects

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If the effectiveness estimates in the economic evaluation differ from the overall synthesis of clinical effectiveness data the reasons for this should be explained. The health effects captured in economic evaluation can range from simple, easily measured outcomes to very complex and diffuse composite measures based on an array of health states and utility values. The more complex the measure, the more discussion will be needed, to provide reassurance that the derived measure is not subject to bias. Measurable health effects should be selected and justified in relation to the primary aim of the health technology. If the primary efficacy variable from the clinical evidence section is not used, the rationale for the new choice of variables should be clearly explained. The reasons for any loss of data compared to the analysis of clinical effectiveness should be clearly outlined. The potential biases introduced by the loss of data should be clearly explained.

Any combination of health effects from a variety of studies to create one overall effect should follow good statistical practice. Measures of central tendency and dispersion should be accompanied by appropriate descriptive statistics on the distributional features of each reported health effect. The time period used to calculate the change in health outcomes should be clearly defined and the points where comparisons are made between the technology and its comparator(s) made explicit. The methods used to examine time-to-event data should be described, paying particular attention to mean time to event data for cost-effectiveness analysis.

When cost-effectiveness analysis is used a clear indication of the manner in which the effect relates to final health outcomes must be given. Where cost-utility analysis is used the techniques used to measure and scale preferences across different combinations of health states need to be described, morbidity and mortality data being presented separately with subsequent aggregation. When health states are measured and then combined with utility values from other studies, all original investigations and sources should be cited. If utility values are generated within the economic evaluation, the specific method used (e.g. visual analogue scale, time-tradeoff or standard gamble) needs to be outlined and qualified by any special techniques that were employed. Studies need to state whether preferences reflect the views of individuals actively participating in the evaluation itself, patients who have direct experience of the health states and/or the care alternatives being scrutinised, or the views of a sample of the general public, and how these individuals were selected.

8. Discounting of Costs and Health Effects
The timing of the costs and benefits should be outlined prior to their discounting. The specific functional form used for discounting must be described, together with an account of how this affects results compared to standard exponential discounting if these differ. Costs should be discounted according to the UK Treasury discount rate (currently 6.0%) and health effects should be discounted using the time preference part of the Treasury discount rate (currently 1.5%). In the sensitivity analysis, the health effects discount rate should be varied to include 0% and the full Treasury discount rate.

9. Summarising Results
For both the technology and its comparator(s), the total costs and total benefits arising from their use should be presented. This can be presented in a variety of ways e.g. a graphical representation of the joint distribution of costs and effects across the cost-effectiveness plane or an incremental cost-effectiveness ratio. Point estimates of the cost effectiveness (incremental cost effectiveness ratio or net health gain) of the technology relative to its comparator(s) should also be presented, together with an appropriate treatment of variability and uncertainty (see below). Each aggregation step required to derive these summary measures (as outlined in this guide) should be presented in sufficient detail for the reader to be able to disaggregate and independently verify any derived results. Where possible, electronic files containing the models, programmes and data for the economic evaluation should be submitted to SMC.

Note that while incremental ratios provide a means of comparing treatment effects relative to costs, there are problems. SMC follows HTBS in explicitly not adopting any form of cost per QALY cut-off" or threshold for acceptance.

Any cost “savings” should be discussed, identifying those that are likely to be realised and those whose impact may be more elusive.

10. Explaining Variability and Uncertainty
The variability associated with point estimates of cost effectiveness should be presented, preferably by presentation of the associated 95% confidence intervals. A variety of methods have been suggested to generate such confidence intervals3. These methods should be clearly described and investigations into assumptions (e.g. the normality of distributions) should be investigated.

The economic evaluation should be subjected to sensitivity analysis. Probabilistic sensitivity analysis is preferred to the more limited one-way sensitivity analysis. For example, probabilistic sensitivity analysis, using a large number of Monte Carlo simulations can be used to examine the effects on the results of an economic evaluation when the underlying variables are allowed to simultaneously vary across a plausible range of predefined distributions. Bayesian approaches capturing probability distributions for the model’s parameters are recommended, provided the methods are explicit and transparent4. Such distributional models are preferred to pure deterministic models as they facilitate the use of cost effectiveness acceptability curves to demonstrate cost-effectiveness. This technique is usually statistically more robust than adopting alternatives such as incremental cost-effectiveness ratios and can also be a powerful presentational tool to present uncertainties around the cost-effectiveness ratios5.

11. Efficiency-Equity Trade Off
Cost-effectiveness analysis provides a summary measure of the efficiency of a technology, but is less explicit about equity implications. Formal techniques for incorporating distributional consequences into cost-effectiveness analysis are not well established, and SMC follows the lead of HTBS in not recommending their use at present\(^6\), the focus being upon patients’ capacity to benefit from treatment. However, discussion of how the technology will reduce inequalities within Scotland would be welcome.