



GUIDANCE ON APPRAISAL STRUCTURE AND EVIDENCE CONSIDERED

1. Structure of Appraisal

The evidence submitted by the applicant company (in Form B or Form C format), the All Wales Therapeutics and Toxicology Centre (AWTTC), clinical experts and patient organisations is first appraised by the New Medicines Group (NMG). In making its recommendations to the All Wales Medicines Strategy Group (AWMSG), NMG appraises the evidence on the clinical effectiveness and cost-effectiveness of the medicine. In certain circumstances, NMG may also consider the innovative nature of the medicine and the particular features of the condition and population for which the medicine is intended.

In making its recommendation to Welsh Government, AWMSG takes into account NMG's recommendations and additionally considers issues of equity. In certain circumstances, AWMSG will also take into consideration the anticipated budget impact and broader societal impact.

There is separate additional guidance for decision-making in relation to life-extending, end-of-life medicines and medicines that have been developed to treat rare diseases.

2. Clinical effectiveness

AWMSG/NMG can take account of the full range of clinical studies that have been carried out and are not expected to restrict themselves to consideration of only certain categories of evidence.

This requires AWMSG/NMG to consider all the evidence they deem relevant, from randomised controlled trials (RCTs) to observational studies, and any qualitative evidence related to the experiences of patients and carers and clinical experts who have used the medicine being appraised or are familiar with the relevant condition. In evaluating the evidence base, AWMSG/NMG will exercise their scientific and clinical judgement when deciding whether particular forms of evidence are fit-for-purpose in answering specific questions.

The importance given to these various kinds of evidence 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. In general, greater importance is given to evidence derived from high quality studies with methodology designed to minimise bias.

AWMSG/NMG's judgements on clinical effectiveness take account of the following factors:

- the nature and quality of the evidence derived from:
 - the applicant company's submission;
 - the assessment conducted by AWTTC;
 - the views expressed by the clinical specialists, particularly their experience of the use of the medicine in clinical practice including the extent and nature of 'off licence' use;

- the views of the patient experts and carers on the experiences of patients who have used the medicine.
- uncertainty generated by the evidence and differences between the evidence submitted for licensing and that relating to effectiveness in clinical practice;
- the robustness and appropriateness of the statistical analyses employed;
- the possible differential effectiveness or greater risk of adverse events in different subgroups of patients;
- the harms and benefits of the medicine as seen from the patient’s perspective;
- the position of the medicine in the overall pathway of care and the alternative treatments that are available, including use of unlicensed comparators.

Whether all or some of the above factors are taken into account in making judgements about the evidence of clinical effectiveness is a matter for AWMSG/NMG’s discretion.

3. Cost-effectiveness

AWMSG take account of how recommendations may enable the more efficient use of available healthcare resources, and the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new medicine. In doing so, it takes into consideration factors listed by the Welsh Government:

- the broad clinical priorities of Health and Social Services in Wales (for example, as set out in National Service Frameworks, Designed for Life and the Review of Health & Social Care in Wales);
- the degree of clinical need of the patients with the condition under consideration;
- the broad balance of benefits and costs;
- the potential for long-term benefits to the NHS of innovation.

AWMSG/NMG take account of how the incremental cost-effectiveness of the medicine being appraised relates to other interventions/medicines currently being used in the NHS, including those that have been the subject of previous appraisals by AWMSG or the National Institute for Health and Clinical Excellence (NICE). AWMSG/NMG will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals.

AWMSG/NMG also have to make judgements on the appropriateness of comparator medicines as perceived by all NHS stakeholders, which is crucial to the cost-effectiveness calculation.

When the evidence on key parameters used to estimate cost-effectiveness (for example, clinical effectiveness and effect on health related quality of life [HRQoL]) has serious limitations and/or when a variety of assumptions have been necessary in the cost-effectiveness modelling, the additional uncertainty this generates is a key factor in underpinning the judgements of AWMSG/NMG. Taking this into account, AWMSG/NMG are likely to consider medicines for which evidence on cost-effectiveness is underpinned by the best-quality clinical data more favourably than those for which supporting evidence is dependent to a large extent on theoretical modelling alone.

AWMSG/NMG’s judgements on cost-effectiveness are influenced by the following factors:

- the strength of the supporting clinical effectiveness evidence;
- the robustness and appropriateness of the structure of the economic models (in particular, whether the model reflects the decision problem at hand) and the uncertainties around the assumptions on which the model structure is based;
- the plausibility of the inputs into, and the assumptions made, in the economic models;

- the range and plausibility of the incremental cost-effectiveness ratios (ICER);
- the likelihood of decision error and its consequences.

AWMSG/NMG will consider carefully which individuals benefit most from the medicine and whether there are subgroups of individuals for whom the effectiveness evidence suggests differential cost-effectiveness. AWMSG/NMG may recommend the use of an intervention for subgroups of the population only when there is clear evidence that the characteristics defining the subgroup influences the effectiveness and/or cost-effectiveness of the intervention.

AWMSG/NMG do not use a fixed ICER threshold above which a medicine would automatically be defined as not cost-effective or below which it would.

Below a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, the decision to recommend the use of a medicine is normally based on the cost-effectiveness estimate and the acceptability of a medicine as an effective use of NHS resources. However, medicines with presented ICERs less than £20,000 per QALY gained may not be recommended if AWMSG/NMG are not persuaded by the plausibility of the inputs to the economic modelling and/or the certainty around the estimated ICER. This might be affected, for example, by sensitivity analysis or limitations to the generalizability of findings regarding effectiveness.

Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the medicine as an effective use of NHS resources will specifically take account of the following factors:

- The degree of certainty surrounding the calculation of ICERs. AWMSG/NMG will be more cautious about recommending a medicine when they are less certain about the ICERs presented.
- The innovative nature of the medicine. AWMSG/NMG will consider whether the medicine:
 - represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment, no consistently satisfactory treatment, treatment that was less safe or treatment that was less convenient) and;
 - can plausibly generate substantial health gains over existing treatments for the individual (e.g. > 1 QALY) or for a population (e.g. > 100 QALYs).
- The particular features of the condition and population receiving the medicine. AWMSG/NMG will consider the underlying severity of the illness, in terms of baseline HRQL and prognosis. AWMSG/NMG recognise society's priority for the expensive relief of a very serious condition over the relatively inexpensive relief of a mild discomfort (which may be calculated to give an equivalent ICER).
- Where appropriate, the broader societal impact. AWMSG will consider whether the medicine has an impact on non-health benefits that are not captured in the QALY (e.g. impact on families and carers, work and schooling), costs to sectors outside the NHS/PSS such as educational services, and productivity losses attributable to changes in health outcomes.

As the ICER of a medicine increases in the £20,000 to £30,000 per QALY range, AWMSG/NMG's judgement about the acceptability of the medicine as an effective use of NHS resources should normally make explicit reference to the relevant factors listed above.

Above an ICER of £30,000 per QALY gained, the case for supporting the medicine on these factors has to be increasingly strong.

AWMSG/NMG have a strong preference for expressing health gains in terms of QALYs. In circumstances where the health gain is expressed in terms of life-years gained, the range of most plausible ICERs that are acceptable will be substantially lower than those described above.

4. Equity

Equity implies the fair distribution of health across individuals. AWMSG will consider whether, by recommending the medicine, inequalities in health will be reduced across Wales. It will consider, for instance, whether the condition being treated is significantly more prevalent in groups of people who may be socially disadvantaged (for example, by virtue of being poor, and/or members of a disenfranchised racial, ethnic, or religious group). It will also take into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: age; sex/gender or sexual orientation; people's income, social class or position in life; race or ethnicity; disability; and conditions that are or may be, in whole or in part, self-inflicted or are associated with social stigma.

5. Budget impact

When the AWMSG considers that a medicine has a large impact on NHS resources within a given disease area, it will want to be increasingly more certain of the cost-effectiveness and may require more robust evidence on the clinical effectiveness and cost-effectiveness.