Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

Guidance on appraisal structure and evidence considered

1.0 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), and by clinical experts and patient organisations, is first appraised by the New Medicines Group (NMG). NMG makes its recommendation to the All Wales Medicines Strategy Group (AWMSG) once it has appraised 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, the particular features of the condition and the population for which the medicine is intended.

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

There is separate additional guidance for decision-making relating to severity of disease (see AWMSG's 'Policy for appraising medicines for severe conditions') and medicines that have been developed to treat very rare diseases (see AWMSG's 'Policy for appraising a medicine for a very rare disease'). Further information and guidance can be found on the AWTTC website under 'All appraisal documents'.

2.0 Evidence considered

AWMSG and NMG can take account of a wide range of evidence and are not expected to restrict themselves to consideration of certain categories of evidence. AWMSG and NMG can consider all the evidence they deem relevant, from randomised controlled trials to observational studies, including real-world data, and any qualitative evidence relating to the experiences of patients, carers and clinical experts who have used the medicine being appraised or are familiar with the relevant condition. In evaluating the evidence base, AWMSG and 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's and NMG's judgements consider 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 using the medicine in clinical practice including the extent and nature of “off-licence” use and;
- the views of the patient experts and carers on the experiences of patients who have used the medicine.

3.0 Clinical and cost-effectiveness evidence

AWMSG and NMG take account of the degree of clinical need of the patients with the condition, the medicine’s clinical effectiveness, and how its incremental cost-effectiveness relates to other interventions or 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 and NMG will want to ensure that their judgements regarding the cost-effective use of NHS resources are consistently applied between appraisals.

AWMSG and NMG also take into account how committee recommendations may enable the more efficient use of available healthcare resources. This includes considering the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new medicine. In doing so, AWMSG and NMG support key Welsh Government priorities for Health and Social Services in Wales (for example, National Service Frameworks, A Healthier Wales: Our Plan for Health and Social Care; The Well-being of Future Generations (Wales) Act 2015, Prudent Healthcare Principles).

AWMSG and NMG’s judgements on clinical and cost-effectiveness consider the following factors:

- the strength of the supporting clinical effectiveness evidence;
- 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 used;
- 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;
- the appropriateness of comparator medicines identified;
- the plausibility of the inputs into, and the assumptions made, in the economic models;
- 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 range and plausibility of the incremental cost-effectiveness ratios (ICER) and;
- the likelihood of decision error and its consequences.

When the evidence on key parameters used to estimate cost-effectiveness (for example, clinical effectiveness and effect on health-related quality of life) 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 underpinning the judgements of AWMSG and NMG. Taking this into account, AWMSG and NMG are likely to consider medicines with economic evaluations underpinned by the best-quality clinical data to have a more reliable estimation of cost-effectiveness than those for which supporting evidence depends to a large extent on theoretical modelling alone.

However, AWMSG recognises that evidence generation can be challenging in certain populations, such as medicines for treating rare diseases. In these specific circumstances, AWMSG and NMG may be able to accept a higher degree of uncertainty when making recommendations. AWMSG and NMG will consider how the nature of the condition or medicine affects the ability to generate high-quality evidence, before applying greater flexibility.

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

4.0 Decision making

4.1 Decisions based on cost-utility analyses

AWMSG and NMG do not use a fixed ICER threshold for approval of medicines. Guidance on the ICERs that AWMSG usually consider cost-effective is detailed below.

Below a most plausible ICER of £20,000 per quality-adjusted life-year (QALY) gained, or £100,000 per QALY gained for medicines for very rare diseases, the decision to recommend the use of a medicine is usually based on the cost-effectiveness estimate and the acceptability of a medicine as an effective use of NHS resources. However, medicines with presented ICERs of less than £20,000 per QALY gained, or less than £100,000 per QALY gained for medicines for very rare diseases, may not be recommended if AWMSG or NMG are unconvinced by the plausibility of the inputs used in the economic model or the certainty around the estimated ICER.

AWMSG can consider other relevant factors alongside the ICERs when making a judgement on the value of a new medicine. The influence of these other factors on the decision to recommend a medicine takes on greater importance as the most plausible ICER increases in the £20,000 to £30,000 per QALY gained range, or above £100,000 per QALY gained for medicines for very rare diseases. In such situations, AWMSG and NMG judgements about the acceptability of the medicine as an effective use of NHS resources should usually explicitly take into account the following additional factors for all medicines.

- The degree of certainty surrounding the calculation of ICERs. AWMSG and NMG will be more cautious about recommending a medicine when they are less certain about the ICERs presented. However, as identified above, AWMSG and NMG can accept a higher degree of uncertainty in specific circumstances.
- The innovative nature of the medicine. AWMSG and NMG will consider whether the medicine:

    - represents a significant improvement on existing therapy (for example, the medicine treats 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 a person (for example, > 1 QALY) or for a population (for example, > 100 QALYs).
- The particular features of the condition and population receiving the medicine. AWMSG and NMG will consider the underlying severity of the illness and recognise society's priority for the expensive relief of a very serious condition over the relatively inexpensive relief of a mild discomfort. In certain circumstances, AWMSG may assign a greater weighting to QALYs if the medicine is to treat a condition that has a high degree of severity (see AWMSG's 'Policy for appraising medicines for severe conditions').
- 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 (for example, 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.

For medicines to treat rare and very rare diseases, all of the above should usually explicitly be taken into account plus the following additional factors:

- whether the medicine can reverse or cure, rather than stabilise the condition; and
- whether the medicine bridges a gap to a definitive therapy (for example, a gene therapy) and that the definitive therapy is currently being developed.

For medicines for very rare diseases only, all of the above should usually explicitly be taken into account plus the following additional factors:

- the impact of the medicine on the overall delivery of the specialised service; and
- any additional requirements relating to infrastructure and staffing.

Above an ICER of £30,000 per QALY gained, or £100,000 per QALY gained for medicines for very rare diseases, the case for supporting the medicine based on these factors has to be increasingly strong.

AWMSG and 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.

For medicines that provide less health benefit at lower cost (that is, ICERs fall in the south-west quadrant of the cost-effectiveness plane), or for economic evaluations where a decision modifier is applied, or comparators have only small differences in associated QALYs or costs, or subgroup analysis is undertaken; AWMSG and NMG will consider the net health benefits (NHB), using values placed on a QALY gain of £20,000 and £30,000, to determine cost-effectiveness (taking relevant decision modifiers into account). If the NHB calculation results in a positive figure this suggests that the overall population health gains will increase as a result of the new medicine,

and that the new medicine is a worthwhile allocation of resources. However, if the NHB is negative, the overall population health gains are reduced, and the new medicine would not be considered a worthwhile resource allocation.

4.2 Decisions based on cost-minimisation analyses

When a cost-minimisation analysis (CMA) is used rather than a cost-utility analysis, AWMSG and NMG will carefully consider the suitability of the evidence underpinning this alternative approach to economic evaluation. For a new medicine to be considered cost-effective by AWMSG and NMG when a CMA is applied, the committees should be satisfied that there are no clinically meaningful differences in the distribution of effects between the medicine and its comparator(s), in all dimensions of health. Also, the most plausible healthcare costs associated with the new medicine should be equivalent to, or lower than, its comparator(s).

5.0 Equity

Equity implies the fair distribution of health across individuals. AWMSG will consider whether, by recommending a medicine, inequalities in health will be reduced across Wales. For example, AWMSG will consider whether the condition being treated is significantly more prevalent in groups of people who may be socially disadvantaged (for example, because of poverty, or because they are members of a disenfranchised racial, ethnic, or religious group). AWMSG 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: age; sex; gender reassignment; sexual orientation; pregnancy or maternity; marriage or civil partnership; people's income, social class or position in life; race; religion or belief; disability; and conditions that are or may be, in whole or in part, self-inflicted or are associated with social stigma.

6.0 Budget impact

When 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 medicine's clinical effectiveness and cost-effectiveness.