Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

Policy for appraising a medicine for a very rare disease

This policy should be read in conjunction with the following documents:

- **AWMSG appraisal principles & process flowcharts**
- **AWMSG Form B guidance notes**
- **AWMSG Guidance on appraisal structure and evidence**
- **NICE health technology evaluations: the manual. Process and methods (PMG36).**

Background

The National Institute for Health and Care Excellence (NICE) published an update to its health technology assessment methods and processes in January 2022. The All Wales Medicines Strategy Group (AWMSG) has since reviewed and updated its process for appraising medicines developed specifically to treat very rare diseases, to align with NICE's highly specialised technologies (HST) programme.

AWMSG continues to take into account a broad range of considerations when appraising a medicine for a very rare disease; cost-effectiveness is only part of the judgement of its value. AWMSG also recognises that a higher level of uncertainty is often associated with these medicines.

What medicines are eligible for appraisal under this policy?

AWMSG's policy for appraising a medicine for a very rare disease applies in exceptional circumstances only:

- to medicines for conditions that have small patient populations who have limited or no treatment options;
- and where the uniqueness of the disease poses significant challenges in terms of evidence generation.

AWMSG will consider medicines as eligible for appraisal under its very rare disease policy if the medicine meets all four of the eligibility criteria outlined in Table 1.

These criteria will allow AWMSG to balance the need to support access to innovative medicines for very rare diseases with the reduction in population health gain that results from applying a higher incremental cost-effectiveness threshold and assigning greater weight to quality-adjusted life-year (QALY) gains (see Table 2).

Table 1. Eligibility criteria for appraising a medicine for a very rare disease

Eligibility criteria		Definition or application
1	The disease is very rare.	The disease has a prevalence of ≤ 1 in 50,000 people in Wales, or affects approximately 63 or less people in Wales*.
2	Usually, no more than 18 people in Wales would be eligible to receive the medicine for the licensed indication being appraised; and no more than 30 people in Wales would receive it for all its indications†.	If more than 18 people in Wales would be eligible, then disease severity, the potential for significant benefits and the unavailability of other effective treatments are all considered§.
3	The very rare disease for which the medicine is indicated significantly shortens life or severely impairs quality of life¶.	Assessment of significance and/or severity will need judgement.
4	There are no other satisfactory treatment options, or the medicine is likely to offer significant additional benefit over existing treatment options.	Satisfactory treatments may include other licensed medicines, medical devices or other methods of treatment used in Wales. Assessment of significance will need judgement.

*In exceptional circumstances, a medicine may be appraised under AWMSG's very rare disease policy if the disease it treats has a prevalence above 1 in 50,000 **and** all the remaining criteria are clearly met.
†Figures extrapolated from the NICE HST routing criteria for application in Wales.
§AWMSG has the discretion to apply some flexibility based on information and evidence gathered.
¶No additional severity modifier QALY weighting is applied. Severity is implicit in the application of the policy for appraising a medicine for a very rare disease.

The All Wales Medicines Strategy Group: AWMSG, highly specialised technologies: HST, National Institute for Health and Care Excellence: NICE, Quality-adjusted life-year: QALY

Size of benefit

AWMSG's approach to appraising a medicine for a very rare disease will consider the size of benefit that the medicine is likely to deliver. This benefit is measured in terms of incremental QALY gains.

Equity and other broader considerations will allow AWMSG to consider a higher cost-effectiveness threshold for medicines developed to treat very rare diseases, usually up to £100,000 per QALY gained. For additional weighting to be applied, AWMSG will need to be satisfied that there is compelling evidence that the medicine offers significant QALY gains.

The incremental number of QALYs gained over the lifetime of a patient, when comparing the new medicine with a relevant comparator(s), will guide AWMSG to apply a QALY weighting between 1 and 3, using equal increments. Table 2 shows how AWMSG will apply these weightings.

Table 2. Size of benefit QALY weightings

Incremental QALYs gained (per patient, using lifetime horizon)	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

Appraisal process for a medicine for a very rare disease

Before an applicant company submits a Form B, it requires confirmation from the All Wales Therapeutics and Toxicology Centre (AWTTC) that the medicine is eligible to be appraised under the very rare disease policy. The applicant company should first complete the AWMSG very rare disease form available on the AWTTC website, providing supporting evidence for each of the four eligibility criteria (see Table 1). The completed form should be sent to AWTTC@wales.nhs.uk.

AWTTC will review the evidence and consider if the medicine meets all four of the eligibility criteria. If it is not clear that all four criteria are met, AWMSG's Medicines for Very Rare Diseases Panel will be convened (usually within eight weeks of receiving the form). The panel will include relevant experts to ensure that appropriate knowledge and specialism is incorporated into the decision-making process. AWTTC will inform the applicant company of the panel's decision, within five working days, in a formal outcome letter outlining the reason(s) for the decision, including identification of which criteria have or have not been met.

An applicant company can challenge the panel's decision, if it thinks that the eligibility criteria have not been applied appropriately. The applicant company should provide adequate explanation for the reasons for their challenge and submit them via email to AWTTC@wales.nhs.uk within seven calendar days of notification of the panel's decision.

AWMSG steering committee will review the challenge and, if accepted, the AWMSG's Medicines for Very Rare Diseases Panel will re-convene as soon as reasonably practicable. No new evidence can be submitted at this point, and no further challenges can be made.

After receiving the Form B submission from a company, the appraisal process for a medicine for a very rare disease is largely the same as the process for all other medicines.

AWMSG recognises that the rarity of a disease can affect the ability to generate high-quality evidence and acknowledges medicines for very rare diseases are often

associated with greater uncertainty than for other medicines. AWMSG will therefore apply greater flexibility in terms of the acceptance of a higher degree of uncertainty when appraising a medicine for a very rare disease.

AWMSG will consider all the evidence they deem relevant, from randomised controlled trials to observational studies, including real-world data. Further information can be found on the AWTTC website regarding guidance on appraisal structure and evidence considered.

The option to convene a meeting of the Clinician and Patient Involvement Group (CAPIG) will be available to the applicant company following a negative recommendation by either the New Medicines Group (NMG) or AWMSG. This forum provides opportunity for further assessment of the benefits of the medicine from the perspective of clinicians and patients. A CAPIG meeting is most likely to be convened following a negative recommendation by NMG and before the medicine is appraised by AWMSG.

Clinician and patient involvement group (CAPIG)

AWTTC will collate views from clinical experts and patient organisations for every medicine that AWMSG appraises. For a medicine to treat a very rare disease, if a CAPIG meeting has been convened, the CAPIG report will identify any broader issues from a patient, clinical and societal perspective and will be presented to AWMSG.

The applicant company may submit supplementary cost-consequence analyses to CAPIG for consideration. Further information on CAPIG is available in the CAPIG information sheet and in the CAPIG terms of reference.

Timelines for appraising a medicine for a very rare disease

The timeline for appraising a medicine for a very rare disease is the same as for other medicines appraised by AWMSG. However, if a CAPIG meeting is convened the process will be extended by a maximum of 12 weeks.