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 Medicines Assessment Process for Licensed and Off-label Medicines, January 2025
- Guidance notes for the submission form for AWMSG Health Technology Assessment
- NICE-wide topic prioritisation: the manual. NICE process and methods (PMG46)

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. NICE updated its definitions in 2025 to provide greater clarity on its routing criteria. AWMSG subsequently updated this policy to maintain full alignment.

In an update to the AWMSG assessment process for licensed medicines in 2025, the Licensed One Wales Medicines Assessment Group (LOWMAG) considers and discusses the evidence presented in an Evidence Summary Report and provides a clear and robust recommendation, with rationale, to AWMSG to endorse and Welsh Government to ratify. However, the process for the assessment of medicine for a very rare disease remains unchanged.

LOWMAG takes 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. LOWMAG 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.

A medicine will be considered eligible for appraisal under the AWMSG very rare disease policy if the medicine meets all four of the eligibility criteria outlined in Table 1.

These criteria will allow LOWMAG 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 and debilitating.	The disease has a point prevalence of ≤ 1 in 50,000 people in Wales, or affects approximately 63 or less people in Wales. 'Disease' refers to a condition for which a diagnosis can be made using the World Health Organization (WHO) International Classification of Diseases (ICD-11) as a guiding tool. It does not refer to subgroups based on age, sex, severity, or genetic subtype. These will only be considered if they are clinically meaningful. The disease is lifelong after diagnosis with current treatment, requiring ongoing clinical management and/or supportive care, and has an exceptional negative impact on people with the disease, and their families and carers. ‘Exceptional negative impact' refers to shortened length of life or severely impaired health-related quality of life. The assessment of this will necessitate an element of subjective judgement.
2	The medicine is an innovation for the very rare disease.	An innovation brings additional health gains to people with the disease compared with existing treatment or best supportive care. This could be an advanced therapy medicinal product (ATMP), a new chemical or biological entity, or a novel drug device combination. The medicine should not be a repurposed one. A repurposed technology means new uses for medicines that are outside the scope of the existing licence for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for

		human use for a particular condition and then using it to treat another condition. This can also include generic treatments or treatments that have had marketing authorisation withdrawn and the developer is seeking a new indication. The medicine's indication should not be a significant extension of an indication from another population or disease.
3	No more than 18 people in Wales are eligible to receive the medicine for its licensed indication† and it is not an individualised medicine.	The medicine must be the first licensed treatment indicated for the very rare disease under consideration. The medicine should not be an extension of an indication from another related population or disease, or subgroup of people with the same very rare disease under consideration. The medicine is unlikely to be suitable for other subgroups of the population with the very rare disease in the future who are outside of its first indication. The medicine has not been developed based on a person's unique genetic profile (n=1), or on the genetic profile of monozygotic twins or triplets.
4	The medicine is likely to offer substantial additional benefit for people with the very rare disease over existing established clinical management, and existing management is considered inadequate.	'Substantial additional benefit' means that the medicine is likely to: significantly redress the reduced length of life, and/or demonstrate substantial improvements in the severely impaired health-related quality of life attributable to the very rare disease, as exemplified by research data on clinically relevant measures (e.g. patient reported outcome measures). If the medicine is a disease-modifying treatment (including curative treatment), there should be no other disease-modifying treatment available in the NHS in Wales for the same ultra-rare disease at the time of the routing decision. If the medicine treats a symptom or set of symptoms unique to the very rare disease, there should be no other treatment available in the NHS in Wales for the same symptom for which the medicine is

		indicated at the time of the routing decision.
†Figures extrapolated from the NICE HST routing criteria for application in Wales. ¶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.		

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 LOWMAG 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, LOWMAG 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 LOWMAG to apply a QALY weighting between 1 and 3, using equal increments. Table 2 shows how LOWMAG 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 completes a submission form for AWMSG HTA assessment, 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, the AWMSG Scrutiny Panel will be asked to decide. Experts will be invited to join the Scrutiny Panel for these decisions to ensure that the appropriate knowledge and specialism is

incorporated into the decision-making process. The applicant company will be informed of the Scrutiny 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 Scrutiny 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 decision. AWMSG Steering Committee will review the challenge and if accepted, will direct Scrutiny Panel to reconsider the evidence and the company response. No new evidence can be submitted at this point, and no further challenges can be made.

After receiving the submission form for a full HTA assessment 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. LOWMAG 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.

LOWMAG will consider all the evidence they deem relevant, from randomised controlled trials to observational studies, including real-world data.

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 LOWMAG. This forum provides opportunity for further assessment of the benefits of the medicine from the perspective of clinicians and patients.

Clinician and patient involvement group (CAPIG)

AWTTC will collate views from clinical experts and patient organisations for every medicine that LOWMAG 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 LOWMAG at a subsequent meeting. LOWMAG will be asked to consider the information given in the report and make a new decision which may uphold the original recommendation or overturn it. The LOWMAG recommendation made after the consideration of the information from CAPIG will be the one sent to AWMSG for endorsement.

The applicant company may submit supplementary cost-consequence analyses to CAPIG for consideration. Further information on CAPIG is available 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.