AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Pathways for access to medicines in NHS Wales

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PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

Pathways for access to medicines in NHS Wales

NHS Wales is required to ensure that valuable NHS resources are used responsibly to benefit as many patients as possible, so decisions to make medicines available are made on the basis of evidence-based decision-making processes. Health boards in Wales have a statutory responsibility to maintain the health of their citizens by providing effective, safe and high quality clinical services. They are also required to ensure the efficient use of their human and financial resources in this regard.

A comprehensive range of NHS healthcare services, including medicines are routinely provided across Wales. In addition, the Welsh Health Specialised Services Committee (WHSSC), working on behalf of the seven health boards in Wales (see Figure 1), commissions certain specified specialised services at all-Wales level.

Figure 1: The seven health boards in Wales

There are four main processes by which new medicines are approved for use in NHS Wales. The main process is Health Technology Appraisal (HTA). The Individual Patient Funding Request (IPFR) system is available for individual patients to access a medicine when deemed appropriate. The One Wales Interim Pathways Commissioning process enables cohorts of patients to access certain medicines. Finally, some medicines which have been excluded for appraisal by the National Institute for Health and Care Excellence (NICE) and the All Wales Medicines Strategy Group (AWMSG) are considered for local formulary inclusion in individual health boards. Each process is described below and their relationships with each other are shown in Figure 3.

1. **Health Technology Appraisal (HTA)**

   Each year, approximately one hundred new medicines, or new formulations of existing medicines, receive a marketing authorisation (MA) from the European Medicines Agency (EMA) or the Medicines and Healthcare products Regulatory Agency (MHRA). HTA is the preferred and also the most common process by which the NHS decides whether the benefit to patients of a particular medicine justifies any additional cost for its purchase and administration. In Wales, a new medicine may be appraised by either AWMSG or NICE.

   AWMSG was established in 2002, as a statutory advisory Welsh Assembly-sponsored public body under the 1977 NHS Act, to provide advice on medicines management and prescribing to Welsh Government's in an effective, efficient and transparent manner.

   AWMSG advice is interim to that of NICE, should NICE subsequently publish guidance for the same medicine and same indication; therefore, NICE guidance supersedes

AWMSG advice. Health boards are expected to implement NICE and AWMSG guidance within two months of final publication. AWMSG membership consists of NHS clinicians, pharmacists, healthcare professionals, academics, health economists, pharmaceutical industry representatives and lay representatives. Members are appointed by the AWMSG Steering Committee through individual nomination, nomination by colleague(s) or appropriate representative committees or organisations, or as a response to open advertisement. Appointments are approved by Welsh Government.

AWMSG was the first public body in the UK to develop an "open" therapeutic appraisal process, having met in public since it was first established in 2002. The pharmaceutical industry (via membership of the Therapeutic Development Assessment [TDA] Partnership Group) regularly meets with representatives from the All Wales Therapeutics and Toxicology Centre (AWTTC). These meetings provide two-way communication to inform process improvement and methodology relating to the appraisal of new therapeutic technologies in Wales. AWMSG also engages with clinical experts, economists, financial and clinical service providers, patient interest groups, and lay representatives in an open and transparent manner.

Pharmaceutical companies are expected to make an initial submission to AWMSG before receiving MA for their product and this early identification is assisted by horizon scanning. The initial submission provides the information required by the AWMSG Steering Committee to decide whether the medicine requires appraisal by AWMSG. Welsh clinical networks and commissioners provide input to the AWMSG Steering Committee, to help to prioritise new medicine submissions suitable for appraisal. AWMSG also provides regional MTCs in Wales with a confidential report detailing the products which are expected to be appraised during the following year.

AWMSG does not appraise medicines that do not have a UK MA nor does it consider "off-label" uses of licensed medicines. In addition, a product is not normally considered for AWMSG appraisal if NICE intends to publish final guidance within twelve months of the date of MA but sometimes an interim HTA is conducted by AWMSG if NHS Wales identifies an urgent significant unmet need.

Where an appraisal by AWMSG is deemed appropriate, pharmaceutical companies are expected to submit their best evidence to demonstrate clinical effectiveness and cost-effectiveness. It is the responsibility of the pharmaceutical company to ensure that their submission is made within three months of receipt of MA, to ensure its timely consideration by AWMSG. The Patient Access to Medicines Service (PAMS) team within AWTTC critiques the information provided by the pharmaceutical company together with any other relevant publically available information to produce an assessment report. Clinical experts are invited to explain the clinical context and outline where, in their view, the new medicine sits within current therapy.

Patients/carers/patient organisations are often able to provide additional insight which is invaluable in considering whether a medicine should be available to patients within NHS Wales; therefore the input of patients and the public is extremely important. PAMS undertakes a search to identify relevant patient organisations, and pharmaceutical companies are also asked to list relevant patient organisations on their submission forms. Patients/carers/patient organisations are invited to outline their experience of the disease/condition in question and any experience they might have of the associated treatments; the appraisal committees are informed of the patient perspective.

The New Medicines Group (NMG) is a subgroup of AWMSG which considers the clinical and cost-effectiveness of the medicine, based on written evidence from the pharmaceutical company, the assessment report, views from clinical experts in the field and relevant patients/carers/patient organisations. NMG makes a preliminary recommendation to AWMSG in relation to each medicine undergoing appraisal. Up to ten NMG meetings are scheduled per year, which are held in private. The pharmaceutical company is sent the recommendation from NMG and is invited to respond in writing.

AWMSG considers NMG's recommendations, the pharmaceutical company's responses, clinical expert opinion, and patients' perspectives. Presently, meetings take place ten times a year, at regular intervals, and are open to the public. The minutes of each meeting are made available on the AWMSG website. Pharmaceutical companies have up to ten working days within which to accept or reject an AWMSG recommendation before it is forwarded to Welsh Government for ratification. There is an established independent review process to address any complaints from a pharmaceutical company regarding an AWMSG recommendation.

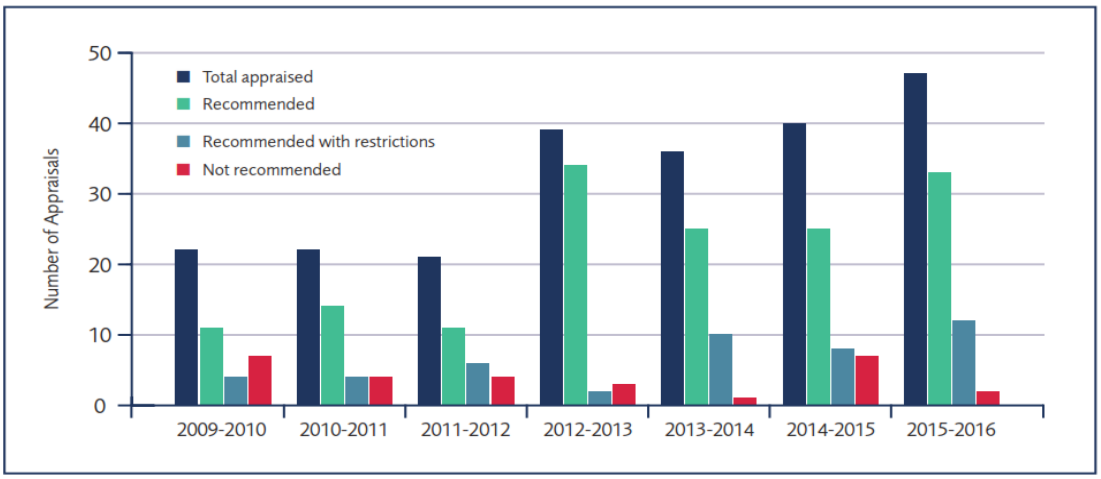
Once a recommendation has received Welsh Government ratification, pharmaceutical companies and key audiences are informed. The final appraisal recommendation is posted on the AWMSG website and disseminated via email to a broad circulation. It is also published in the Chief Medical Officer's (CMO's) Update. If Welsh Government ratifies a positive AWMSG recommendation, then treatment and funding must follow at a local level across Wales.

In 2015–16, 45 of the 47 medicines (96%) appraised by AWMSG were either recommended or recommended for "optimised" use (with restrictions). A medicine may not receive a positive recommendation for use in NHS Wales for four main reasons:

I. It has not yet been appraised by AWMSG (due to non-engagement by the pharmaceutical company) or by NICE.
II. It has been appraised by AWMSG and not recommended for use within NHS Wales.
III. It has been appraised by NICE and not recommended for use in the NHS.
IV. It does not have a marketing authorisation (product licence) in Europe for the purpose for which it has been requested.

In the event that a pharmaceutical company submission is not forthcoming within three months of receipt of the marketing authorisation, AWMSG will issue a Statement of Advice (posted on the AWMSG website) confirming the medicine cannot be endorsed for use within NHS Wales. In 2015–16, 56 such "Statements of Advice" were issued to NHS Wales due to non-engagement with the AWMSG process.

Figure.2. Medicines appraised by AWMSG (dark blue), recommended (green), recommended with restrictions (light blue) or not recommended since 2009–10.



2. Individual Patient Funding Request (IPFR) process

If a medicine is not approved by AWMSG or NICE, or for those medicines excluded from central HTA and not then approved by a health board, a request for funding would normally require individual patient case approval from a health board. This may also be the case for use of a medicine "off-label". In 2010, the Director General, Health and Social Services, Chief Executive, NHS Wales requested that health boards work together with WHSSC and Public Health Wales (PHW) to develop an all Wales policy and standard documentation for the IPFR process. That policy has been in place since September 2011. In October 2013, Welsh Government announced a review of the IPFR process in Wales to explore how it could be strengthened and an independent review group was established in April 2014. The Group's report considered that the IPFR process in Wales was comprehensive and supported rational, evidence-based decision making for medicine and non-medicine technologies not routinely available in Wales. However, the Group also made several recommendations to strengthen and improve the IPFR process and in March 2015 Welsh Government directed health boards and WHSSC to work with AWTTC to implement the report's recommendations.

Most licensed medicines and many evidence-based treatments are routinely available in NHS Wales. Medicines are required by law to be made available (sometimes as an option for treatment) within two months of a positive recommendation by NICE or AWMSG. Some non-medicine treatments (e.g. surgical procedures and other non-medicine technologies) are recommended by NICE, and health boards are encouraged to make these available. IPFRs are considered to be appropriate in the following circumstances:

I. A patient and NHS clinician have agreed together that they would like a treatment that is either new, novel, developing or unproven and is not within the health board's routine schedule of services and treatments (e.g. a request to use a cancer drug that has yet to be approved for use in that particular condition)

II. A patient and NHS clinician have agreed together that they would like a treatment that is provided by the health board in certain clinical circumstances

but is not eligible in accordance with the clinical policy criteria for that treatment (e.g. a request for treatment for varicose veins)

III. A patient has a rare or specialist condition that falls within the service remit of WHSSC but is not eligible in accordance with the clinical policy criteria for treatment (e.g. a request for plastic surgery)

Over the last four years (2012–13 to 2015–16), the average number of IPFRs in Wales has been 656 (range 521–740) per annum, with approximately 57% of these being requests for medicines. Over this same four-year period, approximately 53% (range 50–59) of requests were approved. In the year 2015–16 (the first full year in which the IPFR review Group recommendations were being implemented) the IPFR requests for medicines was the lowest (at 309) in the four-year period, which constituted 45% of all IPFR requests. The approval rate for these medicines requests was also the highest in that same period (at 57%). In contrast the same year saw the number of requests for non-medicinal treatments at its highest level (374) (see Table 1).

Table 1. Medicines and non-medicinal treatments requested and approved by the eight Individual Funding Request Panels in Wales since 2012–13

Year	2012–2013		2013–2014		2014–2015		2016–2016	
	No.	%	No.	%	No.	%	No.	%
IPFR (medicines)	406	60	437	59	348	67	309	45
IPFR (medicines) – approved	216	53	223	51	176	51	176	57
IPFR (treatments)	275	40	303	41	173	33	374	55
IPFR (treatments) – approved	131	48	160	53	86	50	226	60
Total IPFR	681	100	740	100	521	100	683	100
Total IPFR – approved	347	51	383	52	262	50	402	59

3. The One Wales Interim Commissioning Process

Through its Patient Access to Medicines Service (PAMS) section, AWTTC has worked with IPFR panels and NHS Wales to identify certain medicines appearing in the IPFR applications, together with potential clearly defined and specific patient cohorts who may benefit from those medicines. The final decision as to whether or not the One Wales Interim Commissioning Process should be initiated is then made by the AWMSG Steering Committee. PAMS then contacts the pharmaceutical company (if the medicine is licensed for the indication) to explore their willingness to make a binding commitment to; engage in a future NICE or AWMSG HTA (within a specified time, normally 12 months) and provide the evidence to progress a review under the One Wales Interim Commissioning Process.

If there is sufficient evidence to demonstrate clinical and cost effectiveness, then an early HTA would always be the preferred approach. However, in the absence of such a robust evidence base and if the final decision to proceed with the One Wales Interim Commissioning Process is confirmed by the AWMSG Steering Group, PAMS produces an Evidence Status Report (ESR) which may include comparator data, and is compiled in collaboration with the pharmaceutical company and clinicians.

The ESR is then considered by an Interim Pathways Commissioning Group (IPCG). The group directly advises the Executive Committee of Health Board Chief Executives, who are the final decision-makers with regard to One Wales Interim Commissioning Decisions. To ensure transparency, full advice, key findings and minutes of the IPCG meeting are published on the AWTTC website and shared with the pharmaceutical company.

For licensed medicines, the pharmaceutical company is expected to provide PAMS with clinical evidence demonstrating the potential for the medicine in question to address an unmet clinical need. As part of the One Wales Interim Commissioning Process, the pharmaceutical company is also asked to submit a confidential commercial arrangement. This may be applied as a Wales Patient Access Scheme (WPAS) to any subsequent HTA by AWMSG. All commercial arrangements must be agreed prior to drafting the ESR.

Membership of the IPCG is drawn from all IPFR Panels with additional representation from a lay member, industry representative, finance representative, a clinical pharmacologist and a health economist. Clinical experts are invited to attend the IPCG meeting to set the clinical context. IPCG advises in accordance with the General Medical Council (GMC) guidance on unlicensed medicines, and can make interim recommendations for licensed medicines ahead of appraisal by NICE/AWMSG when deemed appropriate. The One Wales Interim Recommendation of the IPCG may be either positive, positive with specific restrictions related to its use (“optimised”) or negative. All health boards are expected to comply with the final One Wales Interim Decision made by the Executive Committee of Health Board Chief Executives.

The duration of a One Wales Interim Decision is on a case-by-case basis. For licensed medicines, it is unlikely to exceed 18 months and would normally be 12 months or until publication/ratification of NICE TA guidance/AWMSG recommendation. Commissioning decisions regarding unlicensed medicines or unapproved pathways are to be reviewed annually.

It is crucial that appropriate patient outcomes are monitored in all of the situations described. If not already available, PAMS ensures that an outcome(s) or data collection tool is developed by the MA holder/manufacturer or by the appropriate clinical group in order to capture relevant data in relation to patient outcomes (including quality of life). This ‘real world’ data may inform the evidence subsequently submitted by the MA holder to either NICE or AWMSG, or, for unlicensed medicines, to the regulatory authorities. The need to capture data on clinical outcomes is expected for both licensed and unlicensed medicines. These data may provide supporting information, especially where the current dataset is immature or scant in terms of clinical effectiveness, or where economic modelling would benefit from the input of values derived from the use of the medicine.

The One Wales Interim Commissioning Process does not apply to medicines that have been appraised by NICE/AWMSG and received a negative recommendation, so as not to undermine the principle that HTA is the most robust and transparent approach to ensuring patients have access to clinically- and cost-effective medicines. For these medicines, the IPFR process is still applicable. The IPCG first met in May 2016 and as of December 2016, the One Wales Interim Commissioning Process had been applied to six medicines, five of them being used off-label (see Table 2). Five of the six medicines were recommended for use (with adherence to the GMC guidelines for off-label prescribing).

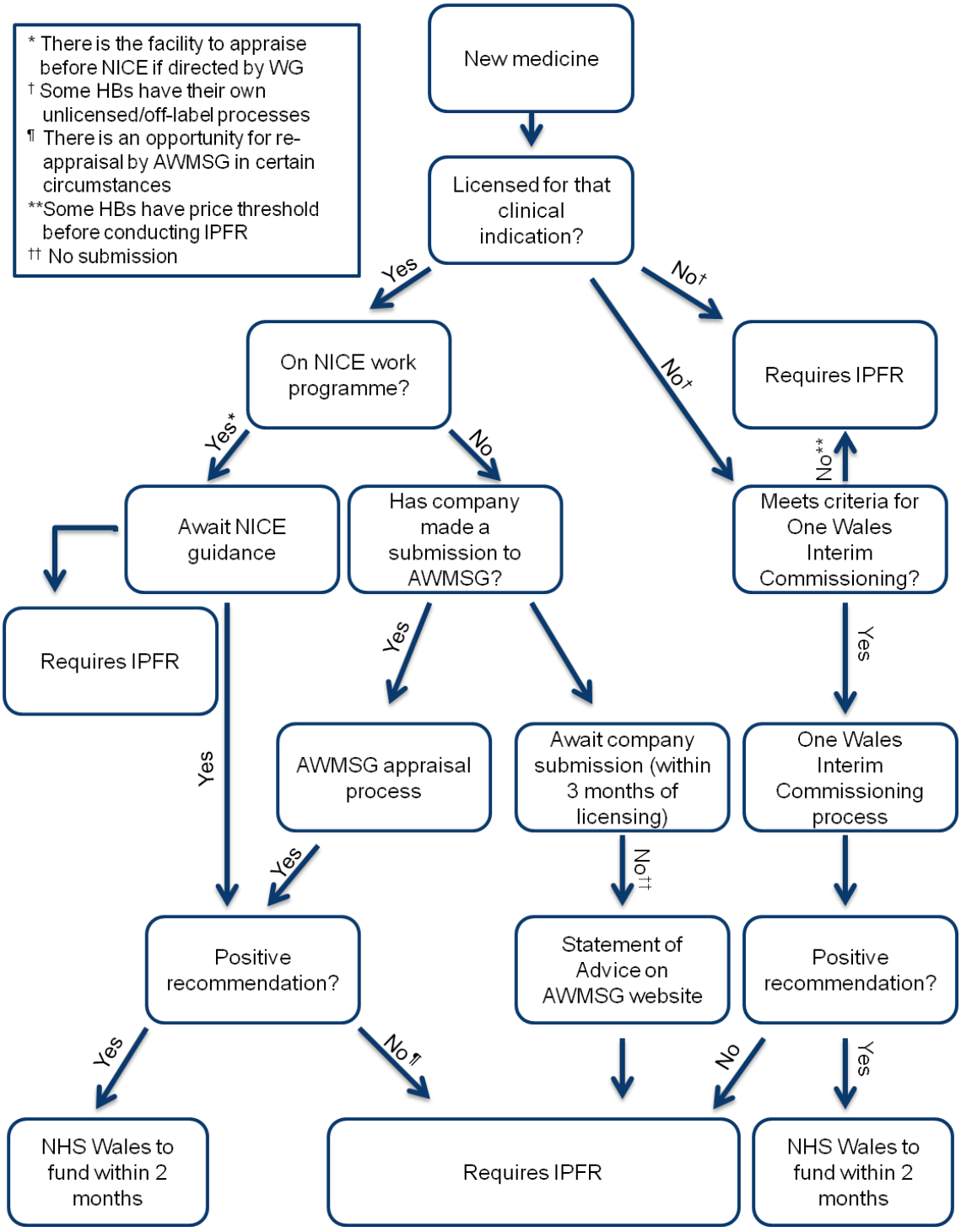
Table 2. Medicines considered by The One Wales Interim Commissioning Process in 2016

Medicine, indication and licensed status	IPCG decision
1. Axitinib, post-pazopanib, for advanced renal cell carcinoma (off-label)	Use supported
2. Docetaxel in combination with hormone therapy for the treatment of metastatic prostate cancer (off-label)	Use supported
3. Bevacizumab (7.5 mg) for the first-line treatment of advanced ovarian cancer in patients at high risk of disease progression (off-label)	Use **not** supported
4. Adalimumab (Humira®) for treatment of paediatric patients with severe refractory uveitis (off-label)	Use supported
5. Adalimumab (Humira®) for the treatment of adult patients with severe refractory uveitis	Use supported
6. Arsenic trioxide (TRISENOX®) for acute promyelocytic leukaemia – first-line therapy in patients unsuitable for anthracycline-based therapy(off-label)	Use supported

4. Consideration of certain medicines by local formulary decision-making groups

For medicines that do not meet the criteria for appraisal by national appraisal bodies (AWMSG or NICE), inclusion on health board medicine formularies is the decision of local health board/NHS trust formulary decision-making groups. Each health board/NHS trust has its own managed entry process for these medicines during which the available evidence on clinical effectiveness, safety, cost-effectiveness and budget impact are assessed. On the basis of this evidence the local formulary decision-making group decides whether or not the medicine is to be included in the local medicines formulary and, if so, its place in therapy (e.g. first line, second line) and who may prescribe, recommend or initiate the medicine (i.e. GP or specialist). Service implications such as Share Care arrangements or enhanced services are also considered.

Figure 3.The pathways to enable access to medicines in Wales.



Glossary of terms and abbreviations

All Wales Medicines Strategy Group (AWMSG): A statutory advisory public body sponsored by the Welsh Assembly that provides advice to the Welsh Government on the managed introduction of new medicines into NHS Wales and on the appropriate use of existing medicines.

All Wales Therapeutics and Toxicology Centre (AWTTC): An NHS organisation providing advice and services in therapeutics and toxicology in Wales, liaising with, informing and assisting healthcare professionals, involving patients and the general public and advising Welsh Government, as well as engaging with the pharmaceutical industry.

European Medicines Agency (EMA): A de-centralised body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

Health Technology Appraisal (HTA): The structured evaluation of the properties and effects of a medicine, ideally with consideration of its clinical effectiveness and cost effectiveness when used for the specified indication.

Horizon scanning: the systematic examination of potential future developments (e.g. in treatments) which are at the margins of current thinking and planning. The AWTTC horizon scanning process gathers intelligence on new medicines which is an essential function to aid better planning and support earlier introduction of new medicines for use in NHS Wales

Individual Patient Funding Request (IPFR): a request made for a medicine that is not routinely funded through NHS Wales.

Marketing Authorisation (MA): the equivalent of a product licence, which, by law, manufacturers must obtain from the appropriate regulatory body before it markets a particular product

Medicines and Therapeutics Committee (MTC): MTCs assess the available evidence on safety, clinical effectiveness and cost-effectiveness and reach a decision regarding the place in treatment of the new medicine/indication. Medicines/new indications that are recommended by MTCs are added to individual health board medicines formularies.

National Institute for Health and Care Excellence (NICE): established in 1998, it is an independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. NICE provides guidance and advice to the NHS in England and Wales on a wide range of topics relevant to healthcare. NICE guidance includes technology appraisals on the use of medicines.

New Medicines Group (NMG): formed in 2007 to enable AWMSG to manage the broadened appraisal process. This group meets month to consider the evidence on new medicines, and to provide preliminary recommendations to AWMSG on the introduction of these medicines in Wales.

Off-label: A medicine or device with an existing UK marketing authorisation that is used outside the terms of its marketing authorisation, for example, to treat a condition or disease not covered by the licensed indication, or using a different dose, route or patient population.

Quality-adjusted life-year (QALY): A composite measure of the state of health of a person or group in which benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a person after a particular treatment or intervention and weighting each year with a quality-of-life score (ranging from 0 for death, to 1 for perfect health, with negative scores being allowed for states considered worse than death).

Ultra Orphan Medicine: Medicines licensed for the treatment of diseases with a UK prevalence of less than 1 in 50,000. This equates to around 60 prevalent cases in Wales.

Wales Patient Access Scheme (WPAS): A way for pharmaceutical companies to make high-cost medicines affordable for NHS Wales. The scheme is proposed by a pharmaceutical company and agreed with the Welsh Government, with input from the Patient Access Schemes Wales Group (PASWG) as part of the AWMSG appraisal process.