Optimising access to medicines in Wales: a review of medicines issued with a statement of non-submission and the impact on medicine availability in Wales compared with other nations

Situation:

The All Wales Therapeutics and Toxicology Centre (AWTTC) has reviewed advice issued between January 2015 to December 2021 when a manufacturer has not engaged in All Wales Medicines Steering Group's (AWMSG's) appraisal process. AWTTC has assessed the impact of the advice and, where data exists, reviewed usage and spend on medicines that have not been appraised and recommended for use within NHS Wales. AWTTC has investigated those medicines where the Scottish Medicines Consortium (SMC) or NHS England commissioning services have published a recommendation for use, to establish whether AWMSG should consider further action which may include change(s) to processes to improve company engagement with the aim of reducing the number of statements of non-engagement.

Background:

A comprehensive report in Q3 2020/2021 was produced by AWTTC to provide an overview of the number of medicines issued with a statement of non-submission, also known as a statement of advice (SOA), issued by AWMSG. The report considered SOAs issued since January 2015 detailing (where available) reasons for non-engagement. The report also provided comparison with the equivalent statements of non-submission issued by SMC. The report concluded that there were several areas which warranted action or further investigation. In April 2021 proposals to update the AWMSG SOA process were endorsed by the AWTTC Industry Forum and the AWMSG Steering Committee.

This final report investigates discrepancies between AWMSG and SMC with respect to, and in particular, where SMC has received a submission or where the SMC status is unknown. It also identifies medicines with an AWMSG SOA that are available through NHS England commissioning and explores potential inequality of access to medicines between the home nations. Where feasible, AWTTC has analysed spend in 2020/21 (and usage) of medicines in NHS Wales for which an SOA has been issued. The detailed results of AWTTC's investigation can be found in Appendix 1 (attached).

Assessment:

Despite an apparently large number of SOAs issued in NHS Wales compared to the equivalent statement of non-submission in SMC, in reality, the number is much closer together (they would now meet the AWMSG exclusion criteria, for example).

AWMSG does not routinely review SOAs issued and so when an exclusion criterion is updated, medicines with an SOA would not be excluded retrospectively. However, AWTTC investigate the appropriateness of the SOA if an issue is raised by the service, patient/patient organisation or other stakeholder, including reviewing IPFR data and identifying patient cohorts. AWTTC has recently discussed the process for assessing a medicine due an SOA before it is issued. The lack of demand/issues raised by the service for the medicines with an active SOA suggests these processes are robust. The limited data on spend for medicines with an active SOA indicates there is unlikely to be routine use and there does not appear to be a particular clinical demand for those medicines. However, there is a possibility that there is a clinical need for some medicines/indications but usage

remains low because of the SOA in place. Considering all these issues there is likely to be little value in using AWTTC resources to review all SOAs routinely. It would seem reasonable to continue to target those medicines which have been identified though service/stakeholder demand only.

Based on the limited data on spend and general enquiries to AWTTC, the higher number of SOAs issued by AWMSG compared with the equivalent non-submission statements from SMC do not appear to be causing an associated discrepancy in access to medicines between the two nations. The difference in prioritising appraisals and exclusion criteria at any one time between the two organisations most likely accounts for the majority of these medicines. Whilst AWMSG has a memorandum of understanding with NICE to avoid duplication of workloads (i.e. the NICE medicine would meet the AWMSG exclusion criteria), SMC do not have such an arrangement and therefore will appraise the new medicines regardless of NICE status (single technology appraisals). This inevitably results in SMC needing to appraise more new medicines than AWMSG and are more likely to need to prioritise which medicines are appraised or advice issued, according to capacity and clinical demand. There are, however, 14 medicines appraised by SMC which have an active SOA with AWMSG (table 1) which could be assessed for re-engagement, although almost all were issued over three years ago. As discussed in the previous report, AWTTC/AWMSG has improved processes and engagement in recent years.

Medicines with current AWMSG SOAs that are available in NHS England though commissioning or agreed guidelines may warrant further investigation; there is currently no equivalent commissioning body in NHS Wales. HTA is the main route for routine access for licensed medicines, unless they fall outside of the criteria for appraisal where health boards can consider whether it is appropriate to include in the local formulary. It is interesting to note that only two of the 19 medicines suitable for appraisal have been appraised by SMC, only one of which received a positive recommendation suggesting this issue is not limited to NHS Wales. AWTTC has already made numerous attempts to secure an HTA submission for those medicines which have been raised as an issue/unmet need. These are examples of scenarios that are increasingly challenging using robust HTA methodology e.g. where the originator medicine loses market exclusivity.

Despite the challenges of the COVID-19 pandemic pharmaceutical industry engagement has remained a priority and a series of open days have been held virtually. Attendance has been high, with positive and constructive feedback received. AWTTC continue to improve and develop relations with the pharmaceutical industry and a new AWTTC industry forum (formerly TDA) has been established reflecting a wider remit and engagement across all areas of AWTTC. During this time, AWMSG also introduced a new process for assessing paediatric licence extensions. The pilot phase is almost complete and a review of the very minor licence extensions will likely be considered again.

Although this review can provide reassurances in the robust and transparent HTA process there are questions raised as to the value of issuing advice for all licensed indications - value in resources required by AWTTC/AWMSG and the value provided to the service and ultimately patients.

Given the findings of the series of reports into SOAs, a regular review of all SOAs is unlikely to be warranted. This is also in keeping by the changes at NICE and AWMSG with regards to reviews of medicine appraisals – both have adopted a process of moving guidance to a ‘static list’ when it is clear there is no new research available that would have any material effect on the current guidance.

Other challenging areas are the appraisal of medicines which have lost exclusivity, biosimilar medicines and antimicrobials. NICE are currently in the process of reviewing their methodology for

HTA and piloting a new evaluation process for antimicrobials. AWMSG has aligned its processes with NICE and will need to review these in light of any changes published.

Conclusion

The discrepancies between the number of SOAs issued by AWMSG and the equivalent status in SMC highlighted in the previous report are less significant than might first appear; a difference in processes and prioritisation between the two organisations are the most likely reasons. AWTTC assess the circumstances and implications for each medicine before issuing an SOA and has a number of processes to trigger a review of an active SOA. AWTTC/AWMSG also regularly review processes to ensure they are fit for purpose. These, combined with good engagement with industry and across stakeholders, has ensured SOAs are providing appropriate guidance to the service and are not having a negative impact compared to elsewhere in the UK. Moving forward AWTTC has improved links with SMC and NICE and is part of new projects such as the innovative licensing and access pathway (ILAP). These closer links will help ensure operational processes continue to be relevant, fit for purpose and related to the current needs of NHS Wales.

Given the changes on the horizon with NICE and the challenges already identified, it is likely that AWTTC/AWMSG will need to review and amend its wider HTA processes again in the very near future. These SOA reports serve as a basis that there can be confidence in the robust and transparent processes that already exist and on which to build.

Recommendations:

1. **Review the exclusion criteria and consider the exclusion of medicines where advice is not required within NHS Wales e.g. where a medicine is not going to be launched in Wales or where clinicians have confirmed there is no demand or unmet need.**

2. **Engage with clinical networks to establish whether medicines appraised for use in Scotland, or available via NHS England commissioning, require assessment for use within NHS Wales.**

3. **Review the recently updated process for AWMSG appraisal of paediatric licence extensions to identify any barriers to engagement and review the requirement for automatic appraisal.**

4. **Review AWMSG's process for evaluation of antimicrobial medicines in light of the publication of the results of the NICE/NHS England/NHS Improvement collaborative pilot project.**

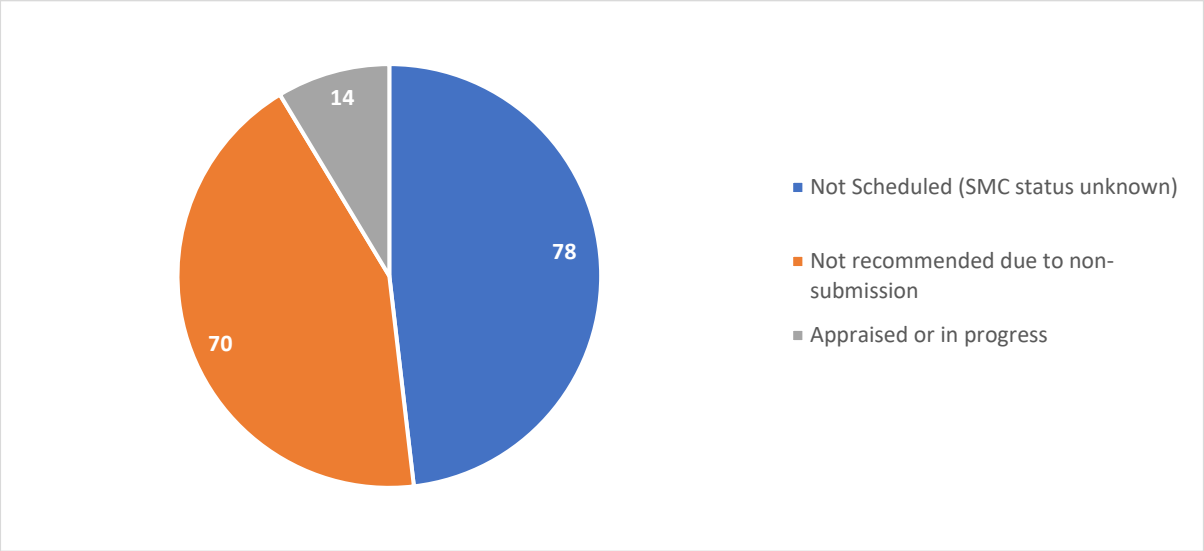
APPENDIX 1 - RESULTS

Scottish Medicines Consortium (SMC)

At time of writing, there are 162 active Statements of Advice (SOAs) issued by the All Wales Medicines Strategy Group (AWMSG) since January 2015; the majority of these (104) have not engaged in the process at all i.e. have not submitted Form A, the initial information required to determine the type of appraisal required. AWTTC consider 31 of the 162 would meet the criteria for a full submission and requested a Form B. Also, 9 limited submissions were requested and 18 were considered paediatric licence extensions.

Of the 162, SMC has issued an equivalent statement of non-submission for 70 of these SOAs and 14 have been appraised or are in progress (Figure 1). This leaves 78 medicines which do not have a corresponding status of non-recommendation due to non-submission with SMC; this was identified as an area for further investigation in the initial SOA report.

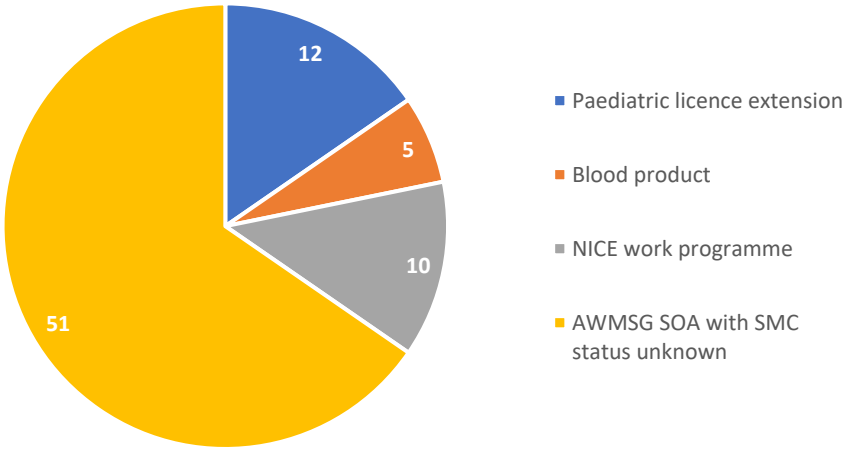
Figure 1. Corresponding SMC status for active AWMSG SOAs issued since January 2015



AWTTC reviewed the 78 medicines not scheduled with SMC and considered current clinical practice in line with the likely exclusion criteria at the time. The exclusion criteria are a list of circumstances where a medicine is unlikely to meet the criteria for HTA. SMC and AWMSG both have these lists of criteria detailing where a medicine is likely to fall outside of their remit. Neither organisation publish a record of every medicine which may meet their exclusion criteria – they are intended to provide broad guidance as to which medicines are unlikely to require HTA. The criteria are also reviewed and updated regularly and are specific to the organisation i.e. they may not be the same.

Of the 78 medicines 12 are for paediatric licence extensions which are currently not routinely appraised by SMC. Five of these medicines are for blood products which would no longer meet criteria for appraisal by AWMSG. An additional ten medicines have been included on the NICE work programme and following the updates to the AWMSG SOA process in April 2021, these would have met the revised exclusion criteria. This leaves 51 medicines which have received an SOA with AWMSG and have no information as to status displayed on the SMC website which warrant further investigation (Figure 2).

Figure 2. Active AWMSG SOAs issued since January 2015 currently not scheduled with SMC



Of these 51 medicines where the SMC status is unknown, 22 were issued in 2018 or earlier i.e. three or more years ago. On review of the AWTTC information held, none of these have been flagged as requiring HTA through stakeholder, service, IPFR or patient engagement. It may be reasonable to assume there is not a high unmet need. Also as SMC have not issued any advice, routine funding in Scotland is unlikely. For context (and not counted in this report), 31 SOAs issued in 2018 or earlier have subsequently been superseded by AWMSG or NICE advice, 5 of the 29 issued in the past three years have been superseded i.e. SOAs are not static and advice changes. Of the 29 issued in the last three years 13 are for antimicrobial, antifungal or antiviral medicines. This is not unexpected given the inherent issues in appraising these medicines through traditional HTA processes. There is a NICE pilot underway to test a new evaluation process and payment model specifically for existing and new antimicrobials. Two medicines are being evaluated as part of the pilot, however when the new process is rolled out it would be reasonable to expect the number of SOAs for antimicrobials to reduce as they are considered by NICE.

There are 14 medicines which currently have an SOA with AWMSG which have been appraised or are undergoing appraisal with SMC (Table 1). All except one of these were appraised in 2018 or earlier, the majority over 5 years ago. The one appraised most recently by SMC was awaiting scope with NICE which was a factor in the applicant company engaging with AWMSG. Of the 14, one was appraised and received a non-recommendation for use which may have been a factor in the MA holder decision to not pursue appraisal by AWMSG. In summary, there are 11 medicines that have been appraised by SMC and recommended (five with restrictions) for use in NHS Scotland, while two medicines are currently in progress.

Table 1. Medicines appraised by SMC with an active AWMSG SOA

Medicine name	Abbreviated indication	SMC status	AWTTC comments
Liraglutide (Victoza®)	Treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control	Recommended	Company is awaiting appraisal by NICE (but does not meet AWMSG exclusion criteria)
Posaconazole (Noxafil®)	IV preparation for treatment of fungal infections in adults	Recommended	Reason for nonsubmission unclear
Febuxostat (Adenuric®)	Prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of Tumour Lysis Syndrome (TLS)	Recommended restricted use	Reason for nonsubmission unclear
Palonosetron (Aloxi®)	Prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in paediatric patients 1 month of age and older	Recommended	Company resources are not available to compile submissions
Sevelamer carbonate (Renvela®)	Control of hyperphosphataemia in paediatric patients (> 6 years of age and a body surface area (BSA) of > 0.75 m2) with chronic kidney disease	Recommended restricted use	Reason for nonsubmission unclear

Medicine name	Abbreviated indication	SMC status	AWTTC comments
Recombinant L-asparaginase (Spectrila®)	A component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia in paediatric patients from birth to 18 years and adult patients	Recommended	Reason for nonsubmission unclear
Ledispavir/sofosbuvir (Harvoni®)	Treatment of chronic hepatitis C in adolescents aged 12 to < 18 years	Recommended restricted use	Reason for nonsubmission unclear
Ledispavir/sofosbuvir (Harvoni®)	Treatment of chronic hepatitis C (CHC) in paediatric patients aged 3 to < 18 years and weighing above 17kg	Recommended restricted use	No response from company
Ospemifene (Senshio™)	Treatment of moderate to severe symptomatic vulvar and vaginal atrophy (VAA) in post-menopausal women who are not candidates for local vaginal oestrogen therapy	Recommended	Company has no plans to launch or actively market product
Triptorelin acetate (Decapeptyl®)	Adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine-responsive early-stage breast cancer in women at high-risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy	Recommended	Company has no plans to launch or actively market product
Budesonide (Jorveza®)	As maintenance therapy for eosinophilic esophagitis in adults (older than 18 years of age)	Recommended restricted use	Company is awaiting appraisal by NICE (but does not meet AWMSG exclusion criteria)

Medicine name	Abbreviated indication	SMC status	AWTTC comments
Buprenorphine/naloxone (Zubsolv®)	Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction	In progress	No response from company

NHS England commissioning

Of the SOAs issued since January 2015 that are still active, 25 are available through NHS England commissioning policies or agreed guidelines[1]. Of these seven are for blood products and so would now meet the AWMSG exclusion criteria. The remaining 18 medicines including the corresponding status with SMC are shown in Table 2. There is one medicine which is available in NHS England and has a positive SMC recommendation for use.

Table 2. Medicines available through NHS England commissioning

Medicine name	Abbreviated indication	NHSE commissioning*	SMC_ status	AWTTC comments
Abatacept (Orencia®)	Moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients from 2 years of age to < 6 years of age	Policy E03X04, Appendix E03/P/d, 2015	Not scheduled	Company has no plans to launch or actively market product. Suggest no action.
Anakinra (Kineret®)	Familial Mediterranean Fever (FMF)	Policy 170062P all ages, 2018	Not scheduled	No response from company. Consider confirming with clinical experts whether advice for Wales is required.
c1-esterase inhibitor (Berinert®)	Prevention of recurrent hereditary angioedema attacks in adolescent and adult patients with C1-esterase inhibitor deficiency	Policy 16045/P, 2016	Not scheduled	No response from company Consider confirming with clinical experts whether advice for Wales is required.
Canakinumab (Ilaris®)	Tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS); hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); Familial Mediterranean Fever (FMF).	Policy 200209P, Feb 2020	Not recommended due to nonsubmission	No response from company. Consider confirming with clinical experts whether advice for Wales is required.
Chenodeoxycholic acid (Chenodeoxycholic acid Leadiant®)	Inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency	Policy 170127P, Jul 2019	Not recommended due to nonsubmission	Company resources are not available to compile submissions and low number of eligible patients in Wales. Consider confirming with clinical experts whether advice for Wales is required.

Medicine name	Abbreviated indication	NHSE commissioning*	SMC_ status	AWTTC comments
Cinacalcet (Mimpara™)	Secondary hyperparathyroidism (HPT) in children on dialysis aged 3 years and older	Policy 16034/P, 2016	Not recommended due to nonsubmission	Extensive communication with clinicians and MA holder. Low numbers of eligible patients in Wales and availability of generics is a barrier to HTA. Consider potential options as part of a review of AWMSG appraisal criteria.
Cobicistat (Tybost®)	HIV-1 infected adults and adolescents aged 12 years and older	Policy F03/P/b 2015 (revised 2018)	Not recommended due to nonsubmission	Low numbers of eligible patients in Wales. Consider confirming with clinical experts whether advice for Wales is required.
Darunavir (Prezista®)	HIV-1 infection in adult patients	Agreed regional guidelines as per BHIVA start/stop criteria	Not scheduled	Company has no plans to launch or actively market product. Suggest no action
Emtricitabine/ tenofovir (Truvada®)	Treatment of HIV-1 infected adolescents	Agreed regional guidelines as per BHIVA start/stop criteria	Not recommended due to nonsubmission	Low numbers of eligible patients in Wales. Consider confirming with clinical experts whether advice for Wales is required.
Ganciclovir sodium (Cymevene®)	From birth until 12 years for the prevention of cytomegalovirus disease using universal prophylaxis in patients with drug-induced immunosuppression	Agreed trust guidelines	Not scheduled	No response from company. Consider confirming with clinical experts whether advice for Wales is required.

Medicine name	Abbreviated indication	NHSE commissioning*	SMC_ status	AWTTC comments
Maraviroc (Celsentri®)	Adolescents and children of 2 years of age and older infected with only CCR5-tropic HIV-1 detectable	Agreed regional guidelines as per BHIVA start/stop criteria	Not recommended due to nonsubmission	Low numbers of eligible patients in Wales. Consider confirming with clinical experts whether advice for Wales is required.
Parathyroid hormone (Natpar®)	Adult patients with chronic hypoparathyroidism	Agreed trust guidelines for specialist endocrinology conditions	Not recommended due to nonsubmission	Company is awaiting appraisal by NICE (but does not meet AWMSG exclusion criteria). Product to be launched in 2023 and therefore no action considered necessary.
Pasireotide pamoate (Signifor®)	Adult patients with Cushing's disease	Policy A03X03/01 (only reference to 2016 draft for consultation online located)	Not recommended due to nonsubmission	Reason for nonsubmission unclear. Consider confirming with clinical experts whether advice for Wales is required.
Posaconazole (Noxafil®)	Intra venous preparation for fungal infections in adults	Agreed trust guidelines	Recommended	Reason for nonsubmission unclear. Consider confirming with clinical experts whether advice for Wales is required.
Rituximab (MabThera®)	Moderate to severe pemphigus vulgaris	Policy 16035/P, 2016	Not recommended due to nonsubmission	AWTTC has pursed this extensively with the MA holder. Decision to appraise with information in the public domain made

Medicine name	Abbreviated indication	NHSE commissioning*	SMC_ status	AWTTC comments
Sodium oxybate (Xyrem®)	Narcolepsy with cataplexy in adult patients, adolescents and children	Policy 210301/P, age 7-19 years only, 2016 updated 2021	Not scheduled	Company believes that product is unlikely to receive a positive recommendation from AWMSG and therefore despite extensive efforts by AWTTC a submission is not forthcoming. Consider confirming with clinical experts whether advice for Wales is required.
Tocilizumab (RoActemra®)	Active systemic juvenile idiopathic arthritis (sJIA) in patients 1 years to < 2 years of age	Policy E03X04, Appendix E03/P/d, 2015	Not scheduled	MA holder will not engage for this licence extension for 1-2 years old. Consider confirming with clinical experts whether advice for Wales is required.

*NHS England drugs list v16.1

Prescribing data, cost analysis

Following comments received from AWMSG SC and the AWTTC Industry Form (formally TDA group) is was suggested that prescribing data could be used to establish the spend in NHS Wales on medicines which have an SOA.

Prescribing data is held in the Comparative Analysis System for Prescribing Audit (CASPA) (NHS Wales Shared Services Partnership; version 1.0.15.0) and Medusa databases for primary and secondary care respectively. Neither of these databases record the indication for which a medicine has been prescribed. Therefore, only medicines which are licensed for a single indication or which have an SOA or non-recommendations for all indications could be analysed for spend in NHS Wales. Of the 162 medicines which have an active SOA only 8 were identified which would be suitable for investigating further. Data were gathered for the financial years 2019/2020 and 2020/2021 for primary and secondary care. Table 3 shows total spend figures.

Table 3. Total spend in NHS Wales on selected medicines with a current AWMSG SOA from April 2019 to March 2021

	Primary care £		Secondary care £		Total £	
	2019/2020	2020/2021	2019/2020	2020/2021	2019/2020	2020/2021
Canakinumab*	NA	NA	11,913	95,307	11,913	95,307
Ketoconazole	5,736	3,048	1,968	0	7,704	3,048
Mercaptamine	1,547	0	13,312	11,636	14,859	11,636
Paliperidone	27,579	25,738	3,922	3,430	31,501	29,168
Pitolisant	0	620	7,812	5,931	7,812	6,551
Safinamide	10,240	14,642	6,663	7,625	16,903	22,267
Total					90,692	167,977
NA: not applicable *multiple indications						

In Wales, despite a lack of advice or where there is a negative recommendation for a medicine, clinicians (in partnership with the patient) may decide a particular medicine is the most appropriate treatment for an individual patient. In these circumstances an individual patient funding request (IPFR) can be made to the health board. This ensures there is a process for accessing medicines not routinely available, even in the absence of HTA advice. Therefore, it is not unexpected that there would be some use and therefore spend for medicines with a lack of HTA advice in NHS Wales, including those with a current SOA. AWTTC routinely monitors IPFR data and if repeat requests for the same medicine and indication are identified, this is flagged as a potential area of unmet clinical need (clinicians may also highlight a medicine with high unmet need to AWTTC). Medicines with an SOA may be revisited and a submission for appraisal encouraged. Likewise, AWMSG may wish to consider further investigation if the spend for a particular medicine indicated a number of patients were accessing treatment suggesting an unmet clinical need. The option exists for AWMSG to appraise a medicine using information in the public domain if a HTA submission is not forthcoming.