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

One Wales Medicines Assessment Group (OWMAG)
Minutes of the Teams meeting held Monday, 11 August 2025

Members in attendance
Andrew Champion, Program Director, AWTTC, Interim OWMAG Chair
Tim Banner, Clinical Director Pharmacy & Medicines Management, representative Cardiff and Vale
Anthony Cadogan, Deputy Chief Pharmacist, representative Velindre
Stuart Wyn Evans, Clinical Effectiveness Pharmacist, representative Swansea Bay
Laurence Gray, Clinical Pharmacologist
Will Hardy, Research Fellow, Bangor University, Health Economist
Kathryn Howard, Head of Pharmacy, Royal Glamorgan Hospital, representative Cwm Taf Morgannwg
William King, Consultant in Public Health, representative Powys
Malcolm Latham, Lay representative
Anghard Lawson, Advanced Pharmacist, NHS Wales Joint Commissioning Committee
Eilir Hughes, Assistant Medical Director, representative Betsi Cadwaladr
Susan Myles, Director, Health Technology Wales

AWTTC
Clare Elliott, Senior Appraisal Scientist
Laura Phillips, Admin Manager
Gail Woodland, Senior Appraisal Pharmacist
Carolyn Hughes, Medical Writer
Sabrina Rind, Senior Pharmacist
Aileen Flynn, VPAG Programme Manager

Observers
Hazel Jones, prospective lay member

Clinical expert
Dr Carey McDonald-Smith

List of abbreviations:

ABPI	Association of the British Pharmaceutical Industry
AWMSG	All Wales Medicines Strategy Group
AWTTC	All Wales Therapeutics and Toxicology Centre
ESR	Evidence status report
ICI	immune checkpoint inhibitor
IPFR	Individual Patient Funding Request
JCC	NHS Wales Joint Commissioning Committee
LVEF	Left ventricular ejection fraction
MMF	Mycophenolate mofetil
NICE	National Institute for Health and Care Excellence
OWMAG	One Wales Medicines Assessment Group
RCT	Randomized controlled trial

Welcome and introduction
The Chair opened the meeting and welcomed members. He introduced himself as the Interim Chair of OWMAG.

Apologies
- Joe Castle, Head of External Affairs and Operations, ABPI Cymru Wales
- Chris Commins, Assistant Finance Director, Aneurin Bevan
- Leo Pinto, Consultant in Public Health, representative Aneurin Bevan
- Michael Thomas, Consultant in Public Health, representative Hywel Dda

Welcome
Dr Andrew Champion welcomed the Group and the meeting observers, including Hazel Jones, who is a prospective lay member for OWMAG. He gave an update on actions since the previous OWMAG meeting: the Group's recommendations for panitumumab and trametinib were endorsed by AWMSG and ratified by Welsh Government. Panitumumab was recommended to treat third-line or later metastatic colorectal cancer, as a re-challenge with an EGFR inhibitor, after previous successful use and after subsequent lines of treatment (after CT DNA). Trametinib was recommended to treat recurrent or progressive low-grade serous ovarian cancer that has progressed after at least one previous platinum-based treatment.

Declarations of interests/confidentiality
The Chair reminded members that all OWMAG proceedings are confidential and should not be disclosed outside of the meeting. Members were reminded that declarations of interest and confidentiality statements are signed by each member on an annual basis. The Chair invited any declarations of interest relating to the medicine being assessed today; there were none.

Assessment
Infliximab for the treatment of grade 3 to 4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy

The Chair introduced the medicine to be assessed: infliximab, and welcomed Dr Carey McDonald-Smith, Associate Specialist in Medical Oncology and Immunotherapy lead for the North Wales Cancer Treatment Centre, to the meeting. The Chair described the role of the clinical expert as an invited observer of the OWMAG meeting to answer questions and input into discussions to enable members to gain a better understanding of the clinical context. The Chair highlighted that clinical experts were nominated by their specialist group or network and should not express their personal opinion or promote the use of a medicine. The Chair invited any declarations of interest from Dr McDonald-Smith; there were none.

The Chair said that Jackie Hodgetts, the helpline support manager for the patient group Melanoma Focus, was unable to attend the meeting and had sent her apologies. He drew the Group's attention to the patient submission that she had submitted for the assessment. The Chair invited Clare Elliott to present the assessment of infliximab.

Clare Elliott presented the key aspects of the clinical effectiveness section of the evidence status report (ESR). Clare briefly explained current treatment options given in some international guidelines for steroid-refractory ICI-induced myocarditis. Infliximab is recommended in some as a second-line immunosuppressant option but there is a paucity of data to inform comparisons between all the different options included and the recommendations in all guidelines are based on low-quality evidence mainly derived from clinical expert opinion, preference and experience. Clare confirmed that there are no RCTs published for infliximab for this treatment and evidence comes from systematic reviews, retrospective case series and case reports with some limited real-world outcomes from NHS Wales. Clare highlighted that taking the evidence as a whole, just over half of patients (where an outcome was reported) showed a clinical response to infliximab, just over a quarter required additional immunosuppressants after infliximab and just under a quarter reported no improvement after treatment with infliximab. She also gave details of the safety profile of infliximab and that it's contra-indicated for use in patients with moderate to severe heart failure and that such patients would receive an alternative immunosuppressant to infliximab.

The Chair introduced the clinical expert, Dr Carey McDonald-Smith, asking her to tell the Group about her experience in treating patients with steroid-refractory ICI-induced myocarditis, what medicines they currently use for treatment and how infliximab would add to the armoury of treatment options.

Dr McDonald-Smith described how myocarditis is becoming more common with the increasing use of immunotherapy. Clinicians are becoming used to looking out for it more, because it used to be a much-overlooked toxicity, as most patients present with fatigue rather than overwhelming cardiac symptoms. The diagnosis is often difficult, and cardiologists are now becoming more familiar with the immune checkpoint inhibitor (ICI) toxicities. She highlighted ongoing work with cardiologists across the UK to develop consensus guidelines for baseline testing.

Diagnosis is by high cardiac enzymes, cardiac MRI and ECG changes, and high-dose steroids will be started. Often patients have triple M syndrome (myocarditis, myositis and myasthenia gravis). These patients have a very high mortality rate, so agents are needed that can address all toxicities and to try to manage each one individually as well. Combination immunosuppression is used, including corticosteroids with other immunosuppressive drugs.

Dr McDonald-Smith highlighted the paucity of information and guidelines. In the past clinicians have used mycophenolate mofetil (MMF) and tacrolimus, each of those has its own problems. MMF has a slow onset of action (several weeks) and often these patients are deteriorating quickly and there is a very high mortality rate. She said that there have been subsequent deaths, even using infliximab; that sometimes these toxicities can be overwhelming despite what medicines are used. She stated the need to be as aggressive as possible. Tacrolimus has also been used, but it needs therapeutic monitoring, which is usually not available on site, but sent to a specialist laboratory and it can take several days to get a result.

Dr McDonald-Smith said that infliximab is used across different ICI toxicities. Clinicians are very familiar with using it in colitis, and it is used because of its fast onset of action. Usually for myocarditis, patients are generally inpatients because they need cardiac monitoring, so initiating doses will generally be as an inpatient but subsequent doses can be given on an outpatient basis. Infliximab can be given fairly quickly and easily intravenously as an outpatient and doesn't require additional therapeutic monitoring and, unlike tacrolimus and MMF which are oral treatments, it doesn't require patient compliance in remembering to take tablets.

Clinicians are very aware that infliximab should only be used in patients with good or fairly good cardiac function and not in those with impaired cardiac function or heart failure. Heart failure is generally not a very common feature of myocarditis (which is the inflammation of the heart muscle) but if patients have pre-existing cardiac problems some cardiac impairment can happen. She said that the negative effects of suppressing the immune system can result in infections, something they make patients aware of when discussing infliximab, and that clinicians will monitor closely. There are guidelines for using prophylaxis in these patients to avoid the impact of immunosuppression, such as prophylactic antibiotics. She said that using infliximab is preferred over other second-line immunosuppressant options as its specificity of immunosuppressive activity is less likely to affect the efficacy of the cancer treatments in comparison to agents with a broader spectrum of immunosuppressive activity. Infliximab can sometimes have unwanted negative effects, but overall, the benefit of use in treating the myocarditis promptly and effectively outweighs the risks.

Dr McDonald-Smith said that most clinicians were fairly used to using infliximab and have used it for other ICI-induced toxicities. She said at present access to infliximab for these patients is by non-formulary request which involves completing paperwork which can cause delays, when it's important to treat as soon as possible. She said that in clinicians' experience in Wales, infliximab has had a positive impact on managing myocarditis, particularly if there are other toxicities involved.

The Chair thanked Dr McDonald-Smith and asked about preserved ejection fraction and elevated TNF-alpha levels – and whether clinicians would specifically look out for these when using this treatment. Dr McDonald-Smith said that they definitely looked at cardiac function, but did not look specifically at TNF-alpha levels.

Dr McDonald-Smith said that tocilizumab is a fairly new treatment for managing toxicities and only in the last few months have they become familiar with it and started to use it more. She had not used it herself to treat myocarditis but would consider using it in future and she thought that its use would increase in future. She said she had used MMF but had not seen such good results with MMF in terms of immunosuppression and resolution of toxicity; several of the patients they had given infliximab to had had full resolution of the toxicity and were now leading normal lives.

The Chair asked about patient numbers in Wales, as the ESR mentioned 1% of patients treated with ICIs would develop cardiotoxicity. Dr McDonald-Smith said that 2 years ago 1% of patients seemed like a reasonable figure, but that numbers were now increasing. They had seen 6 or 7 cases in the past year, in one part of Wales.

She thought that the latest evidence was a cardiotoxicity rate of 1% to 6%, perhaps due to increased awareness and diagnosis. They were also seeing more cases of triple M syndrome, which has a very high mortality rate.

Clare Elliott said that clinicians had estimated 42 patients each year would develop myocarditis and 1 in 5 of them would probably be given tocilizumab, so 34 patients would be treated with infliximab for ICI myocarditis per year; Dr McDonald-Smith confirmed this.

A member of the Group asked about patient numbers, the current use of infliximab in England and Scotland, the numbers of IPFRs for it in Wales and their outcomes, and the clinical trials of abatacept (when these were likely to report) and what other treatments might be on the horizon for this patient group. Dr McDonald-Smith said that no medicines are licensed to treat this indication, because of the paucity of information; two studies were ongoing but abatacept can't be used as a comparator. She said clinicians in Wales work closely with colleagues in England and Scotland, and while she couldn't say what happens in England or other areas, the advice on national clinical forums is often to give infliximab. When treating grade 3 or 4 myocarditis she said that clinicians would often be getting advice from colleagues in England and Scotland. She reiterated that they wanted the best outcomes for patients in Wales, without having to complete a lot of paperwork.

Clare Elliott said that there had not been IPFR submissions in Wales because infliximab is now relatively cheap and it is mostly accessed by non-formulary request on a named patient basis, but which can cause delays through paperwork. She said that time is of the essence in treating this condition and although there were outcome data from 5 patients in Wales to date, clinicians indicated they wished to use infliximab in some other patients but whose condition deteriorated, or they couldn't get the infliximab in time. She said that the guidelines recommended a number of second-line immunosuppressive treatments, abatacept being one, but this was not used in Wales and that guidelines state that clinician preference is a major factor in the choice of agent used.

One member asked how long patients would be treated with infliximab for, and how long before treatment changed to something else if there was no response to infliximab, and whether ICI therapy would be stopped. Dr McDonald-Smith said that patients were initially treated with high-dose oral steroids, then intravenous methylprednisolone, and if there was no response within 48–72 hours then they would look for to add an additional immunosuppressant agent. Infliximab has a faster onset of action than MMF or tacrolimus. They would give a second dose of infliximab after 2 weeks and could give a third dose 6 weeks later. She thought that giving all 3 doses would probably give the best outcome. If no improvement was apparent after the first dose, an alternative second-line immunosuppressive agent may be considered. Dr McDonald-Smith confirmed that ICI therapy would be stopped with immediate effect, even for a grade 2 toxicity. She said that ICI toxicities usually happened after several doses of ICI and could happen at any time for up to 2 years after ICI treatment.

One member asked if after getting a partial response to infliximab, clinicians would then add in another treatment, such as MMF. Dr McDonald-Smith said that she had often used the two in combination, and if getting a partial response would give a third dose and continue the MMF. In general, they would aim to give 3 doses, unless patients developed overwhelming toxicity and heart failure.

A member asked about the patients being treated, and their stage of life and life expectancy. Dr McDonald-Smith said that it would be patients of all ages, as ICI therapy was used to treat a range of cancer types: melanoma, renal cancer, lung cancer. The patients would be those who were deemed fit enough to withstand a severe toxicity. After a severe toxicity patients would remain under the care of the immunotherapy toxicity team for several months, sometimes up to a year. Successful cases could go back to leading fairly normal lives.

The Chair concluded questions about the clinical effectiveness and asked Clare Elliott to present the cost effectiveness evidence and budget impact. Clare Elliott explained that there were no published cost-effectiveness studies, as there was so little clinical evidence and consultation with AWTTC health economists confirmed that a meaningful cost-effectiveness analysis would not be possible. She presented the budget impact, which estimated costs for 34 patients per year in Wales. Clare explained that the degree of displacement of the comparator treatments, MMF and tacrolimus, is difficult to estimate at present but that based on their low acquisition costs of both, the impact of their displacement on the overall budget impact would be expected to be modest. From the outcome data provided, not all patients will receive three doses of infliximab, therefore the budget impact may be overestimated. Due to the lack of comparative data between treatments, any additional benefit from infliximab cannot be quantified and taken into account in budget impact calculations.

One member asked about the numbers of patients and how much costs would change if the calculations were based on 1%, 4% or 6% of patients, and also about the costs of treating serious infections, such as sepsis. Clare Elliott said that the patient estimates came from the clinicians in Wales, and were the numbers they would expect to treat and were not based on incidence rates but on the number of patients in Wales currently presenting with this toxicity who were unresponsive to steroids. She confirmed that as usage of ICIs grows and also, as identification of myocarditis is growing, patient numbers are expected to increase over the next few years, having an additional budgetary impact in Wales. Dr McDonald-Smith said that all patients on immunosuppressants or long-term steroids would be on prophylactic antibiotics and the costs would not be specific to infliximab. She said that adding additional immunosuppression would cause higher infection rates but it would be difficult to estimate if due to infliximab or another immunosuppressant.

One member asked about the acceptability to patients of ICI treatment and toxicities. Dr McDonald-Smith said that patients are willing to accept infliximab because the alternative is having the toxicity and then dying of the toxicity. In some cases, they weren't able to give infliximab because of the rapid rate of deterioration of the patient or because of delays in access, which is something they want to avoid. She said good patient counselling is important, at the start of immunotherapy, warning patients

about the risks of ICIs and the treatments for treating any resulting toxicities, and making decisions with patients. The Group's lay member said that whatever the type of treatment is, patients want informed consent; they want to be given that choice as soon as possible. And they also want access to that treatment as soon as possible. For this group of patients it seems that a delay in access to infliximab could be catastrophic for some.

The Group's lay member was then invited to provide comment on the patient and public perspective. The lay member highlighted that steroid-refractory ICI myocarditis affected 34 people, and that perhaps not having a standardised approach or standardised access could adversely affect some patients. Anything that reduces the bureaucracy and increases the speed of access would be welcomed. There seems to be a consensus across the UK about using this treatment. Patients do like not to be admitted to hospital, so if there is a choice that they are treated as an outpatient, that makes things easier and will save the costs of inpatient days. It's not an expensive medicine, so from a patient perspective, patients would think why can't I have access to it? The lay member said he thought there were no good reasons for not making infliximab routinely available for this group of patients.

Clare Elliott presented the wider health and social aspects which re-iterated the points made by the Group's lay member. She also said that the equality and health impact assessment did not find any potential negative or an unequal impact on people based on their protected characteristics and would expect a potential positive impact on people with ICI-induced myocarditis and their families and carers.

The Chair invited the Group to ask any further questions not covered in the discussions so far.

The Chair thanked Dr McDonald-Smith, who then left the meeting. The Chair summarised the main points of the assessment, highlighting the uncertainty and limited evidence. Clare Elliott said that any decision made today would be reviewed in 12 months, with new patient outcome data from the clinicians, and the Group could re-consider any decision then.

The Chair asked the Group if there were any outstanding issues that required discussion before the vote was opened for the infliximab assessment. The OWMAG recommendation to go to the All Wales Medicines Strategy Group (AWMSG) for endorsement was agreed.

Date of advice: Monday 11 August 2025

Using the agreed starting and stopping criteria infliximab can be made available within NHS Wales for the treatment of grade 3–4 steroid refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy.

Infliximab should be prescribed on the basis of lowest acquisition cost.

The risks and benefits of the off-label use of infliximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

The Group then discussed the wording for the decision rationale document which accompanies the recommendation when it is presented to AWMSG for endorsement. The Group acknowledged that the review of the recommendation after 12 months will provide more evidence on the effectiveness of infliximab and its associated costs for this intervention in NHS Wales. A draft was agreed which will be circulated to members after the meeting for comment before final sign-off.

The Chair thanked the Group and closed the meeting.