GIG CYMRU NHS WALES
Cyd-bwyllgor Comisiynu
Joint Commissioning Committee

Drug Treatment for Paroxysmal Nocturnal Haemoglobinuria

Policy Position Statement: PPS152

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Target Audience	Chief Executives, Medical Directors, Directors of Finance, Directors of Pharmacy, Haematology Consultants, Haematology Specialised Nurses, PNH Support Charity, PNH National Service, Drug Manufacturers
Description	NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy
Document Update Information	Transferred to new template Addition of the following drugs: ravulizumab; pegcetacoplan; iptacopan; danicopan in combination with ravulizumab or eculizumab; crovalimab

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Policy Statement

NHS Wales Joint Commissioning Committee (NWJCC) will commission eculizumab, ravulizumab, pegcetacoplan, iptacopan, danicopan in combination with ravulizumab or eculizumab and crovalimab for people with paroxysmal nocturnal haemoglobinuria (PNH) in accordance with the criteria outlined in this document.

Welsh Language

NWJCC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience, the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this, NWJCC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation

NWJCC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the NWJCC commitment.

Disclaimer

NWJCC assumes that healthcare professionals will use their clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply this document. This document may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.
NWJCC disclaims any responsibility for damages arising out of the use or non-use of this policy.

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of treatment for PNH for people resident in Wales. This service will only be commissioned by the NHS Wales Joint Commissioning Committee (NWJCC) and applies to residents of all seven Health Boards in Wales.

In creating this document NWJCC has reviewed the relevant guidance issued by the All Wales Medicines Strategy Group (AWMSG) and the National Institute of Health and Care Excellence (NICE) and has concluded the following drugs should be made available:

- Eculizumab[1]
- Ravulizumab[2]
- Pegcetacoplan[3]
- Iptacopan[4]
- Danicopan in combination with ravulizumab or eculizumab[5]
- Crovalimab[6]

1.1 Background

Paroxysmal nocturnal haemoglobinuria (PNH) is a very rare (often referred to as an ultra orphan disease) blood condition where the individuals' red blood cells are attacked by a part of the immune system called the 'complement system'[7]. This leads to the haemolysis (breakdown) of red blood cells, resulting in anaemia which is responsible for many of the symptoms of the disease. White cells and platelets are also affected, increasing the risk of thrombosis.[8]

There can be a marked variation in the signs and symptoms of PNH, both between patients and in the same patient at different times[8]. Some people exhibit mild or no symptoms, whereas others may be affected by numerous symptoms and complications. Symptoms include:

- **Anaemia**: Anaemia occurs commonly in PNH due to the constant destruction of red blood cells. Anaemia causes increased tiredness, fatigue and breathlessness.

[1] AWTTC recommendation: Eculizumab for PNH
[2] Overview | Ravulizumab for treating paroxysmal nocturnal haemoglobinuria | Guidance | NICE
[3] Overview | Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria | Guidance | NICE
[4] Overview | Iptacopan for treating paroxysmal nocturnal haemoglobinuria | Guidance | NICE
[5] Overview | Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria | Guidance | NICE
[6] Overview | Crovalimab for treating paroxysmal nocturnal haemoglobinuria in people 12 years and over | Guidance | NICE
[7] What is PNH? – PNH Support
[8] National PNH service: Patient Information

- **Haemoglobinuria**: Dark or black urine presents due to the destruction of red blood cells (haemolysis) that occurs in the circulation releasing haemoglobin and this then overflows through the kidneys into the urine.
- **Abdominal pain, dysphagia and erectile dysfunction**: High levels of free haemoglobin bind to nitric oxide (which helps to regulate movement of the intestine muscles). The resulting lower levels of nitric oxide result in spasms, abdominal discomfort, difficulty in swallowing and erectile dysfunction.
- **Kidney damage**: The severity of renal issues in PNH patients can vary from mild to severe and renal function needs to be closely monitored.
- **Jaundice**: The continued destruction of red blood cells results in an increased level of bilirubin (a breakdown product of haemoglobin). This increased level of bilirubin leads to yellow discolouration of the sclera (whites of the eye) and the skin.
- **Thrombosis**: Blood clots (thromboses) is a complication in patients with PNH. The risk can be decreased with early treatment.

It is not fully understood what causes PNH[8]. Haematopoietic cells (immature cells than can develop into all types of blood cell) are produced from stem cells inside the bone marrow. A genetic change occurs resulting in the production of red blood cells, white blood cells and platelets that lack specific surface proteins (making them more susceptible to haemolysis and causing thrombosis). This genetic change occurs after birth meaning that PNH is acquired rather than inherited.

PNH affects both men and women, all races and all ages and people can be diagnosed at any age[7].The prevalence in the United Kingdom is around 16 people per million[8]. Extrapolating to cover the Welsh population, this equates to around 48 people in Wales.

With the development of treatments for PNH, life expectancy for patients with PNH is near normalised. The treatments included in this policy vary in the way they work. Below is a brief description of each treatment mechanism of action:

Eculizumab
Eculizumab is a C5 complement protein inhibitor. It blocks the activation of complement thereby preventing complement from attacking the PNH red blood cells[8,9]. Eculizumab has been proven to reduce the symptoms experienced in PNH and has been shown to improve people's quality of life[8]. It also reduces the risks of many of the complications of PNH, such as thrombosis and renal failure. Eculizumab is administered by intravenous injection with initiation and maintenance dosing[9]. Biosimilars are available. Providers will only be reimbursed for the cost of the best value product.

[9] Eculizumab | Drugs | BNF | NICE

Ravulizumab
Ravulizumab is also a C5 complement protein inhibitor and works in the same way as eculizumab[8,10]. In contrast to eculizumab, ravulizumab is administered by intravenous infusion every 8 weeks as opposed to ever 2 weeks.

Pegcetacoplan
Pegcetacoplan is a C3 complement inhibitor[11] administered by subcutaneous infusion twice a week. This is a proximal complement inhibitor, which works by interfering with early phases of complement activation, eventually preventing C3-mediated extravascular hemolysis in addition to intravascular hemolysis[12]. Pegcetacoplan is administered by subcutaneous injection with initiation and maintenance dosing[11].

Iptacopan
Iptacopan is a proximal complement inhibitor which targets factor B and prevents the activation of C3 convertase, thereby inhibiting the complement cascade that leads to haemolysis[13]. Iptacopan is administered orally[13].

Danicopan in combination with ravulizumab or eculizumab
Danicopan is a proximal complement inhibitor which binds to factor D and prevents activation of the complement alternative pathway, thereby inhibiting the complement cascade that leads to haemolysis[14]. It reduces extravascular haemolysis in patients on C5 inhibition.Danicopan is administered orally[14].

Crovalimab
Crovalimab inhibits activation of the C5 protein, thereby inhibiting intravascular haemolysis by a similar mechanism to eculizumab and ravulizumab. Once the initial loading treatments have been given, it's a subcutaneous monthly injection[15].

1.2 Equality Impact Assessment

The Equality Impact Assessment (EIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable NHS Wales Joint Commissioning Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

[10] Ravulizumab | Drugs | BNF | NICE
[11] Pegcetacoplan | Drugs | BNF | NICE
[12] Frontiers | Anti-complement Treatment for Paroxysmal Nocturnal Haemoglobinuria
[13] Iptacopan | Drugs | BNF | NICE
[14] Danicopan | Drugs | BNF | NICE
[15] Crovalimab | Drugs | BNF | NICE

The drugs in this policy have either been subjected to an EIA through the Cwm Taf Morgannwg (CTM) EIA or by adopting the EIA already carried out by NICE.

An EIA was carried out for eculizumab using the CTM template. The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken. An EIA was carried out by NICE during the evaluation of the remaining drugs listed in this policy; ravulizumab[16], pegcetacoplan[17], iptacopan[18], danicopan with ravulizumab or eculizumab[19] and crovalimab[20].

[16] equality-impact-assessment-guidance-development ravulizumab
[17] equality-impact-assessment-guidance-development pegcetacoplan
[18] equality-impact-assessment-guidance-development iptacopan
[19] equality-impact-assessment-guidance-development danicopan
[20] equality-impact-assessment-guidance-development crovalimab

2. Recommendations

The recommendations below represent the views of AWMSG and NICE, arrived at after careful consideration of the evidence available. Health professionals are expected to take into account the relevant AWMSG and NICE guidance, alongside the individual needs, preferences and values of the patient.

2.1 Inclusion Criteria

Drug Treatment	Recommendation
Eculizumab	AWMSG Advice 0509: Eculizumab for the treatment of paroxysmal nocturnal haemoglobinuria Eculizumab is recommended for restricted use within NHS Wales according to agreed guidelines for the treatment of paroxysmal nocturnal haemoglobinuria.
Ravulizumab	NICE TA698: Ravulizumab for treating paroxysmal nocturnal haemoglobinuria Ravulizumab is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria in adults: • with haemolysis with clinical symptoms suggesting high disease activity, **or** • whose disease is clinically stable after having eculizumab for at least 6 months, **and** • the company provides it according to the commercial arrangement.
Pegcetacoplan	NICE TA778: Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria Pegcetacoplan is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults who have anaemia after at least 3 months of treatment with a C5 inhibitor. It is recommended only if the company provides pegcetacoplan according to the commercial arrangement.
Iptacopan	NICE TA 1000: Iptacopan for treating paroxysmal nocturnal haemoglobinuria

	Iptacopan is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults with haemolytic anaemia. Iptacopan is only recommended if the company provides it according to the commercial arrangement.
Danicopan in combination with ravulizumab or eculizumab	NICE TA1010: Danicopan with ravulizumab or eculizumab for treating paroxysmal nocturnal haemoglobinuria Danicopan is recommended, as an add-on to ravulizumab or eculizumab as an option for treating paroxysmal nocturnal haemoglobinuria (PNH) in adults who have residual haemolytic anaemia, only if: • they have clinically significant extravascular haemolysis while on treatment with a complement component 5 inhibitor (C5 inhibitor) and • the company provides it according to the commercial arrangement. This recommendation is not intended to affect treatment with danicopan that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.
Crovalimab	NICE TA1019: Crovalimab for treating paroxysmal nocturnal haemoglobinuria in people 12 years and over Crovalimab is recommended, within its marketing authorisation, as an option for treating paroxysmal nocturnal haemoglobinuria in people 12 years and over who weigh 40 kg or more. It is recommended for people who: • have haemolysis with clinical symptoms indicating high disease activity • are clinically stable after having a complement component 5 inhibitor for at least the past 6 months.

	Crovalimab is only recommended if the company provides it according to the commercial arrangement.

2.2 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement to their health due to the treatment being given.

If no improvement to a patient's health has been recorded then clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

2.3 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.4 Designated Providers

PNH National Service
Department of Haematology,
Level 3,
Bexley Wing,
St James' Institute of Oncology,
Beckett Street,
Leeds
LS9 7TF

*Please note that Haematologists in local Health Boards may prescribe the drugs listed in this policy for PNH under the advice of the PNH National Service. This will include having access to complete the appropriate Blueteq® forms.

2.5 Patient Pathway (Annex i)

See Annex i for patient pathway details.

2.6 Transition arrangements

Transition arrangements should be in line with Transition from children's to adults' services for young people using health or social care services, NICE guidance NG43 and the Welsh Government Transition and Handover Guidance

Transition involves a process of preparation for young people and their families for their transition to adulthood and their transition to adult services. This preparation should start from early adolescence 12-13 year olds. The exact timing of this will ideally be dependent on the wishes of the young person but will need to comply with local resources and arrangements.

The transition process should be a flexible and collaborative process involving the young person and their family as appropriate and the service.

The manner in which this process is managed will vary on an individual case basis with multidisciplinary input often required and patient and family choice taken into account together with individual health board and environmental circumstances factored in.

For the specialised paediatric services it commissions, the JCC will routinely commission treatment up until a patient is 16 years old. The JCC does not commission specialised paediatric services for patients aged 18 years and older. For patients aged 16 or 17 years of age, the JCC will continue to commission ongoing specialised treatment initiated before the patient's 16th birthday and under the ongoing care of a specialised paediatric team.

2.7 Mechanism for funding

The drugs listed in this policy will only be funded for patients registered via the Blueteq® system and where an appropriately constructed MDT has approved its use within highly specialised centres.

Where the patient meets the criteria in this policy and the referral is received by an agreed centre, a Blueteq® form should be completed for approval.

For further information on accessing and completing the Blueteq® form please contact NWJCC using the following email address: NWJCCblueteq@wales.nhs.uk.

If a non-contracted provider wishes to treat a patient that meets the criteria they should contact NWJCC at nwjccipc@wales.nhs.uk. They will be asked to demonstrate they have an appropriate MDT in place.

Funding is approved on the basis that the drugs are prescribed and administered in accordance with their marketing authorisation.

The companies have a commercial arrangement. This makes the drugs listed in this policy available to the NHS with a discount. The size of the discount is commercial in confidence. Health Boards in Wales should refer to the AWTTC Commercial Medicines Access References Tool (CMART) for further information on the Patient Access Scheme (PAS) price.

If treatment is discontinued, it is the responsibility of the prescribing team to discontinue the Blueteq® form.

2.8 Action to be taken

- Health Boards and NWJCC are to circulate this Policy Position Statement to all Hospitals/MDTs to inform them of the conditions under which the drugs referenced in this policy will be commissioned.
- NWJCC are to ensure that all providers are purchasing the drugs referenced in this policy at the agreed discounted price.
- Providers should ensure any proposed treatments are recommended by the PNH service following patient consultation.
- Providers are to ensure the need to approve the drugs referenced in this policy at the appropriate MDT and are registering use on the Blueteq® system, and the treatment will only be funded where the Blueteq® minimum dataset is fully and accurately populated.
- Providers should work to written quality standards and provide monitoring information to NWJCC on request.

3. Listening to People:

3.1 Complaints, Incidents and Redress Process

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to Listening to People, The NHS Wales Complaints, Incidents and Redress Process – People's Guidance 2026. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to NWJCC.

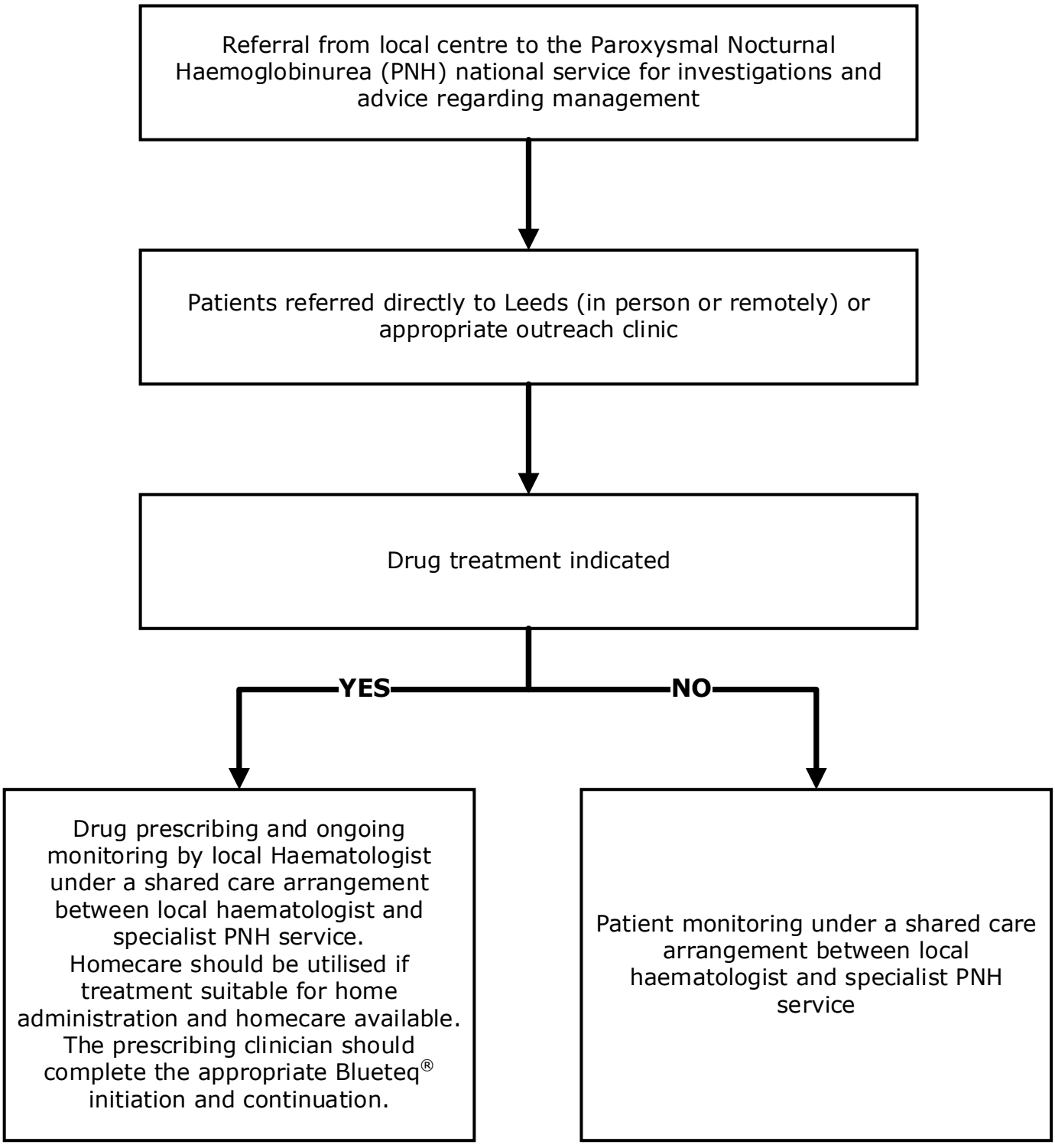
3.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Individual Patient Funding Requests

Annex i Patient Pathway



Annex ii Codes

The list of ICD codes below is indicative and is not exhaustive. The ICD10 codes have been provided and verified by the Information Standards Team at Digital Health and Care Wales (DCHW). Additional codes may be used for contract monitoring purposes, furthermore some codes may cover indications not included within this policy.

Code Category	Code	Description
CD-10	D59.5	Paroxysmal nocturnal haemoglobinuria

Contact Us

If you have a question related to this document you can contact us using one of the methods outlined below.

If you would like this document in an alternative format and/or language, please contact us for assistance.

Email:

NWJCC consultation mailbox – NWJCC.Consultation@wales.nhs.uk

Telephone:

General Enquiries – 01443 433112

Website:

Contact us - NHS Wales Joint Commissioning Committee

Writing:

If you wish to contact the NHS Wales Joint Commissioning Committee, you can write to us at one of our locations below, we welcome correspondence in Welsh or English:

South Wales Offices
Unit 1, Charnwood Court, Heol Billingsley, Nantgarw, CF15 7QZ
Unit G1 The Willowford, Main Avenue, Treforest Industrial Estate, Pontypridd, CF37 5YL

North Wales Offices
Unit 3, Media Point - Unit 3, Mold Business Park, Mold, CH7 1XY
Preswylfa, Hendy Road, Mold, CH7 1PZ