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Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Commissioning Policy: CP254

Bevacizumab for the treatment of vestibular schwannomas in Neurofibromatosis Type 2 (now known as NF2-related vestibular schwannomatosis) (all ages)

August 2023

Version 1.0

PARCH - RESPECT

PARTNERIAETH - PARTNERSHIP

GWELLA AC ARLOESI - IMPROVEMENT & INNOVATION

Document information	
Document purpose	Commissioning Policy
Document name	Bevacizumab for the treatment of neurofibromatosis type 2 (NF2) related vestibular schwannomatosis (all ages)
Author	Welsh Health Specialised Services Committee
Publication date	August 2023
Commissioning Team	Neurosciences and Long Term Conditions (LTC)
Target audience	Chief Executives, Medical Directors, Directors of Finance, Directors of Nursing, Chief Pharmacists, Directors of Planning and Commissioning, Neurologists, Neurosurgeons.
Description	NHS Wales propose to routinely commission this specialised service in accordance with the criteria described in this policy
Document No	CP254
Review Date	2026

Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) will commission bevacizumab for the treatment of NF2-related vestibular schwannomatosis (all ages) in accordance with the criteria outlined in this document.

In creating this document WHSSC has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Welsh Language

WHSSC 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 Act (1993), 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, WHSSC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered and people have access to either a translator or 'Language-line' if requested. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation
WHSSC 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 WHSSC commitment.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy.

This policy 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.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy.

1. Introduction

This policy has been developed as a Commissioning Policy for the planning and delivery of bevacizumab for people of all ages with NF2-related vestibular schwannomatosis who are resident in Wales. This service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 Plain Language Summary

Neurofibromatosis Type 2 (NF2) is a rare genetic condition caused by a faulty gene that leads to uncontrolled tumours (growths) developing along nerves. The tumours are usually non-cancerous but may cause a range of symptoms. Almost everyone with NF2 develops tumours along the nerves that are responsible for hearing and balance (vestibular schwannomas also known as acoustic neuromas).[1] These usually cause symptoms[2] such as:

- Loss of hearing that gradually gets worse over time usually resulting in complete deafness if untreated,
- Hearing ringing or buzzing in the ears (Tinnitus), and
- Balance problems – particularly when moving in the dark or walking on uneven ground.

1.2 Aims and Objectives

This policy aims to define the commissioning position of WHSSC on the use of bevacizumab for people with NF2-related vestibular schwannomatosis.

The objectives of this policy are to:

- ensure commissioning for the use of bevacizumab is evidence based
- ensure equitable access to bevacizumab
- define criteria for people with NF2-related vestibular schwannomatosis to access treatment
- improve outcomes for people with NF2-related vestibular schwannomatosis .

1.3 Epidemiology

The UK prevalence of NF2 is around 1:58,000[3] giving a prevalence in Wales of 51 people, based on a population of 3.108 million in Wales in 2021[4]. Around 10% of vestibular schwannomas have a rapid growth rate based on

[1] NHS 111 Wales, NHS 111 Wales - Health A-Z : NF2
[2] NHS Choices. Acoustic neuroma (vestibular schwannoma). Apr 2016. Available at: http://www.nhs.uk/Conditions/Acoustic-neuroma/Pages/Introduction.aspx.
[3] Evans DGR et al. Schwannomatosis:a genetic and epidemiological study Available at: Schwannomatosis: a genetic and epidemiological study - PubMed (nih.gov)
[4] Stats Wales. Population estimates by local authority and year. Mid-year 2021.22. Available at: https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Authority/populationestimates-by-localauthority-year.

data from patients attending one of the specialised clinics treating NF2 in the UK[5].

1.4 Current Treatment

The treatment of NF-related vestibular schwannomatosis aims to preserve hearing in at least one of the ears[6]. Approximately 10% of vestibular schwannomas have a rapid growth rate, based on data from patients attending one specialised clinic for treating neurofibromatosis type 2 in the UK[7].

Treatment options include:

- Conservative and medical management, and
- Surgery and radiotherapy.

Other anti-angiogenic agents (lapatinib, erlotinib, everolimus, imatinib and pazopanib) have been studied in the treatment of vestibular schwannomas in NF2, but there is not enough evidence to draw any conclusions about their benefits.[8]

There are currently no licenced medicines specifically to treat NF2-related vestibular schwannomatosis as an alternative to surgery and stereotactic radiotherapy.

1.5 Proposed Treatment

Bevacizumab is used for the treatment of rapidly growing NF2-related vestibular schwannomatosis as an alternative to surgery and stereotactic radiosurgery[9].

The use of bevacizumab to treat NF2-related vestibular schwannomatosis is off label however, it is recognised as a treatment for this indication in adult patients and older children.

Bevacizuamab is a monoclonal antibody that inhibits tumour growth by binding to vascular endothelial growth factor (VEGF), a key driver of angiogenesis and vascologenesis. The expression of VEGF and its receptor

[5] Li KL, Djoukhadar I, Zhu X et al. Vascular biomarkers derived from dynamic contrast-enhanced MRI predict response of vestibular schwannoma to antiangiogenic therapy in type 2 neurofibromatosis. *Neuro-Oncology.* 2016;18(2):275-282.
[6] Lloyd SKW, King AT, Rutherford SA et al. Hearing optimisation in neurofibromatosis type 2: systematic review. Clinical Otolaryngology. 2017;00:1-9
[7] Li KJ, Djoukhadar I, Zhu X et al. Vascular biomarkers derived from dynamic contrast –enhanced MRI predict response of vestibular schwannoma to antiangiogenic therapy in type 2 neurofibromatosis. Neuro-oncology. 2016;18 (2): 275-282.
[8] Lloyd SKW, King AT, Rutherford SA et al. Hearing optimisation in neurofibromatosis type 2: systematic review. Clinical Otolaryngology. 2017;00:1-9
[9] Morris KA, Golding JF, Axon PR, et al. Bevacizumab in neurofibromatosis type 2 (NF2) related vestibular schwannomas: a nationally coordinated approach to delivery and prospective evaluation. Neuro-Oncology Practice. 2016; 3 (4):281-289

VEGFR-1 have been detected in vestibular schwannomas and their level correlates with growth rate of tumours.

Bevacizumab can stop the tumour from developing new blood vessels, thus reducing the supply of oxygen and nutrients which can cause the tumour to shrink, stop growing or grow more slowly.

Bevacizumab is given by intravenous infusion every two or three weeks. As bevacizumab use in vestibular schwannoma is off-label, there is no single recommended dose for this indication and local agreed dosing policies within the specialised centres should be followed.

Assessment and management of bevacizumab for patients with rapidly growing vestibular schwannomas will follow the current National Protocol (Appendix 1).

1.6 Off-label use

Bevacizumab is not licenced to treat this indication and is therefore "off–label". A clinician considering prescribing a medication outside of the terms of a product licence (off-label) should do so in accordance with the Medicines and Healthcare Products Agency (MHRA) and the General Medical Council (GMC) guidance which applies throughout the UK.

The risk and benefits of off-label use of bevacizumab should be clearly stated and discussed with the patient to enable informed consent.

Should clinicians consider the treatment appropriate for their patients and they have followed local medicines governance arrangements for off-label use, WHSSC will meet the cost under the criteria set out in 2.1.

1.7 What NHS Wales has decided

WHSSC has carefully reviewed the evidence for the use of Bevacizumab for the treatment of NF2-related vestibular schwannomatosis (see section 3). We have concluded that there is enough evidence to fund the use of Bevacizumab, within the criteria set out in section 2.1.

1.8 Relationship with other documents

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

- **Relevant NHS England policies**

- NHS Commissioning Board. Clinical Commissioning Policy: vestibular schwannoma and other cranial nerve neuromas. Apr 2013. Available at:https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/04/d05-p-a.pdf
- NHS Commissioning Board. NHS Standard contract for neurofibromatosis type 2 service (all ages). Section B part 1: service specifications. Apr 2013. Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-neurofib-2.pdf

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee have approved funding of Bevacizumab for people (all ages) with NF2-related vestibular schwannomatosis in line with the criteria identified in this policy.

2.1 Inclusion Criteria

To be eligible for treatment with bevacizumab the following should be met:

- At least one rapidly growing vestibular schwannoma defined as schwannoma growth ≥4mm by linear diameter or ≥60% volume over the preceding 12-month period, **or**
- A growing schwannoma that does not meet growth criteria but is an imminent threat to neurological functions.

- For patients aged 16 and over with schwannomas that meet either of these growth criteria, at least two NF2 MDT's should confirm that the eligibility criteria are met and bevacizumab treatment is appropriate.
- For patients under 16 and for schwanommas that do not meet either of these growth criteria but are an imminent threat to neurological function, all four NFT2 MDT's should confirm that eligibility criteria are met and bevacizumab treatment is appropriate.
- The potential benefits of bevacizumab outweigh the potential risks.

2.2 Exclusion Criteria

- A history of major bleeding diathesis or blood clotting.
- Evidence of tumour invading a blood vessel wall.
- Major surgery, open biopsy or traumatic injury within 28 days.
- Peptic ulcer disease or on chronic daily treatment with aspirin or clopidogrel.
- Unhealed wounds or fractures.
- History of Cerebral Vascular Accident (CVA), uncontrolled seizures, Myocardial Infarction (MI), Transient Ischaemic Attacks (TIA) unstable angina, arrhythmias.
- Pregnancy or lactating patients. Patients must use an effective method of contraception through treatment.

2.3 Stopping Criteria

Clinicians should consider stopping treatment if a patient relapses, stops responding or if there is evidence of disease progression.

Advice can be found in the National Specialised Commissioning protocol for the administration of bevacizumab in patients with Neurofibromatosis Type 2 – version13, updated August 2018 (Appendix 1).

2.4 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.

2.5 Acceptance Criteria

The service outlined in this policy 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.

2.6 Patient Pathway

Bevacizumab will only be commissioned and funded via the centres included in section 2.7. Shared Care arrangements may be in place to deliver treatment closer to home.

2.7 Designated Centre

NHS England has four national treatment centres that are commissioned to offer specialist treatment of NF2-related vestibular schwannomatosis[10]. WHSSC will fund bevacizumab through the following designated NHS England specialised centres:

- Cambridge University Hospitals NHS Foundation Trust
  Hills Road
  Cambridge
  CB2 0QQ.

[10] NHS Commissioning Board. NHS Standard contract for neurofibromatosis type 2 service (all ages). Section B part 1: service specifications. Apr 2013. Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-neurofib-2.pdf

- Manchester University Hospitals NHS Foundation Trust
  St Mary's Hospital
  Oxford Road
  Manchester
  M1 6FU

- Guy's & St Thomas' NHS Foundation Trust
  1st Floor
  Southwark Wing
  Guy's Hospital
  London
  SE1 9RT

- Oxford University Hospital NHS Trust
  Level 3, West Wing
  John Radcliff Hospital
  Headington
  Oxford
  OX3 9DU

2.8 Exceptions

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, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.9 Blueteq and reimbursement

Bevacizumab for vestibular schwannoma in NF2 will only be funded for patients registered via the Blueteq system and where treatment is initiated by a consultant experienced in the treatment of patients with vestibular schwannoma in NF2.

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 WHSSC using the following e-mail address: WHSSC.blueteq@wales.nhs.uk

If a non-contracted provider wishes to treat a patient that meets the criteria they should contact WHSSC (e-mail: wales.ipc@wales.nhs.uk). They will be asked to demonstrate they have an appropriate MDT in place.

Bevacizumab will only be funded by WHSSC when the lowest acquisition cost drug is used.

2.10 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner. Specifically:

- NHS number, Hospital Number, date of birth, gender, ethnicity, postcode
- Responsible Clinician, Designated NF2 Centre
- Treatment start date, regimen used, treatment end date
- Reason for stopping (e.g. progression, end of regimen, toxicity etc.)
- Audiology (date, result) & Volumetric MRI (date, diameter of primary lesion, volume) at baseline (0 months), 3 months, 6 months, 9 months and 12 months, and the same parameters from the assessment preceding the baseline assessment.
- Treatment-related toxicity
- Any surgery in the 12 months following commencement of treatment (date, procedure, reason, outcome, and complications)
- 10m timed walk (document assisted/unassisted): best of 3 trials at the defined time points in the appendix.

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this.

2.11 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinicians considering treatment should:

- discuss all alternative treatments with the patient;
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment via the completion of a Blueteq form.

In all other circumstances an IPFR must be submitted.

Action to be taken

- Health Boards are to circulate this commissioning policy to all Hospitals/MDTs to inform them of the conditions under which the treatment included in this policy will be commissioned.
- Health Boards are to ensure that all providers are purchasing bevacizumab at the lowest acquisition cost.
- Health Boards are to ensure that all providers understand the need to approve the treatment listed in this policy at the appropriate MDT, and are registering use on the Blueteq system. The treatment will only be funded where the Blueteq minimum dataset is fully and accurately populated.
- The Provider should work to written quality standards and provide monitoring information to WHSSC on request.

3. Evidence

WHSSC is committed to regularly reviewing and updating all of its commissioning policies based upon the best available evidence of both clinical and cost effectiveness.

In creating this policy, WHSSC commissioned the All Wales Medicines Strategy Group (AWMSG) to produce an evidence review on the clinical and cost effectiveness of bevacizumab for the treatment of NF2 related vestibular schwannomatosis (see Appendix 2). The evidence review was presented to the WHSSC Prioritisation Panel in July 2021 who recommend bevacizumab for the treatment of vestibular schwannoma in neurofibromatosis type 2 as a high priority. Funding was approved in the 2022-2025 WHSSC Integrated Commissioning Plan[11].

Efficacy/Effectiveness

In open-label and retrospective studies bevacizumab treatment appears to result in the shrinkage of vestibular schwannomas and hearing improvement in around one-third to one-half of patients with progressive vestibular schwannomas in neurofibromatosis type 2. This is supported by a 2019 meta-analysis of 8 studies using bevacizumab doses of 5 to 10 mg/kg every 2-6 weeks and over a mean follow-up period of 14 months[12]. Response to treatment may be poorer in children.

A 2017 systematic review of hearing optimisation in neurofibromatosis type 2 concluded that using bevacizumab may prolong hearing preservation in people with rapidly growing tumours and is probably more effective than hearing preservation surgery and radiotherapy in preserving hearing[13]. This was based on a review of 7 studies using bevacizumab doses of 2.5 to 10 mg/kg every 2 weeks and over a mean follow-up period of 21 months[11].

Safety

Studies showed that bevacizumab treatment was generally well tolerated; the most common treatment-related adverse events were hypertension, proteinuria, and amenorrhea. One study used dose reductions from 5 mg/kg every 2 weeks to 2.5 mg/kg every 2 or 3 weeks, to minimise side effects during treatment[14]. Testing for proteinuria should be done before

[11] Integrated Commissioning Plan 2022-2025 - Welsh Health Specialised Services Committee (nhs.wales)
[12] Lu VM, Ravindran K, and Graffeo CS. Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: a systematic review and meta-analysis of treatment outcomes. Journal of neuro-oncology. 2019;144(2):239-248.
[13] Lloyd SKW, King AT, Rutherford SA et al. Hearing optimisation in neurofibromatosis type 2: a systematic review. Clinical Otolaryngology. 2017;00:1-9.
[14] Farschtschi S, Kollmann P, Dalchow C et al. Reduced dosage of bevacizumab in treatment of vestibular schwannomas in patients with neurofibromatosis type 2. European Archives of Oto-Rhino-Laryngology. 2015;272(12):3857-3860

starting bevacizumab and monitoring of blood pressure, proteinuria, and signs and symptoms of CNS bleeding are recommended during treatment[15]. The high incidence of amenorrhea may be an issue for females of child-bearing age.

3.1 References

The full evidence status report can be found in Appendix 2.

3.2 Date of Review

This document is scheduled for review in 2026 where we will check if any new evidence is available. If no new evidence or intervention is available the review date will be progressed.

If an update is carried out the policy will remain extant until the revised policy is published.

4. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services 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).

This policy has been subjected to an Equality Impact Assessment.

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.

[15] Roche Products Limited. Avastin®. Summary of Product Characteristics. Jun 2017. Available at: https://www.medicines.org.uk/emc/medicine/15748

5. Putting Things Right:

5.1 Raising a Concern

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 the LHB for NHS Putting Things Right. 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 WHSSC.

5.2 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 an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

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: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

Annex i Abbreviations and Glossary

Abbreviations

NF2 Neurofibromatosis Type 2

AWTTC All Wales Therapeutics and Toxicology Centre

IPFR Individual Patient Funding Request

WHSSC Welsh Health Specialised Services

MI Myocardial Infarction

TIA Transient Ischaemic Attack

Glossary

Individual Patient Funding Request (IPFR)

An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)

WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.

Vestibular schwannomas (also known as acoustic neuromas)

Vestibular schwannomas affect the eight cranial nerve which is responsible or transmitting sound and equilibrium (balance) information from the brain to the inner ear. About 5% of vestibular schwannomas are associated with the hereditary disease neurofibromatosis type 2.

Neurofibromatosis type 2

Neurofibromatosis type 2 is caused by a faulty gene which can lead to uncontrolled growths developing in the nervous system. In half of the cases of NF2 the faulty gene is passed from a parent to their child. Only 1 parent needs to have the faulty gent for their child to be at risk of developing the condition.

Appendix 1

UK NF2 BEV Protocol v13.0 August 8 2018

National Specialised Commissioning protocol for administration of Bevacizumab in patients with Neurofibromatosis Type 2 -version 13 (Updated August 2018)

Background

Since 2008 case reports have circulated suggesting improvements in hearing and tumour shrinkage in NF2 associated vestibular schwannomas. In 2009 the outcomes of 11 patients treated with Bevacizumab in whom the majority had hearing improvement or tumour shrinkage were published[1]. A follow up publication of 31 patients from the same group demonstrated durable responses at 1 and 3 years for over half of patients[2].

Since 2010, Bevacizumab has been available in the UK for treatment of rapidly growing schwannomas in NF2 patients via centralized specialist NF2 multidisciplinary clinics on the basis of positive international experience. In total, 143 patients have now been treated under that service. We have published the results of the first 61 patients[3]: 2 year progression free survival was 63% with median 15 months of follow up. Hearing was maintained or improved in 86% of assessable patients. In a separate report[4], toxicity of the first 80 patients with median follow up of 33 months has been reported: the most common toxicities reported were fatigue, hypertension and infection. In total, 24 % had at least one ≥ grade 2 hypertension event recorded; 17.5 % had ≥ grade 2 proteinuria. A total of 143 patients have now been treated with bevacizumab for NF2-related tumours via the specialised commissioning service. The cohort results are evaluated annually and remain consistent with the published results.

This document outlines the process for assessment of patients regarding eligibility for treatment and monitoring for safety and response to treatment to guide practice in the nationally commissioned NF2 clinics.

1. Eligibility

1.1 Inclusion criteria

To be eligible for treatment with bevacizumab (Avastin®) the following conditions
MUST be met:

- At least one growing schwannoma with a rate of growth averaged over a 12 month period of ≥4mm by linear dimension or 60% by volume OR a symptomatic cystic ependymoma OR a growing schwannoma that does not meet growth criteria but is an imminent threat to neurological function.
- For patients aged 16 years and over with schwannomas that meet growth criteria and symptomatic cystic ependymomas, at least two NF2 MDTs must confirm that eligibility criteria are met and bevacizumab treatment is appropriate.
- For patients aged under 16 years, and for schwannomas that do not meet growth criteria but are an imminent threat to neurological function all four NF2 MDTs must confirm that eligibility criteria are met and bevacizumab treatment is appropriate. Responses to the applying centre must be sent within 6 weeks of the initial request.
- The potential benefits of bevacizumab outweigh the potential risks.

In addition, the following laboratory and clinical criteria **SHOULD** be met prior to initiation of first treatment:

- WBC ≥ 2.0 $x10^9$/l, neutrophils ≥ 1.0 $x10^9$/l and platelets ≥ 100 $x10^9$/l
- Adequate liver function: bilirubin ≤ 1.5 x upper limit normal (ULN), AST and/or ALT ≤ 2.5 x ULN
- Adequate renal function: GFR (measured or calculated) ≥ 90 ml/min/1.73 m^2,creatinine ≤ 1.5 x ULN for age.
- First early morning urine protein:creatinine ratio (PCR) <50 mg/mmol. Serum albumin within normal range
- INR ≤ 1.5, APTT ≤ 1.5 x ULN
- Normal blood pressure: systolic and diastolic ≤ 95^{th} centile for age, gender or height (children). In adults, BP of <140/90 mmHg with use of antihypertensives as required.

If the indices above are not met, treatment may go ahead if in the opinion of the treating MDT the potential benefits of bevacizumab treatment outweigh the potential risks. The risks and benefits, decision making process and discussion with the patient and/or carers must be clearly documented in the patient record. Specific guidance for the management of renal toxicity is given below.

1.2 Exclusion Criteria

- Evidence of tumour invading a blood vessel wall
- Major surgery, open biopsy or traumatic injury within 28 days
- Peptic ulcer disease, or on chronic daily treatment with aspirin or clopidogrel
- Unhealed wounds or fractures
- Bleeding diathesis
- History of CVA, uncontrolled seizures, MI, TIAs, unstable angina, arrhythmias
- Pregnant or lactating patient. Patients must use an effective method of contraception throughout treatment.

2. Protocol for treatment

Patients who meet the eligibility criteria for initiation of treatment should be assessed and treated according to the following protocol. A summary schedule of assessments is given in Appendix 1.

2.1 Baseline (time 0), pre treatment assessment

- Volumetric MRI of target lesion and additional known intracranial and intra- spinal tumours. Refer to Appendix 2 for the MRI sequences to be obtained.
- Audiology assessment with speech discrimination score, Sentence testing must be performed if SDS<50.
- Toxicity investigations as described in Inclusion Criteria
- Bone age assessment (X-ray of left hand & wrist) if patient has not completed growth.
- Offer sperm banking to male patients +/- egg or embryo storage to female patients
- Baseline QOL assessment using NFTI-QOL
- Assessment of balance including 10m timed walk
- Assessment of coordination

2.2 Bevacizumab treatment

Within 2 weeks of the baseline assessment start bevacizumab 5mg/kg 2-weekly or 7.5mg/kg 3-weekly.

Prior to each dose of bevacizumab the following should be measured and where relevant should meet the standards set out in the eligibility criteria above:

- Weight, performance status, blood pressure
- FBC, renal function, albumin, urine dipstick

2.2.1 Management of renal toxicity

Hypertension and proteinuria have been reported to occur very commonly in patients receiving bevacizumab and can be dose-limiting. Both are believed to correlate with cumulative administered dose. Bevacizumab can be a long-term medication in the setting of NF2 and close attention must therefore be paid to renal health. The following criteria for treatment in the presence of proteinuria have been agreed.

- Early morning urine samples should be used if possible.
- If proteinuria ≥2+ is present on urine dipstick, measure urine PCR.
- If PCR is above ULN, check FBC, LDH, haptoglobins and a blood film, looking for thrombotic microangiopathy.
- If PCR is above ULN and the risk/benefit analysis as judged by the NF2 MDT supports continued treatment with bevacizumab, continue to monitor PCR with each subsequent dose of bevacizumab while proteinuria remains ≥2+ on urine dipstick.
- If PCR is ≥ 100 mg/mmol, or above 50 mg/mmol with new microscopic haematuria, refer to nephrology and consider starting ACE inhibitor. Treatment with bevacizumab may continue with nephrology input if risk/benefit analysis supports continued treatment.
- If PCR is ≥ 200 mg/mmol, stop bevacizumab treatment, liaise with nephrology and NF2 MDT. Treatment may re-commence if the proteinuria improves but must be undertaken with great caution, and the discussion and decision making process clearly documented.
- Hypertension in adults should be managed according to the NICE guidance on diagnosis and management of hypertension in adults.
- In the presence of proteinuria or hypertension requiring treatment, the patient must be discussed at the NF2 MDT as part of the risk/benefit analysis.
- Particular care must be paid to children who develop hypertension and proteinuria during bevacizumab treatment. Treatment may only continue in conjunction with expert paediatric nephrology input.

2.3 After 3 months of treatment

- Audiology assessment with speech discrimination score, Sentence testing must be performed if SDS<50.

2.4 After 6 months of treatment

- Repeat imaging of target lesion(s).
- If the target tumour is stable in size as defined in the Glossary, (Appendix 3) compared to *the 0-month scan* reduce to a maintenance treatment dose of 2.5 mg/kg of bevacizumab 4-

weekly.

- If the target tumour shows a reduction in size compared to 0-month scan continue treatment dose at 5 mg/kg 2-weekly or 7.5 mg/kg 3-weekly. Scan at 3-monthly intervals. Once tumour volume becomes stable on 2 successive 3-monthly scans reduce to a maintenance dose of bevacizumab 2.5 mg/kg 4-weekly.
- If target tumour has significantly increased in size (see Appendix 3) compared to the 0-month scan AND there is no significant improvement in hearing (see Appendix 3), consider either increasing to 10 mg/kg 2-weekly, or a dose- equivalent 15 mg/kg 3-weekly regimen, for a trial period of 3 months or stop treatment. Treatment with the higher dose regimen will require co-approval by the paired centre and copy to Oxford. If after 3 months there is continued tumour growth bevacizumab should be stopped.
- If a patient is considered to be progressing on the basis of both hearing and radiologic assessments a justification must be made to the partner lead centre of another reproducible measure to justify ongoing treatment.
- If a patient's tumour has previously progressed on a low dose regime of 2.5 mg/kg 4-weekly, a high dose maintenance regimen may be used.

2.5 Additional assessments on treatment

- Target lesions ± additional symptomatic lesions should continue to be re-assessed at 6-monthly intervals if the target lesion(s) is stable. If the target lesion has been stable for at least two years and treatment with bevacizumab is continuing, consider 12-monthly imaging in the absence of symptomatic deterioration.
- Audiology assessment with speech discrimination score as per the table in Appendix 1. Sentence testing must be performed if 0<SDS<50 at 6 month intervals.
- If a patient is deaf and has 2 audiology assessments consistent with this, they do not need ongoing audiology reviews on the schedule unless they report an improvement in hearing.
- Continue clinical assessments per table in Appendix 1.

2.6 Stopping Rules at any point on treatment

- Any NCI CTC Grade ≥3 toxicity including persistent grade ≥3 hypertension despite appropriate medical management unless the NF2 MDT consider the risks of stopping bevacizumab outweigh the risks of continuing bevacizumab.
- PCR ≥ 200 mg/mmol
- Clinically significant ongoing proteinuria where risk:benefit analysis assessed by NF2 MDT with nephrology input favours stopping

treatment.
- Gastrointestinal perforation or fistula formation
- Wound healing complications until any relevant wound is healed
- Serious thrombotic episode or acute coronary or cerebrovascular episode,
- Bleeding episode
- Non-GI fistula formation
- Ongoing tumour progression on radiologic and hearing assessments (see Appendix 3)

2.7 End of treatment assessment

This must be done if the patient stops treatment because of failure to respond to treatment or side effects, or if the patient decides to come off treatment electively.

- Volumetric MRI according to Appendix 2
- Audiology assessment with speech discrimination score, Sentence testing must be performed if SDS<50.
- Toxicity investigations described in Inclusion Criteria
- X-ray left hand & wrist for growing patients
- NFTI-QOL assessment
- Assessments of balance and coordination as described above in 2.1.
- Blood Pressure

3. Elective/planned breaks in treatment

- At 2 years, if there is no evidence of tumour growth on a maintenance dose of bevacizumab the patient should be given the opportunity to consider an elective break in treatment. This discussion with the patient and decision should be documented in the patient record.
- If a patient electively stops treatment, monitoring of the target lesion should continue according to the schedule of assessments (Appendix 1).
- If surveillance imaging shows tumour growth, treatment may be re-started at a suitable dosing schedule at the discretion of the NF2 MDT
- If a patient continues treatment at 2 years then this decision must be reviewed and documented annually.
- Any patient who has been treated with bevacizumab must have on-going annual monitoring of blood pressure and urinalysis.
- Risk of subfertility and early menopause must be assessed in female patients by assessing hormonal status (FSH/oestradiol/LH) and menstrual history. This essential data will be centrally gathered to

inform our understanding of late effects of exposure to Avastin.
- Ongoing monitoring data (4.5-4.6) must be submitted to Oxford for central audit.

4. Governance processes

In order to support these complex prescribing decisions and ensure decisions are made rapidly the following process is required:-

- Each centre is to be paired to another centre.
- *Manchester to Oxford*
  Oxford to Guys
- *Guys to Cambridge*
  Cambridge to
  Manchester
- As a centre identifies a patient who meets the criteria and they think would benefit from bevacizumab they will send appropriate clinical information and MRI scans to their paired centre's clinical lead or nominated recipient, at this time they will also notify the NSCT of the patient's details. The receiving centre will retrieve the scans from Burnbank Image Exchange Portal (IEP) as required for satellite centre patients.
- The paired centre will consider the case in their weekly MDT and inform the referring centre and NSCT of the outcome of their review.
- Oxford centre will collate referral numbers, all clinical, side effect and scan data for audit.

4.1 Clinical Audit of Outcomes

- Each centre is expected to record and submit to NCG the following data on each patient:-
- NHS number, Hospital Number, Date of birth, Gender, Ethnicity, Postcode
- Responsible Clinician, Centre
- Treatment Start Date, Regimen Used, Treatment End Date
- Reason for stopping (e.g. progression, end of regimen, toxicity etc)
- Audiology (Date, Result) & Volumetric MRI (Date, Diameter of primary lesion, Volume) at baseline (0 months), 3 Months, 6 Months, 9 months and 12 Months, and the same parameters from the assessment preceding the baseline assessment.
- Treatment-related toxicity
- Any surgery in the 12 month following commencement of treatment (date, procedure, reason, outcome, and

complications)

- 10m timed walk (document assisted/unassisted): best of 3 trials at the defined time points in the appendix.

Repeat imaging of target lesion(s).

5. Document review tracking

Dr Tom Kenny	August 2010
Updated Gareth Evans	November 2011
Approved Dr Tom Kenny	January 2012
Updated Gareth Evans	July 2012
Updated National meeting	June 2014
Updated National meeting	June 2015
Updated National meeting	July 2018

Appendix 2

All Wales Therapeutics & Toxicology Centre, Evidence Status Report: Bevacizumab (Avastin®) for the treatment of vestibular schwannoma in neurofibromatosis type 2 (June 2021 update)

This is available from WHSCC upon request. Please email CTT_WHSSC_Consultation@wales.nhs.uk.