NHS England

Engagement Report

Topic details

Title of policy or policy statement:	Sirolimus in extra-cranial slow flow vascular malformations refractory to standard therapies (all ages)
Programme of Care:	Internal Medicine
Clinical Reference Group:	Specialised surgery in children, vascular disease
URN:	2316

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered.

2. Background

Slow-flow vascular malformations are inborn errors of formation of blood vessels caused by genetic mutations. The types of blood vessels affected in slow-flow vascular malformations include veins, lymphatics and capillaries. They do not involve the high pressure and blood flow of arteries. Slow-flow vascular malformations have been estimated to affect about 1-1.5% of the population and, although often present at birth, can develop at any age.

The way slow-flow vascular malformations develop over a patient's life is unclear. Patients are thought to be born with slow-flow vascular malformations and associated syndromes which grow with them. As they grow, they cause compression and damage to surrounding structures. Slow-flow vascular malformations can affect any organ system. Patients with slow-flow vascular malformations may suffer with debilitating symptoms and complications including pain, swelling, ulceration, bleeding, blood clots, infection, disfiguration, organ failure, limb loss, and death. Patients with slow-flow vascular malformations also demonstrate significantly poorer quality-of-life and mental health when compared to the general population. In addition, slow-flow vascular malformations carry significantly negative socio-economic impact due to the lifelong nature of the condition and the involvement of patients of relatively young age groups.

Current treatment:

Treatment of symptomatic slow-flow vascular malformations is limited to supportive (such as compression hosiery) and medical measures (such as pain medication and antibiotics to treat episodes of infection), and invasive procedures (including excision or debulking surgery, sclerotherapy and cryotherapy). Supportive and medical measures are often not effective in providing satisfactory outcomes to patients with significant symptoms. As a result, invasive procedures are the mainstay of treatment for these patients.

In patients with large and widespread lesions, or those located within challenging anatomy, invasive procedures are however ineffective in managing severe symptoms and complications.

There are no licensed treatments available for patients with extra-cranial slow-flow vascular malformations refractory to standard care.

Sirolimus:

The proposed intervention is for the use of oral sirolimus (also known as rapamycin) in patients with extracranial slow-flow vascular malformations who are refractory to standard care. Sirolimus inhibits or blocks a protein known as the mammalian target of rapamycin (mTOR). This protein is involved in pathways which regulate several cell functions including growth, proliferation and metabolism. Sirolimus inhibits the mTOR pathway which is overactive as a result of genetic mutations in patients with certain slow-flow vascular malformations.

Sirolimus is not licenced for the use in extracranial slow-flow vascular malformations, and therefore, use will be off-label.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition underwent a four-week stakeholder testing between the 6th August to 1st September 2024 with registered stakeholders from the following Clinical Reference Groups:

- Specialised surgery in children
- Vascular disease

Respondents were asked the following consultation questions:

- Do you support the proposal for routine commissioning based on the evidence review and within the criteria set out in the proposal?
- Do you believe that there is any additional information that we should have considered in the evidence review?
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available?
- Do you support the Equality and Health Inequalities Impact Assessment?
- Does the Patient Impact Summary present a true reflection of the patient and carers lived experience of this condition?
- Do you have any further comments on the proposal?
- Please declare any conflict of interests relating to this document or service area.

The comments have then been shared with the Policy Working Group (PWG) to enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

A 13Q assessment has been completed following stakeholder testing.

The Programme of Care (PoC) has decided that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which widens the range of treatment options without disrupting current care or limiting patient choice, and therefore further public consultation was not required. This decision has been assured by the Patient Public Voice Advisory Group.

4. Engagement Results

The policy proposition received 6 stakeholder responses:

- 2 Clinicians
- 1 Patient Voice
- 1 Public Health Body
- 1 NHS Foundation Trust
- 1 Professional Organisation

Given the rarity of extra-cranial slow flow vascular malformations, this was deemed a good number of responses and there was a range of stakeholders represented. All stakeholders agreed with the policy proposition and felt that this offered patients a positive change.

In line with the 13Q assessment it was deemed that further public consultation was not required.

5. How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the PoC. The following themes were raised during engagement:

Keys themes in feedback	NHS England Response
Relevant Evidence	
One stakeholder commented that more information is needed regarding why no evidence was identified for cost-effectiveness and what will be done to resolve this.	Page 4 of the evidence review shows that no trials related to the cost effectiveness of sirolimus were found that matched the agreed PICO. The lack of trials into cost-effectiveness is expected given the rare and heterogenous nature of the condition. The main outcomes of the included studies as a result were clinical effectiveness and safety. The policy proposition will follow the published methods and cost effectiveness will be assessed following financial impact assessment and at Clinical Priorities Advisory Group (CPAG).
One stakeholder commented that they were concerned that there was only 'low certainty' evidence for safety.	The GRADE system is used to rate the quality of the evidence from very low to high. This is based on several factors including study design, risk of bias, imprecision and sample size. Appendix G on page 73 outlines why the included papers in the evidence review were given a certain GRADE scoring.

	The statement “The included studies provide very low certainty evidence that many patients reported adverse events during sirolimus treatment; however, most were not severe.” means that among the studies that had safety data, the reported side effects were not severe. However, there were weaknesses in the study design/paper that means the evidence reviewers could not be confident in the results. It is common for evidence to be low/very low certainty as these patient populations are small and it is difficult to perform large scale, randomised studies. The PWG and Clinical Panel agreed that despite the outcomes for all the criteria assessed were very low/low evidence, the cumulative positive effects of all these criteria may be significant and should not be underestimated.
Impact Assessment	
All stakeholders supported the PIA. One stakeholder commented that the PIA form could be improved by adding recognition of the life-long nature of the condition.	The Patient Impact Assessment (PIA) has been reviewed and it has been added that patients add debilitating, lifelong symptoms.
Current Patient Pathway	
One stakeholder commented that sirolimus use should be subject to full discussion between the clinician and patient, including the potential risks. One stakeholder commented that it should be made clear in the patient pathway that sirolimus should only be started after discussion between the clinician and patient and MDT discussion.	The policy proposition states under the starting criteria that sirolimus can only be used in these patients following MDT discussion and “patients need to have received adequate pre-treatment counselling, in the form of both written and verbal information... Patients need to receive this information prior to starting treatment, to ensure they have adequate decision-making time.” As part of pre-treatment counselling, patients will be informed about the potential risks. The patient pathway has been amended so that it is clear that sirolimus should only be started after counselling patients about the treatment, including risks and benefits.
Potential impact on equality and health inequalities	
All stakeholders supported the EHIA.	As outlined in the Equalities and Health Inequalities Impact Assessment (EHIA),

One stakeholder commented that the EHIA fails to expand on measures that will be put into place to ensure that patients will disabilities are not disadvantaged with access to sirolimus (e.g. patients with disabilities may have difficulty travelling to specialist centres for appointments).	commissioned providers should work with local agencies to ensure adequate access of sirolimus to patients with disabilities. This is done through providers, rather than through NHS England as part of the policy development process.
Changes/addition to policy	
One stakeholder commented that there needs to be mandating of a registry and data collection to help improve data on the benefits and adverse events across subgroups before the sirolimus policy can proceed.	The policy proposition has been amended. Under the monitoring section, the policy states that patients should have their clinical data submitted for audit as part of the Rare Disease Collaborative Networks (RDCN) so that the benefits and risks of sirolimus for this indication can be better assessed.

6. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

The following change(s) based on the engagement responses has (have) been made to the policy proposition:

- Policy proposition:
    - Patient pathway – the flowchart on page 6 has been amended so that it is clear that sirolimus should only be started after counselling patients about the treatment
    - Audit requirements – this section has been amended to include that centres part of the Rare Disease Collaborative Network should submit clinical data for audit
- PIA: the form was reviewed and it was added that symptoms were life-long

7. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

No.