Clinical Priorities Advisory Group Summary Report

Agenda item	4.2
Date of Meeting	11/05/-13/05/2026
Title of the Proposition	Sirolimus in extra-cranial slow flow vascular malformations refractory to standard therapies (all ages)
Unique Reference Number	2316
Programme of Care	Internal Medicine
Clinical Reference Group	Specialised surgery in children, vascular disease
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Sirolimus is recommended to be available as a routine commissioning treatment option for patients of all ages with slow flow vascular malformations refractory to standard therapies within the criteria set out in this document.

Slow-flow vascular malformations are inborn errors of formation of blood vessels (veins, lymphatics and capillaries) caused by genetic mutations. They can affect any organ system

Unique reference number: 2316

and over a patient's lifetime, these malformations can grow. This can cause compression and damage to surrounding structures. As a result, patients may suffer with debilitating symptoms and complications from pain, swelling and bleeding to organ failure, limb loss and death. Patients often have poor mental health and quality of life. Currently, treatment of slow-flow vascular malformations is limited to supportive (e.g. compression stockings), medical measures (e.g. pain medication) and surgery (e.g. excision and cryotherapy). These measures however are often not effective, and surgeries can be high-risk.

Sirolimus (also known as rapamycin) is an oral tablet that blocks a protein known as the mammalian target of rapamycin (mTOR). This protein regulates cell growth.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☐
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒
	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Group membership	☒
	Other (please state if required)	☐

3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).

Evidence Review Summary

In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the clinical effectiveness and safety of sirolimus compared with no sirolimus?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Disease response **Certainty of evidence:** Very low	This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total, one randomised trial, three single-arm trials and one prospective case series provided evidence relating to disease response in patients with extracranial slow-flow vascular malformations. Overall response was measured using a composite measure and presented as complete response (CR), [good response (GR)][1], partial response (PR), stable disease (SD) and progressive disease (PD). Treatment efficacy was indicated by a CR/GR/PR. The outcomes used to create this composite measure varied between studies. All results were compared to baseline. At six months: • One single-arm trial (Adams et al 2016, n=57) reported disease response following six courses[2] of treatment (168 days). No patients had a complete disease response, but 47 patients (83%, 95%CI 70% to 95%) reported a partial response to sirolimus treatment.[3] This result was *statistically significant*, demonstrating a benefit of sirolimus treatment. **(VERY LOW)** • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported that 79.1% of patients had a response to sirolimus (n=53) at six

[1] not presented in all studies
[2] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks.
[3] This composite measure was established by noting changes in at least 1 parameter: response by radiologic imaging, health quality-of-life questionnaire [Pediatric Quality of Live Inventory 4.0 (3-18 years) and Infant Scales (≤2 years) or the Functional Assessment of Chronic Illness System (>18 years)] or using defined clinical criteria in a functional impairment score (measures of organ function).

Outcome	Evidence statement
	months[4]. No patients were categorised as having a complete response and no statistical comparisons were reported. **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported that 72.2% of patients had a response to sirolimus (n=91).[5] No patients were reported to have a complete response; 4.0% had a good response and 68.3% had a partial response. No statistical comparisons were reported. **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=57) reported disease response following 12 courses[6] of treatment (336 days). No patients had a complete response, but 45 patients (85%, 95%CI 73% to 97%) had a partial response to sirolimus treatment. This result was *statistically significant*, demonstrating a benefit of sirolimus treatment. **(VERY LOW)** • One randomised trial (Maruani et al 2021, n=59) reported *no statistically significant change* in the volume of the vascular malformation following sirolimus treatment (-0.002mm^3; 95%CI -0.004mm^3 to 0.001mm^3; p=0.24) in children with complex slow-flow vascular malformations.[7] **(VERY LOW)** At 24 months: • One single-arm trial (Ji et al 2021, n=126) reported that 78.6% of patients had a response to sirolimus treatment (n=99). No patients had a complete response but 22.2% had a good response and 56.3% a partial response to sirolimus treatment. No statistical comparisons were reported. **(VERY LOW)** • One prospective case series (Tian et al 2020, n=56) reported that 30 children with lymphatic malformations had a complete or partial response to sirolimus therapy (n=2 CR; n=28 PR; 89%)[8]. Disease response was higher in those that had longer courses of sirolimus therapy; 1 to 6 months of sirolimus: 73.3% complete or partial response, 7 to 12 months: 93.8% complete or partial response, 13 to 24 months: 96% complete or partial response. These results were statistically significant when compared to those with stable disease or progressive disease. **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six months and 12 months of sirolimus treatment, a statistically significant higher proportion of patients were classed as having a**

[4] The composite measure was established by noting a change in at least 1 parameter: response to pain symptoms, health related quality of life (Paediatric Quality of Life Inventory / SF-36 / Physical Component Summary), clinical symptoms related to the vascular malformation – excluding pain, response to imaging (MRI)
[5] The response measure was based solely on changes in the volumetric measurements of VA lesions on MRI. CR = complete resolution of measured VAs at 12 months; GR = decrease of ≥75% but <100%; PR = decrease of ≥20% but <75%; SD = Increase of <20% but decrease of <20% in volumes of VA lesions; PD = Increase of ≥20% in volume of index LMs compared with baseline volume
[6] A course of treatment was equal to 28 days. Courses were taken consecutively with no break, thus six courses represented 168 days; 12 courses 336 days / 48 weeks of sirolimus treatment.
[7] difference in the volume of the vascular malformation between the observational period and the interventional period
[8] The composite measure was determined based on changes in the volumetric measurements of VA lesions on MRI, clinical changes in the lesion and/or changes in symptoms. CR = complete disappearance of either the lesion (clinical and/or radiological), and the symptoms; PR = reduction of >20% in size of the lesion (clinical and/or radiological) and improvement in symptoms; PD = enlargement of >20% in size of the lesion (clinical and/or radiological) or as new lesions appearing; SD = none of the above

Outcome	Evidence statement
	partial disease response compared to progressive disease or stable disease. One randomised trial found very low certainty evidence of no statistically significant disease response following oral sirolimus treatment in children with extracranial slow-flow vascular malformations. Two single-arm trials provided very low certainty evidence that following six months and 24 months of sirolimus treatment, a higher proportion of patients were classed as having a disease response compared to those having no response; the data were not statistically compared. One prospective case series found very low certainty evidence that in children with extracranial lymphatic malformations, disease response was statistically significantly higher following 13 to 24 months of sirolimus treatment when compared to those that received one to six months of sirolimus treatment. All results were compared to baseline data.
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients as individuals with extracranial slow-flow vascular malformations which have failed standard therapy as it can have life-threatening complications. Improved survival is an important marker of effective treatment. One single-arm trial provided narrative evidence relating to overall survival in children with extracranial slow-flow vascular malformations. Narrative data was provided from one paediatric single-arm trial. • One single-arm trial (Ji et al 2021, n=126) reported that two children died due to disease progression during follow-up (mean length of follow-up 3.0 years; range 0.4 to 4.5 years). **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a low mortality rate in children with extracranial vascular malformations treated with sirolimus during three years of follow-up.**
Symptom alleviation **Certainty of evidence:** Very low	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, one randomised trial and two single-arm trials provided evidence relating to symptom alleviation in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported that 37 (55.2%) patients had an improvement in their pain scores following six months of sirolimus therapy[9]. Following treatment with sirolimus, pain scores were *statistically significantly decreased* by a mean score of -1.8 (95%CI -2.8 to -0.8; p<0.001). **(VERY LOW)** At 12 months: • One single-arm trial (Ji et al 2021, n=126) reported a *statistically significant decrease* in functional disability[10] following six months (baseline: 2.6, six months: 2.0; p<0.001) and 12 months (six months: 2.0, 12 months: 1.3; p<0.001) of sirolimus treatment. **(VERY LOW)**

[9] Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults

[10] Disease severity was recorded using a scale of 0 to 5 with higher values representing more profound symptoms and/or functional disability

Outcome	Evidence statement
	• One randomised trial (Maruani et al 2021, n=59) reported that pain[11] decreased for all children following sirolimus treatment (mean±SD – start of sirolimus treatment: 3.49±3.23 to end of trial: 1.76±2.29). No statistical comparisons were reported. **(VERY LOW)** • The same trial (Maruani et al 2021, n=59) also reported a decrease in the overall number of children oozing or bleeding from their malformations following sirolimus therapy (start of sirolimus therapy: 33.9%, 12 months: 13.6%). No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a statistically significant improvement in pain scores for patients with extracranial slow-flow vascular malformations following sirolimus therapy. A randomised trial provided very low certainty evidence that pain and bleeding / oozing decreased for all children following sirolimus therapy; the before and after effects were not compared statistically. Finally, another single-arm trial provided very low certainty evidence of a statistically significant decrease in functional disability in children following 12 months of sirolimus treatment. All results were compared to baseline.**
Important outcomes	
Radiographic changes **Certainty of evidence:** Very low	Changes to the appearance of scans or the location of malformations are important to patients as they are used to help determine treatment success and requirement for further treatment. Imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features. One randomised trial and two single-arm trials provided evidence relating to radiographic changes in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=62) reported that 39 (62.9%) patients had no change in the volume, 22 (35.5%) had decreased volume and one patient (1.6%) had an increased volume in their extracranial vascular anomaly following six months of sirolimus therapy. The differences were not statistically compared. **(VERY LOW)** • One single-arm trial (Adams et al 2016, n=57) reported that following six courses of sirolimus treatment (168 days) there was *no statistically significant* MRI response to treatment; 20 (35%) children and adults had partial response on MRI (95%CI 20% to 51%) and 36 (63%) reported stable disease (95%CI 47% to 79%). **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=53) reported that following 12 courses of sirolimus treatment (336 days) there continued to be *no statistically significant difference* in the MRI response to treatment; 28 (52%) of children and adults had partial response on MRI (95%CI 36% to 69%) and 25 (48%) reported stable disease (95%CI 31% to 64%). No patients reported complete resolution or disease progression at this timepoint **(VERY LOW)**

[11] Pain was self-assessed using a visual analogue scale 0 – 10, where 0 means no pain and 10 signifies the worst pain imaginable

Outcome	Evidence statement
	• One randomised trial (Maruani et al 2021, n=59) reported a small decrease in the median volume of the extracranial vascular malformation following sirolimus treatment (start of sirolimus treatment: 158mm^3 (IQR 48 to 510); end of trial: 151mm^3 (IQR 31 to 420)). No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six months of sirolimus therapy a higher proportion of patients had no change to the volume of their extracranial vascular malformation on MRI measurements compared to either an increased or decreased volume; the data were not statistically compared. A second single-arm trial provided very low certainty evidence of no statistically significant change in the volume of the vascular malformation on MRI following six and 12 courses of oral sirolimus treatment; following 12 courses of sirolimus treatment all patients had either no increase or a reduction in the volume of their vascular malformation (not statistically significant). A randomised trial provided very low certainty evidence of a small decrease in the volume of the extracranial vascular malformation following 12 months sirolimus treatment; the data were not statistically compared. All results were compared to baseline.**
Organ specific disease response **Certainty of evidence:** Very low	This outcome is important to patients as objective measures of functioning of affected organs. Disease activity results might not be expected to return to normal following treatment; however, stabilisation may indicate treatment has successfully limited disease progression. In total, one randomised trial and one single-arm trial provided evidence relating to organ specific disease response in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. *Functional impairment score*[12] • One single-arm trial (Adams et al 2016, n=57) piloted a new functional impairment score which measured improvements in target organ dysfunction using previously validated instruments. The authors reported that adults and children were *statistically significantly more likely* to report an organ response than no organ response following both six courses and 12 courses of sirolimus therapy (n (%, 95%CI)), at six months: PR 40 (71%, 95%CI 56% to 85%); SD: 17 (29%, 95%CI 15% to 44%); at 12 months: PR 42 (80%, 95%CI 67% to 94%); SD n=11 (16%, 95%CI 4% to 28%).[13] **(VERY LOW)** *Skin and subcutaneous disease activity: Global assessment by physician, patient and parent* • One randomised trial (Maruani et al 2021, n=59) used the global assessment of efficacy[14] as a marker of skin disease activity. Skin malformations were assessed using the VAS scale by physician, patient and parent at one month following sirolimus initiation, three months post-sirolimus initiation and at the final 12 month visit (visit three to visit 12 months, physician assessment: 2.64±2.56 to

[12] The functional impairment score was adopted from the measures of organ function that have been validated in the quantification of adverse event results from medical therapies and procedures. The instrument was piloted in the present study. Changes were defined as - CR: no evidence of organ dysfunction due to disease; PR: improvement in target organ dysfunction by at least 1 grade; PD: worsening in target organ dysfunction by at least 1 grade; SD: no change in target organ dysfunction

[13] Each sirolimus course lasted 28 days.

[14] Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient.

Outcome	Evidence statement
	4.85±2.58; patient assessment: 4.04±3.52 to 5.95±3.18; parent assessment: 3.24±2.81 to 5.32±2.77. All assessors found a *statistically significant increase* in skin and subcutaneous disease resolution following the introduction of sirolimus (p<0.001). **(VERY LOW)** **One single-arm trial provided very low certainty evidence that following six and 12 courses of sirolimus therapy, patients were statistically significantly more likely to report an organ response than no organ response. One randomised trial provided very low certainty evidence of a statistically significant improvement in skin and subcutaneous disease resolution using a physician, patient and parent visual analogue scale in children treated with sirolimus. All results were compared to baseline.**
Quality of life **Certainty of evidence:** Very low	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making. One randomised trial and three single-arm trials provided evidence relating to quality of life in patients with extracranial slow-flow vascular malformations. All results were compared to baseline. At six months: • One single-arm trial (Harbers, Zwerink et al 2023, n=44) reported that 65.9% (n=29) patients had an improved quality of life following six months of sirolimus therapy. No statistical comparisons were reported. **(VERY LOW)** • One single arm trial (Harbers, Bouwman et al 2023, n=44) reported participants' health related quality of life[15] before and after six months of sirolimus treatment. The HRQoL scores in the trial were compared to that of the general Dutch population, For adults, the authors reported that the quality of life scores for all domains except mental health were statistically significantly worse in patients with an extracranial slow-flow vascular malformation compared to the general Dutch population, whereas after six months of sirolimus treatment, there was no statistically significant difference in the quality of life scores between adults with an extracranial slow-flow vascular malformation diagnosis and the general Dutch population in the domains of social functioning, role limitations – emotional, mental health and energy levels/vitality. For the domains of physical functioning, role limitations – physical, pain and general health perception the study population continued to have *statistically significantly worse* HRQoL scores than the general Dutch population. **(VERY LOW)** • One single-arm trial (Adams et al 2016, n=57) reported that following six courses of sirolimus treatment (168 days) there was an increase in quality of life of the children and adults included in the trial;[16] 18 (32%) children and adults had complete response

[15] HRQoL was assessed by Research and Development-36 (SF-36) for adults, the parents' version of the Paediatric Quality of Life Inventory 4.0 Generic Core Scales for the parents of children aged 2–17 years and the children's PedsQL version for children aged 5–17 years. For all HRQoL measures a higher score indicates a better QoL.

[16] Quality-of-Life (QoL) changes were measured as CR: normalisation of QoL criteria; PR: improvement of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with baseline; PD: worsening of self-report PedsQL by >4.4 or proxy-report PedsQL by >4.5 or FACT-G by >3.99 compared with

Outcome	Evidence statement
	(95%CI 17% to 47%), 30 (52%) had a partial response (95%CI 36% to 68%) and nine (16%) reported stable disease (95%CI 4% to 28%). No statistical comparisons were reported. **(VERY LOW)** At 12 months: • One single-arm trial (Adams et al 2016, n=53) reported that following 12 courses of sirolimus treatment (366 days) there was an increase in quality of life of the children and adults included in the trial; 21 (39%) children and adults had complete response (95%CI 22% to 55%), 26 (50%) had a partial response (95%CI 34% to 67%), five (9%) reported stable disease (95%CI 0% to 19%) and one patient (2%) reported progressive disease (95%CIs not reported). No statistical comparisons were reported. **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported that the majority of children (n=100, 79.4%) had an improvement in their quality of life scores from baseline following 12 months of sirolimus treatment; 18 children reported a worsening in their HRQoL from baseline (14.3%). No statistical comparisons were reported. **(VERY LOW)** • One randomised trial (Maruani et al 2021, n=59) reported that the number of children reporting that their vascular malformation had "no effect on their life" increased from 16 patients (27.1%) at start of sirolimus treatment to 32 (54.2%) following sirolimus treatment. No statistical comparisons were reported. **(VERY LOW)** **One single-arm trial provided very low certainty evidence of a statistically significant increase in the quality of life scores for both children and adults following six months of oral sirolimus treatment. For adults, before sirolimus treatment, the quality of life scores for all domains except mental health were statistically significantly worse in the study population compared to the general Dutch population; whereas after six months of sirolimus treatment, the quality of life scores for the domains of social functioning, role limitations – emotional, mental health and energy levels/vitality were not statistically significantly different in the study population compared to the general Dutch population. One single-arm trial reported very low certainty evidence of an increase in quality of life scores following six and 12 courses of sirolimus treatment. One randomised trial and one single-arm trial provided very low certainty evidence of improvements in quality of life scores following sirolimus treatment at 12 months follow-up. All results were compared to baseline.**
Activities of daily living (ADLs) **Certainty of evidence:** N/A	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. The complications of slow-flow vascular malformations can lead to progressively worsening physical symptoms and altered ability to complete ADLs without assistance. **No evidence was identified for activities of daily living.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety of sirolimus is important to patients as it allows comparison of interventional approaches. One randomised trial, three single-arm trials and one prospective case series provided evidence relating to adverse events in patients with extracranial slow-flow vascular malformations.

baseline; SD: ≤4.4 change in self-report of PedsQL or ≤4.5 change in proxy-report PedsQL or ≤3.99 change in FACT-G compared with baseline

Outcome	Evidence statement
	Number of adverse events (AEs) • One single-arm trial (Harbers, Zwerink et al 2023) reported a total of 276 adverse events in 67 patients over a six month period; seven AEs were categorised as serious AEs of which three were deemed attributable to sirolimus. **(VERY LOW)** • One single-arm trial (Adams et al 2016) reported two AEs leading to a sirolimus dose reduction and two AEs leading to drug discontinuation out of 60 patients. **(VERY LOW)** • One single-arm trial (Ji et al 2021) reported a total of 290 AEs in 126 patients during 12 months of sirolimus treatment. Patients were reported to have 23 Grade 3 AEs and 4 Grade 4 AEs. Twelve adverse events led to temporary sirolimus discontinuation, and seven AEs led to a reduction in the target serum level. **(VERY LOW)** • One randomised trial (Maruani et al 2021) reported 43 of 59 patients experiencing one of 101 nonserious adverse events possibly related to sirolimus (73%). Patients experiencing nonserious adverse events had a median age of 14 (IQR 11 to 17). The authors reported 5 of 59 patients experienced a serious AE possibly related to sirolimus (5%; 5 events; median age 15, IQR 10 to 19). The authors further reported AEs probably related to sirolimus, including 35 patients reporting 89 nonserious AE events with no serious AEs (median age 12, IQR 8 to 14). **(VERY LOW)** • One prospective case series (Tian et al 2020) reported a total of 37 AEs in their cohort of 56 children, three of which were serious AEs. **(VERY LOW)** *Specific AEs* • One single-arm trial (Harbers, Zwerink et al 2023, n=67) reported the most common AEs possibly, probably or definitely related to sirolimus were infection (n=13), neurologic toxicity (n=11), gastrointestinal toxicity (n=10), general symptoms (n=7) and metabolic toxicity (n=10). One Grade 4 AE was noted, Infection, and rated as being “possibly” related to sirolimus treatment. **(VERY LOW)** • One single-arm trial (Adams et al 2016, n=60) reported the most common AEs to be blood/bone marrow (n=30), gastrointestinal (n=33), metabolic/laboratory (n=12) and pain (n=11). Grade 3/4 AEs were most likely to be blood/bone marrow (n=30), gastrointestinal (n=10), infection (n=22), metabolic/laboratory (n=11) and pulmonary/upper respiratory (n=7). **(VERY LOW)** • One single-arm trial (Ji et al 2021, n=126) reported the most common AEs to be mucositis (n=47), upper respiratory infection (n=33), nausea/vomiting (n=27), increased liver enzyme levels(n=25) and thrombocytosis (n=25). Grade 3/4 AEs were most likely to be upper respiratory infections (n=8) and increased liver enzyme levels (n=6). **(VERY LOW)** • One prospective case series (Tian et al 2020, n=56) reported the most common AEs in their paediatric population with lymphatic malformations to be oral mucositis (n=17), upper respiratory infection (n=6), pneumonia (n=4), cystic haemorrhage (n=4) and rash (n=3). Severe AEs were reported for oral mucositis (n=1) and pneumonia (n=2); the two children with pneumonia were treated in ITU and required temporary sirolimus discontinuation. **(VERY LOW)**

Outcome	Evidence statement
	All five included studies provide very low certainty evidence that many patients with extracranial slow-flow vascular malformations reported adverse events during sirolimus treatment; however, most were not severe. The most common adverse events reported across the included studies were infections, particularly respiratory, and mucositis.
Abbreviations AE: adverse event; C-DLQI: Children-Dermatological Life Quality Index; CI: confidence interval; CR: complete response; FACT-G: Functional Assessment of Cancer Therapy – General; GR: good response; HRQoL: health related quality of life; IQR: interquartile range; ISSVA: International Society for the Study of Vascular Anomalies; ITU: intensive therapy unit; LM: lymphatic malformation; MCS: mental component summary; mL: millilitres; MRI: magnetic resonance imaging; n: number; ng: nanograms; NRS: numeric rating scale; PCS: physical component summary; PD: progressive disease; PedsQL: Paediatric Quality of Life Inventory; PR: partial response; QoL: quality of life; RAND-36: Research and Development-36; SD: stable disease; SD: standard deviation; SF-36: Short Form 36; TNO-AZL: Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek van het Academisch Ziekenhuis in Leiden Preschool Children; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation	

In people with extracranial slow-flow vascular malformations that are refractory to standard therapies, what is the cost effectiveness of sirolimus compared with no sirolimus?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from sirolimus more than the wider population of interest?

Outcome	Evidence statement
Slow-flow malformation type (venous, lymphatic and venolymphatic)	One randomised trial reported subgroup results by slow-flow malformation type (venous, lymphatic and venolymphatic) for the critical outcomes, disease response and symptom alleviation, and for the important outcomes, radiographic changes, organ specific disease response and quality of life. All results were compared to baseline. **Critical Outcomes** **Disease response** • One randomised trial (Maruani et al 2021; venous: n=22, lymphatic: n=18, venolymphatic: n=19) reported a *statistically significant decrease* in the volume of the extracranial lymphatic malformations following sirolimus treatment (LM, n=17, -0.004; 95%CI -0.006 to -0.002; p<0.001). The authors reported, however, *no statistically significant change* in the volume of extracranial venous malformations or extracranial venolymphatic malformations following sirolimus treatment (VM: p=0.24; combined: p=0.70). **Symptom alleviation** • One randomised trial (Maruani et al 2021) reported lower pain scores following sirolimus treatment across all extracranial vascular malformation types; this was most pronounced in those with lymphatic malformations (mean±SD – start of sirolimus treatment to end of trial; venous malformations: 3.24±3.03 to 2.40±2.39; lymphatic malformations: 2.21±2.98 to 0.58±1.25; venolymphatic malformations: 5.08±3.18 to 2.14±2.61; total: 3.49±3.23 to 1.76±2.29). No statistical comparisons were reported.

	• One randomised trial (Maruani et al 2021) reported less bleeding and oozing for those with extracranial lymphatic and extracranial venolymphatic malformations following sirolimus treatment; there was a small increase in the number of patients with bleeding and/oozing in those with extracranial venous malformations (venous malformations: baseline: 0%, 12 months: 9.1%; lymphatic malformations: baseline: 44.4%, 12 months: 22.2%; venolymphatic malformations: baseline: 52.6%, 12 months: 10.5%). No statistical comparisons were reported. **Important Outcomes** **Radiographic changes** • One randomised trial (Maruani et al 2021) reported a decreasing volume of extracranial lymphatic and extracranial venolymphatic malformations following sirolimus treatment but an increasing volume of extracranial venous malformations (venous malformations: baseline: 128, IQR 24 to 276, 12 months: 135, IQR 23 to 311; lymphatic malformations: baseline: 173, IQR 47 to 343, 12 months: 145, IQR 17 to 373; venolymphatic malformations: baseline: 189, IQR 79 to 832, 12 months: 151, IQR 49 to 800;). No statistical comparisons were reported. **Organ specific disease response** *Skin and subcutaneous disease activity* • One randomised trial (Maruani et al 2021) used the global assessment of efficacy[17] as a marker of skin disease activity. Skin malformations were assessed using the VAS scale by physician, patient and parent at one month following sirolimus initiation, three months post-sirolimus initiation and at the final 12 month visit (Physician assessment, visit three to 12 months; venous malformations: 1.77±2.05 to 4.60±2.16; lymphatic malformations: 3.64±2.82 to 5.08±2.75; venolymphatic malformations: 2.94±2.70 to 5.00±3.14). A *statistically significant increase* in the VAS score was noted by the physician, patient and parent for extracranial venous malformations, extracranial lymphatic malformations and extracranial venolymphatic malformations following sirolimus treatment ($p<0.001$). **Quality of Life (QoL)** • One randomised trial (Maruani et al 2021) reported that the number of children reporting that their vascular malformation had “no effect on their life” increased for each vascular malformation type following sirolimus treatment (venous malformations: baseline: 18.2%, 12 months: 45.5%; lymphatic malformations: baseline: 55.6%, 12 months: 77.8%; venolymphatic malformations: baseline: 10.5%, 12 months: 42.1%); no statistical comparisons were reported. **One randomised trial reported outcomes for patients treated with sirolimus by extracranial slow-flow vascular malformation type: venous malformations, lymphatic malformations and venolymphatic malformations; a**ll results were compared to baseline**. The authors reported a statistically significant decrease in the volume of the lymphatic malformations following sirolimus treatment but no statistically significant effect of sirolimus on venous or venolymphatic malformations. Pain symptoms were alleviated across all three malformation types, though the score decreases were most pronounced in those with lymphatic malformations. Bleeding and oozing were decreased in those with lymphatic and venolymphatic malformations and slightly increased in those with venous malformations. MRI changes were noted for each of the malformation types following sirolimus treatment; increasing volume for venous malformations and decreasing volume for lymphatic and venolymphatic**

[17] Score was assessed using a visual analogue scale at each visit (0=no efficacy; 10=complete resolution) by the physician, parent and patient

	malformations. Quality of life and skin disease activity were reported to improve across all disease malformation types.
Age Group (Children and Adults)	One single-arm trial reported subgroup results by age group (children and adults) for the critical outcomes, disease response and symptom alleviation, and the important outcomes, radiographic changes, organ specific disease response, quality of life and safety. All results were compared to baseline. **Critical Outcomes** **Disease response** • One single-arm trial (Harbers, Zwerink et al 2023) reported 30/32 children with extracranial slow-flow vascular malformations (93.8%) had a partial response and 2/32 (6.3%) reported stable disease following six months of sirolimus treatment. No children reported a complete response or progressive disease. The adults in the study had a lower disease response rate with 23/35 (65.7%) reporting partial response, 9/35 (25.7%) stable disease and 3/35 (8.6%) progressive disease. No adults had a complete response. The groups were not statistically compared. **Symptom alleviation** • One single-arm trial (Harbers, Zwerink et al 2023) reported *statistically significantly lower* pain scores for adults with extracranial slow-flow vascular anomalies following sirolimus treatment (EMM[18] difference: -1.9, 95%CI -3.2 to -0.5, p<0.001); when examining children separately, *no statistically significant difference* on pain scores before and after sirolimus treatment was found (EMM difference: -1.5, 95%CI -3.1 to 0.08, p>0.05).[19] When reporting symptoms other than pain, 22/35 (62.9%) of adults and 28/32 (87.5%) of children reported an improvement in symptoms following six months of sirolimus treatment. No statistical comparisons were reported for this measure. **Important Outcomes** **Radiographic changes** • One single-arm trial (Harbers, Zwerink et al 2023; n=31 children, n=31 adults) reported that the majority of both children and adults had either no change in the volume or a decreasing volume of their extracranial slow-flow vascular malformations following six months of sirolimus treatment (n, %; children: no change – 19, 61.3%, decreased volume – 12, 38.7%, increased volume – 0, 0%; adults: no change – 20, 64.5%, decreased volume – 10, 32.3%, increased volume – 1, 3.2%). The groups were not statistically compared. **Organ specific disease response** *Hepatic (liver) disease activity: D-dimer level* • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported a decrease in D-dimer levels following six months of sirolimus therapy in both adults and children (children - baseline: 1345 ng/mL (95% CI 620 to 2770); six months: 1070 ng/mL (95%CI 860 to 2580); adults - baseline: 1315 ng/mL (95%CI 820 to 2300); six months: 1030 ng/mL (95%CI 600 to 2280). The results were *not statistically significant*. **Quality of Life (QoL)** • One single-arm trial (Harbers, Zwerink et al 2023) reported that a large majority of (15/18, 83.3%) children had improved quality of life following six months of sirolimus treatment; 3/18 (16.7%) had no change in their quality of life and no children reported a worsening in their quality of life. In adults, 14/26 (53.3%) reported improved quality of life, 8/26 (30.8%) reported no

[18] EMM: estimated marginal mean
[19] Pain was recorded using the Children and Infants Postoperative Pain Scale for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years and numeric pain rating scale (NRS) for adults.

	change and 4/26 (15.4%) reported worsening quality of life. The results were not statistically compared. • One single arm trial (Harbers, Bouwman et al 2023) detailed participants' health related quality of life before and after six months of sirolimus treatment. Both children (n=18) and adults (n=26) had a statistically significant increase in their quality of life following sirolimus treatment (child reported: +9.9, p<0.05; parent reported: +10.9, p<0.05; adult MCS score: +3.6, p<0.005; adult PCS score: +6.2, p<0.005). **Safety** • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported all adverse events in both children and adults. The adults had proportionally more adverse events than the children (64.1% vs 35.9%) but the distribution of the adverse events between the AE Grades was similar between the two age groups (children – Grade 1: 72.7%, Grade 2: 22.2%, Grade 3: 4.0%, Grade 4: 1.0%; adults – Grade 1: 73.4%, Grade 2: 25.4%, Grade 3: 1.1%, Grade 4: 0%). • One single-arm trial (Harbers, Zwerink et al 2023, children: n=32; adults: n=35) reported serious adverse events that were suspected to be related to sirolimus. No adults reported serious adverse events, whilst three serious adverse events were reported in children. **One single-arm trial reported outcomes for patients with extracranial slow-flow vascular malformations treated with six months of sirolimus by age group: children and adults; all results were compared to baseline. The authors reported a better disease response in children compared with adults; however, the groups were not statistically compared. Pain symptoms were statistically significantly lower for adults following sirolimus treatment, but no statistically significant difference was seen for children. Symptoms other than pain were alleviated for both children and adults, though the decreases were most pronounced in children. The changes were not statistically compared. The majority of both children and adults had either no change in the volume or a decreasing volume of their extracranial slow-flow vascular malformations on MRI; no statistical analysis was performed. Liver function and quality of life were both reported to improve for children and adults. More adverse events were reported in the adult population but there were fewer severe adverse events in this population.**
Abbreviations **EMM: estimated marginal mean; IQR: interquartile range; LM: lymphatic malformation; mL: millilitres; MRI: magnetic resonance imaging; n: number; ng: nanograms; NRS: numeric rating scale; QoL: quality of life; VA: vascular anomalies; VAS: visual analogue scale; VM: venous malformation**	

From the evidence selected what were the ongoing schedules/doses used for sirolimus?

Outcome	Evidence statement
Sirolimus dose	Evidence about sirolimus doses came from one randomised trial, three single-arm trials and one prospective case series. • Two single-arm trials (Adams et al 2016 and Ji et al 2016) and one prospective case series (Tian et al 2020) used pharmacokinetically guided dosing when treating children with complicated vascular anomalies. A starting sirolimus dose of 0.8 mg/m^2, twice daily, was used and increased until plasma levels reached between 10 and 15 ng/mL. • One single-arm trial (Adams et al 2016) used the same protocol for treating young adults with complicated vascular anomalies; starting dose of 0.8 mg/m^2, twice daily, and increased until plasma levels reached between 10 and 15 ng/mL.

	• One single-arm trial (Harbers, Zwerink et al 2023) also began with a paediatric sirolimus dose of 0.8 mg/m^2, twice daily, and an adult dose of 1mg, twice daily. Dose adjustments were made until plasma levels reached between 4 and 10 ng/mL. • Maruani et al 2021 began their paediatric patients with slow-flow vascular malformations on a starting sirolimus dose of 0.08 mg/kg/d dose, twice daily and increased until plasma levels reached between 4 and 12 ng/mL at day 15. **One randomised trial, three single-arm trials and one prospective case series started every paediatric patient with vascular malformations on an initial sirolimus dose of 0.8 mg/m^2, twice daily. Dose adjustments were made until the desired plasma levels were reached; in two single-arm trials and the prospective case series this was between 10 and 15 ng/mL, in one randomised trial it was between 4 and 10 ng/mL, and in one single-arm trial it was between 4 and 12 ng/mL. One single-arm trial started adults on a twice daily 0.8 mg/m^2 sirolimus dose and increased until plasma concentrations reached 10 to 15 ng/mL, whilst another single-arm trial began all >18 years on a 1 mg sirolimus dose, twice daily, with increases until plasma concentrations reached between 4 and 10 ng/mL.**
Abbreviations **kg: kilogram; m: metres; mg: milligrams; mL: millilitres; ng: nanogram**	

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have severe problems in walking about
- **ability to provide self-care:** Patients have severe problems in washing or dressing
- **undertaking usual activities:** Patients unable to do their daily activities
- **experience of pain/discomfort:** Patients have severe pain or discomfort
- **experience of anxiety/depression:** Patients may be extremely anxious or depressed

Further details of impact upon patients:
The patient group included in this policy proposition are the most severely affected and symptomatic patients, therefore the impacts on their life will be at the most severe end of the spectrum. Patients may experience debilitating, life-long symptoms and complications including pain, swelling, ulceration, bleeding, blood clots, infection, organ failure, limb loss, and death. Symptoms and complications can be challenging to manage, leading to exclusion from normal family, social and work life, with potentially significant financial impact. There is a significant impact on quality of life and mental health and well-being. Social exclusion and low mood are frequently reported.

Further details of impact upon carers:
The impact of the disease and the treatment required is debilitating for patients. Carers are required to perform and support nearly all aspects of the patient's life, from personal care to transport to and support at frequent hospital visits and stays. The caring role is full time and impacts on the carer's social and work life, and carers can become socially excluded and anxious in the same way as patients.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	No specific risk factors were identified for extracranial slow-flow vascular malformations. It was noted that these vascular malformations can occur at all ages and equally in both sexes. A policy proposition for sirolimus for refractory malformations is anticipated to offer an improvement in the outcomes of these patients. There are no anticipated adverse impacts of commissioning sirolimus for this population.
13Q Assessment	
PPVAG outcome	No consultation required
Were PPVAG assured of the level of stakeholder testing?	Yes
Rare Disease Advisory Group	
Not Applicable	
Pharmaceutical	
Yes The Clinical Commissioning Policy Proposition recommends the use of sirolimus as a treatment option for people with extracranial slow-flow vascular malformations refractory to standard therapies. This recommendation is outside the marketing authorisation for sirolimus, so use is off-label. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined in the policy proposition documentation. Sirolimus is included on the NHS Payment Scheme Annex A, so is a high-cost drug.	
National Programme of Care	
The proposal received the full support from the Internal Medicine National Programme of Care.	