Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

Medicine details	
Name, brand name	Sildenafil
Manufacturer	Generic manufacturers: Pfizer Ltd, Sigma Pharmaceuticals, Aurobindo Pharma – MilPharm Ltd, Accord, Actavis, Dr Reddy's
Proposed indication	1. Raynaud's Phenomenon (RP) secondary to systemic sclerosis 2. Severe Primary RP
Requested by	SASH Rheumatology Department and Rheumatology Network.

SUMMARY

Clinical Effectiveness

There are a limited number of trials that have looked into sildenafil as a treatment option for RP, and there have been no trials that directly compare sildenafil with IV iloprost for RP. The results available showed promise that sildenafil improves the frequency and duration of Raynaud's attacks, improves Raynaud's condition score and improves finger blood flow when compared to placebo. The number of patients in the trials reviewed is small which limits the significance of the results.

Secondary RP:
A NICE evidence summary from 2015[1] on the use of sildenafil with digital ulcers in association with systemic sclerosis has been included and referred to in this application. That summary reviewed the relevant evidence available for sildenafil use in RP and should be taken into consideration. Although the focus is on its use on digital ulcers the evidence reviewed within the summary was not limited to digital ulceration. The evidence also included Raynaud's specific end points such as Raynaud's condition score, attack frequency and attack duration.

Two additional RCTs and one meta-analysis were found in addition to this evidence summary and are included in the evidence section of this application[2-4].

For patients with digital ulceration in systemic sclerosis there is an NHS England Clinical Commissioning policy that states the sildenafil should be used prior to IV iloprost[5]. This is also supported by the British Society of Rheumatology (BSR) and European League Against Rheumatism (EULAR) with the strength of the recommendation graded as A[6-7].

In terms of patients without digital ulcers, EULAR recommends that PDE-5 inhibitors (e.g. sildenafil) should be used after calcium channel blockers (CCB) and before IV iloprost (strength of recommendation; A)[7]. BSR does not make a specific recommendation but does state that PDE-5 inhibitors are being increasingly used (level of evidence; IIa, strength of recommendation; C)[6].

Primary RP:
There is very little evidence with regards to primary RP with only 2 patients included in one of the trials meaning that no statistical significance could be drawn but the results were supportive of the use of sildenafil[8]. It is felt that despite the lack of evidence, offering sildenafil to these patients as a possible alternative may still be beneficial due to the

significant impact on the patient, the secondary care providers as well as the CCG who burden the cost of IV iloprost. IV iloprost would still be a treatment option so if sildenafil did not provide the desired outcomes then the patient could then receive iloprost.

It is expected that sildenafil will improve the quality of life as discussed in the below section 'patient factors'. Sildenafil is not replacing IV iloprost, which will remain a treatment option, but is an additional option prior to it. The aim is to avoid or delay the use of iloprost.

Safety

SPC on licensed products provides information with regards to cautions, contraindications, interactions and adverse effects.
The main thing to monitor is blood pressure, with a possible adverse effect of hypotension. Hypotension may affect the tolerance of sildenafil and subsequent titration.

Patient factors

Introducing sildenafil into the RP pathway would be a beneficial alternative to patients. It can be monitored in primary care once initiated, and it also offers them an oral treatment that does not require numerous day case admissions for infusions as is the case with IV iloprost. It would be more acceptable to the patient due to not requiring up to 5 consecutive days of infusions and should also reduce the time off from work these patients require to attend such infusions. Moreover, iloprost has been reported to wear off between infusions, whereas taking sildenafil consistently should maintain patients' symptoms.

Sildenafil does not remove IV iloprost from the pathway so it does remain an alternative option. The aim is to avoid or delay the use of iloprost and use it as a last resort.

Cost implications

	Estimate cost for 28 days	**Estimated annual cost**
Generic sildenafil (Drug Tariff September 2020)	£21-£24.15	£273-£313.95
Revatio® brand (Drug Tariff September 2020)	£446.33	£5802.29
Iloprost (Colonis Pharma Ltd)	£360 per 5 day treatment cycle	£720-£1440 depending on number of cycles*

*At SASH, patients can receive 2-4 series of infusions of iloprost per year depending on the severity of their RP, as well as whether it responds to warmer weather. After speaking to the rheumatology team, most patients receive 4 series of infusions per year.

This means that the annual cost of iloprost per patient can range from £720 - £1440 for the drug alone, plus the additional associated hospital costs such as appointment and infusion costs.

Currently the trust is on a block contract, but when this reverts back to cost per case the associated hospital costs are around £450 per day, equivalent to £2250 per treatment cycle with an estimated annual cost of £4500 - £9000.

This equates to an estimated total cost for iloprost of £5220-£10,440 annually per patient.

In addition, there are still some patients who are yet to be changed over from epoprostenol (unlicensed indication) to iloprost.

From March 2019 - April 2020 inclusive, the following are the costs of iloprost.

Trust	CCG	Cost of iloprost (drug only)
Frimley Park Hospital	Guildford and Waverly CCG	£720.00
	Surrey Heath CCG	£1, 872.00
SASH	East Surrey CCG	£1. 685.40
Total		**£4, 277.40**

Relevant guidance / reviews

Secondary RP:
The following recommendations have been used to guide this application:

- NHS England Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis[5].
- BSR and BHPR guideline for the treatment of systemic sclerosis[6].
- Update of EULAR recommendations for the treatment of systemic sclerosis[7].
- NICE evidence summary on the use of sildenafil in digital ulcers[1].

The summary of these guidelines is to use sildenafil in severe RP secondary to systemic sclerosis following initial standard treatment with vasodilators including CCB, ACEi, ARBs or fluoxetine. This is in patients with or without digital ulcers. Sildenafil should also be used prior to the use of IV iloprost.

The choice of initial vasodilators varies between guidelines with only CCB being consistently first line treatment. ACEi are recommended in NHSE Commissioning Policy but are not recommended in either the BSR or EULAR guidelines for RP. Fluoxetine is also mentioned in the NHSE Commissioning Policy but the evidence for its use is not as strong with the EULAR guidelines stating that the strength of its recommendation was C.

Brighton APC has already approved the use of sildenafil for RP associated with scleroderma in adults under a blue recommendation for shared care in response to the NHS England Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis.

Primary RP:
There is no guidance or reviews for treating primary RP apart from NICE CKS which states that after trying nifedipine they should be referred to secondary care[9].

Likely place in therapy relative to current treatments

To offer sildenafil prior to the use of IV iloprost in patients with severe RP, either secondary to systemic sclerosis, or primary RP, after initial vasodilator therapy has been tried. For specifics regarding patient suitability see the section ‘Other considerations’ in ‘Medicine details.’

The use of sildenafil prior to IV iloprost follows the recommendations laid out in the British Rheumatology (BSR and BHPR) guidelines as well as the European (EULAR) guidelines[6-7].

Sildenafil is suitable for shared care following initiation by a specialist.

Recommendation to APC

RP secondary to systemic sclerosis, or primary RP with a blue recommendation.

Brighton APC has given us permission to use and adapt their information sheet.

Medicine details	
Name and brand name	Sildenafil – available as generic. Brands available include Anorix, Grandipam, Mysildecard, Revatio, Nipatra, Viagra and Vizarsin.
Licensed indication, formulation and usual dosage	Generics and some brands (Anorix, Nipatra, Viagra, Vizarsin) are licensed for erectile dysfunction in men (25-100mg when required). Other brands (Grandipam, Mysildecard, Revatio) are licensed for pulmonary hypertension in adults and children (20mg TDS). Proposed dosage for RP is sildenafil 25mg – 50mg tds No sildenafil product is licensed for RP so its use would be regarded as 'off-label'.
Summary of mechanism of action, and relevant pharmacokinetics	Potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) -specific phosphodiesterase type 5. Therefore, inhibits the breakdown of cGMP – this elicits smooth muscle relaxation and vasodilatation in the systemic circulation, increasing blood flow in the extremities.
Important drug interactions	**See SPC for sildenafil for full details. Available at: https://www.medicines.org.uk/emc** **Alpha-blockers** – caution. In susceptible individuals may lead to symptomatic hypotension, most likely to occur within 4 hours post-sildenafil dosing **Clarithromycin** – caution. Increases serum concentrations of sildenafil. Reduce dose of sildenafil if hypotension symptoms develop **Erythromycin** – caution. Increases serum concentrations of sildenafil. Reduce dose of sildenafil if hypotension symptoms develop **Grapefruit juice** – avoid. May increase serum concentrations of sildenafil **Itraconazole** – avoid. Increases serum concentrations of sildenafil. Consider dose reduction if unavoidable **Ketoconazole** – avoid. Increases serum concentrations of sildenafil. Consider dose reduction if unavoidable **Nicorandil** – avoid. Potentiates the hypotensive effects of nicorandil **Riociguat** – contraindicated. Augments systemic hypotensive effects of sildenafil **Ritonavir** – avoid. Substantially increases serum concentrations of sildenafil **Nitrates** – avoid. Increased risks of hypotensive effects **Saquinavir** - avoid. Substantially increases serum concentrations of sildenafil **Pulmonary artery hypotension drugs** – caution. Potentiation likely
Monitoring requirements	Blood pressure. Symptom control and quality of life - frequency and severity of Raynaud's phenomenon attacks. Side effects as per SPC. Most common adverse effects include headache, dizziness, flushing, vision changes, nausea, dyspepsia, nasal congestion.
Prescribing considerations	Blue – suitable for prescribing in primary care following initiation by a specialist.

	Brighton APC has given us permission to use and adapt their information sheet.
Other considerations	Proposed treatment groups: 1. RP secondary to systemic sclerosis. 2. Severe primary RP. Patient suitability: Severe RP with or without digital ulceration. Patient is following lifestyle management as laid out in the NICE CKS guidance for RP. Severe symptoms despite optimal treatment with calcium channel blockers and angiotensin receptor blocker. Treatment to be offered prior to use of iloprost.

Potential patient group (if appropriate to include)	
Brief description of disease	Raynaud's Phenomenon (RP) can be primary (80-90%) or secondary (10-20%)[9]. It is a phenomenon that involves the vasospasm of blood vessels in the extremities such as the digits. This can cause the affected area to change colour and can be painful, limiting everyday tasks. Primary RP does not have a link to any other disease and secondary RP can be a sign of a potentially serious health condition, usually an auto-immune condition e.g. lupus, vasculitis and scleroderma. Vasodilators are the general treatment for RP but side effects must be balanced with any potential benefit. In severe RP digital ulcers can occur and are associated with digital vasculopathy. They can be painful and difficult to treat and heavily impair a person's quality of life. The aim of treatment is to improve symptoms such as pain and loss of hand function but also to heal any ulcers present, prevent new ulcers from forming, prevent infection and reduce any associated morbidity[6,9].
Potential patient numbers per 100,000	Establishing the true prevalence of Raynaud phenomenon (RP) is hampered by the lack of a well-defined reproducible "gold standard" diagnostic test. Community-based surveys have been performed to estimate the prevalence of RP in the general population. In these surveys, estimates of the prevalence of RP have ranged from 3 to 20 percent in women and 3 to 14 percent in men[10]. Of these, we do not have data for the number which will require treatment and how many will progress to require iloprost.
Outcomes required	We are trying to achieve the option of the off-label use of sildenafil with shared care in patients with: 1. RP secondary to systemic sclerosis. 2. Severe primary RP.

	The aim is to use sildenafil prior to iloprost, which is a licensed medicine for RP. We have permission to use and adapt the information sheet from Brighton APC and we also have support of the Rheumatology Network. Iloprost requires close monitoring during the infusion, with measurement of blood pressure and heart rate at the start of the infusion and at each rate change. It is also given over 6 hours over 5 consecutive days and requires a hospital day case admission for it to be administered. Iloprost is more expensive than sildenafil, not only in terms of drug cost but also the cost of administering it and appointment costs. See section below on 'Impact to secondary care and CCGs' for associated cost savings. **Impact to patients:** — Provides an alternative treatment option that may be more acceptable to patients. Iloprost often requires repeated infusions with the range being from 2 to 4 infusions per year for SASH patients, with the majority receiving 4 infusions. Iloprost wears off between infusions leading to a reduction in quality of life. Sildenafil is an oral tablet that is taken every day so its effects should be maintained. — It does not replace iloprost which would still remain a treatment option after sildenafil but may avoid or delay moving to iloprost. — Reduces the burden on attending hospital for up to 5 consecutive days 2 – 4 times per year. **Impact to primary care prescribers:** — Sildenafil is initiated by specialists for RP and primary care prescribers will be supported by a shared care agreement. — No significant monitoring that needs to be undertaken by primary care prescribers. — We have permission to adapt and use the information sheet from Brighton APC. **Impact to secondary care and CCGs:** — Fewer patients requiring iloprost infusions should reduce appointments. This would free up appointment times for other patients. — It would also free up infusion chairs and reduce the workload around administering iloprost. — Significant cost savings to the local health economy. There would be reduced appointment costs as patients would be managed in primary care following initiation of sildenafil. — One 5 day treatment course of iloprost costs £360 (see health economic consideration section), with the majority of SASH patients requiring up to 4 infusions per year as per the Rheumatology team. This equates to an annual cost of £1440 for the drug alone. This excludes the associated hospital costs which are around £2250 per patient for a 5 day treatment course.

	In summary, there is benefit in using sildenafil for not only the patients but also the providers as well as the CCG with minimal support by primary care prescribers.

Summary of current treatment pathway

Primary care:

Currently there is no guidance on the Surrey PAD in regards to the treatment of RP in primary care, however recent guidance revised in February 2020, is available from NICE CKS[9].

Briefly, from age 5 years onwards, treatment in primary care involves:

- **Refer to rheumatology:**
  - All people with suspected secondary Raynaud's phenomenon.
    - If an occupational cause is suspected, refer to an occupational medicine specialist or vascular clinician with expertise in this area (depending on local protocol).
  - All children aged 12 years or younger with Raynaud's phenomenon.
  - If symptoms are worsening, severe or unresponsive to standard treatment.

- reviewing and stopping, if possible any drug that may be causing or exacerbating RP,
- lifestyle measures for all people with Raynaud's phenomenon:
  - Keep the *whole* body (including the hands and feet) warm:
    - Avoid sudden temperature changes.
    - Do not allow the hands and feet to get cold.
    - Wear gloves and warm footwear in cold environments.
    - Consider using hand and foot warming devices — information available from the Scleroderma and Raynaud's UK website.
- Avoid or stop smoking — see the CKS topic on Smoking cessation.
- Try to minimize stress if this is a trigger.
- Exercise regularly.
- If lifestyle measures fail and symptoms are having a significant negative impact, consider a trial of nifedipine as prophylaxis.
- Refer people with symptoms that are poorly controlled or worsening despite appropriate treatment

Secondary care:

Nifedipine
Angiotensin receptor blocker
IV iloprost

In summary, patients with severe, or secondary RP, should be referred to secondary care. They should follow lifestyle advice first line as set out on NICE CKS. Subsequent treatment should start with nifedipine. In practice at SASH after nifedipine they use an ARB such as losartan. Following failure, patients would move onto IV iloprost.

The responsible commissioners for iloprost are CCGs. Iloprost for RP is a RED drug and treatment should be initiated and monitored by specialists in hospitals. There should be no prescribing in primary care[11].

Evidence review

There are a limited number of trials that have looked into sildenafil as a treatment option for RP. There were also no studies found that directly compared iloprost and sildenafil for treating RP.

Digital ulcers are a consequence of severe Raynaud's and a **NICE evidence summary** was written in 2015 for its use in digital ulceration[1]. Although this application is to include patients without digital ulceration all of the evidence included in the evidence summary was not limited to just digital ulceration. Their other outcomes, which ranged from Raynaud's Condition Scores, duration of RP attacks as well as attack frequency are all mentioned in the evidence summary and are positive for using sildenafil. The NICE evidence summary concluded that 'A meta-analysis of 3 small RCTs found a statistically significant benefit for PDE5 inhibitors as a class compared with placebo for digital ulcer healing (p=0.01) and improvement (p=0.002)'.

Since this evidence summary was written there have been **two additional trials**, and a meta-analysis. One trial, by Andrigueti et al[2], looked at the effect of sildenafil on blood flow in RP patients secondary to systemic sclerosis. The other trial, Hachulla et al[3], which looked at the efficacy of sildenafil in systemic sclerosis for digital ulcer healing, was referenced in the NICE evidence summary with its Clinical Trials identifier NCT01295736, and has since been published. Moreover, there has also been a meta-analysis by Roustit et al[4] which looked at phosphodiesterase-5 inhibitors as a class for the treatment of secondary Raynaud's.

All three of these pieces of evidence are included below and should be considered alongside the NICE Evidence Summary.

Andrigueti et al[2] was a double-blind, placebo-controlled 1:1 parallel treatment study looking at the effect of sildenafil on microvascular blood flow in patients with systemic sclerosis. 41 patients were recruited and randomly assigned to either placebo (n=20) or sildenafil 50mg twice daily (n=21). Inclusion criteria included at least 1 RP attack per day for the week before the trial and to have had a disease duration of less than 5 years. The primary end point was changes in finger blood flow (FBF) before and after a cold stimulus. After 8 weeks of treatment the sildenafil group showed a significantly higher mean percentage change from baseline in FBF compared to placebo both before the cold stimulus (mean change of 28.1% versus 1.7%, p=0.026) and after (mean change of 62.4% versus 6.8%, p=0.028). 2 weeks after treatment ended the FBF values were re-tested and in both groups were similar to their baselines.

There were several secondary end points for this study. One of which was the duration of RP attacks which significantly decreased after 8 weeks in the sildenafil group compared with the placebo group (p=0.042). The frequency of RP attacks based on the percentage change from baseline hadn't yet reached statistical significance for the sildenafil group but was trending towards improvement (p=0.069). The Raynaud's Condition Score was also similar between the 2 groups after 8 weeks so was not statistically significant. 2 weeks after completing treatment the end points were re-assessed. After these 2 weeks there were no significant changes in any of the end points between the 2 groups suggesting a loss of efficacy after the end of the treatment.

4 patients presented with active digital ulcers at the beginning of the study (3 in the sildenafil group, 1 in placebo group). After 8 weeks the 3 patients receiving sildenafil their ulcers had completely healed, and 2 weeks after treatment they were still ulcer free. The patient in the placebo group remained with the digital ulcer throughout the study.

Limitations again include the size of the study, which may have been compounded by the exclusion of patients with >5 years disease history. This study was also carried out in a tertiary centre so there may have been selection bias for more severe disease.

From a safety perspective headaches were more frequent in the sildenafil group (33%) versus placebo group (5%). Flushing (18%) and nausea (9%) were reported only in the sildenafil group. No patients withdrew from the study

Hachulla et al[3] was a randomised, double-blind, two-parallel arm, placebo-controlled multicentre study looking at the efficacy of sildenafil on digital ulcer healing in 84 patients with systemic sclerosis. Inclusion criteria included patients with at least 1 digital ulcer. Patients had to withdraw if their digital ulcer(s) worsened.

Patients were separated into 2 parallel arms based on their number of digital ulcers (<3 digital ulcers, and ≥ 3 digital ulcers) to ensure patients with severe disease were balanced between the 2 groups. Participants were then assigned on a 1:1 basis to sildenafil 20mg three times a day or placebo for 12 weeks.

Non-statistical differences in healing rates were seen between placebo and sildenafil, notably due to high placebo healing rates, however the reduction in the mean number of digital ulcers per patient was in favour of the sildenafil group compared with placebo at weeks 8 (p=0.04) and weeks 12 (p=0.03) as a result of the greater healing rate. There was also no difference between the 2 groups in terms of pain and RP severity which both decreased over time.

Limitations of this study did include the inaccurate evaluation of time to healing as digital ulcers were either classed as healed or not healed at each visit which were 4 weeks apart with no means to assess when exactly the ulcer healed. Furthermore, the dose of sildenafil used was lower compared to other studies so further studies would need to be conducted using higher, or titrated doses.

Adverse events led to the discontinuation of 5 patients from the sildenafil group (drowsiness, syncope, headache, facial oedema, n=1 each) and 3 in the placebo group (leg oedema, headache and vomiting, dizziness; n=1 each).

Roustit et al[4] completed a systematic review and meta-analysis of double-blind, randomised controlled trials looking at the efficacy of phosphodiesterase-5 inhibitors as a drug class in the treatment of secondary Raynaud's Phenomenon.

6 trials were included involving 244 participants, 1 with sildenafil (Fries et al) one with modified release sildenafil (Herrick et al), 1 with Vardenafil and 3 with Tadalafil.

This meta-analysis concluded that PDE-5 inhibitors significantly decreased Raynaud's Condition Score (-0.46, p=0.002), as well as significantly decreased both the daily frequency of ischaemic attacks (-0.49, p=<0.0001) and daily duration of RP attacks (-14.62, p=<0.0001). However, because this meta-analysis focuses on not just sildenafil but also vardenafil and tadalafil it may be unreliable when considering the effect of sildenafil in Raynaud's Phenomenon

There is very little evidence with regards to primary RP. One trial, Fries et al, had included 2 patients with primary RP and concluded that clinical symptoms had improved including the mean frequency of Raynaud's attacks, cumulative attack duration as well as their

Raynaud's condition score[8]. However, due to the fact that there were only 2 patients no statistical analysis could be carried out.

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs

On a national level there are shared care guidelines in place in 3 separate areas (Basingstoke, Southampton and Winchester District Prescribing Committee, The Therapeutics Advisory Group for CCGs in Norfolk and Waveney, and Dorset Medicines Advisory Group). They are all for secondary RP with ulceration and the latter 2 are due for review.

In October 2014, the Brighton APC approved sildenafil for off-label use in RP as per NHSE clinical commissioning policy. It has a BLUE recommendation (Specialist initiation without shared care guidelines) with an information sheet for the following organisations:

- Brighton and Hove CCG
- Horsham & Mid Sussex CCG
- High Weald Lewes Havens CCG
- Brighton and Sussex University Hospitals NHS Trust

This recommendation was made on the basis of the NHS England policy 'Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis'[5] – see section below.

Looking at local trusts DTCs:

Trust	Sildenafil for RP on Formulary?	Comments
Brighton and Hove CCG	Y	For off-label use in RP as per NHSE clinical commissioning policy. 'Blue' recommendation.
Royal Surrey County Hospital NHS Foundation Trust	Y	For digital ulcers in systemic sclerosis or RP. 'Red' indication, must be initiated by Rheumatologist specialist
Ashford and St Peters Hospital NHS Trust	X	'Red' listed for vasodilator therapy as per the North West London Formulary
Epsom and St Helier University Hospitals NHS Trust	X	
Frimley Health area prescribing committee	X	Restricted for ICU use if used as vasodilator
Surrey and Sussex Healthcare NHS Trust	X	

Recommendations from national /

EULAR (European League against Rheumatology) recommendations for the treatment of systemic sclerosis[7].
For Raynaud's Phenomenon:

regional decision making groups	Dihidropyridine-type calcium antagonists, usually nifedipine, should be used first line. *PDE-5 inhibitors should also be used in the treatment of Raynaud's Phenomenon.* Intravenous iloprost should be used in severe Raynaud's after oral therapy and experts recommend that intravenous prostanoids are considered when oral therapies (including calcium channel blockers and PDE-5 inhibitors) have failed For digital ulcers: PDE-5 inhibitors should be considered in treatment of digital ulcers in patients with systemic sclerosis. **BSR and BHPR guideline for the treatment of systemic sclerosis[6].** For Raynaud's Phenomenon: First line is calcium channel blocker or angiotensin receptor blocker. Other treatments include SSRIs, alpha blockers and statins. Sildenafil is being increasingly used, then to use IV prostanoid. For digital ulcers: Sildenafil should now be used before considering IV prostanoids IV prostanoids and bosentan, in line with the current NHS England Clinical Commissioning policy. **NHS England Clinical Commissioning policy – Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis[5].** Sildenafil should be used after standard medical treatment with calcium channel blockers, ACEi, losartan, fluoxetine for Raynaud's Phenomenon. It should be used first line as an alternative to treatment with IV prostanoid (or prescribed in combination) at a dose of 25mg TDS increasing to 50mg TDS. Patients should have at least 6 weeks of standard treatment and 6 weeks of sildenafil before moving to IV prostanoid. **NICE CKS – Raynaud's Phenomenon[9]** -Refer patients to secondary care if it is suspected that it is secondary Raynaud's, or if they are under 12 years old. -After trying lifestyle measures, if symptoms are having a significantly negative effect then can try nifedipine as prophylaxis in adults (refer if under 18). If symptoms remain poorly controlled after trying nifedipine then refer to secondary care. Sildenafil use in RP secondary to systemic sclerosis is supported by national recommendations, as well as European guidelines, so is strongly supported by expert advice.
Stakeholder views	Already supported by the Rheumatology Network.
CCG priorities	See under 'Outcomes required' in 'potential patient group' section above.

Health economic considerations

Cost per year per patient

The estimated 28 day cost of generic sildenafil at a dose of 25mg to 50mg three times a day (Drug Tariff September 2020):

Name	Category	Pack size	Price	Cost for 28 days (tds dosage) for 21 packs
Sildenafil 25mg	Cat M	4	100p	£21.00

	<table><tr><td>Sildenafil 50mg</td><td>Cat M</td><td>4</td><td>115p</td><td>£24.15</td></tr></table> Estimated annual costs: £273 - £313.95
Alternative treatments cost per patient per year	•The estimated 28-day cost of sildenafil (Revatio®) at a dose of 20 mg 3 times daily is £446.33 (Drug Tariff September 2020) Estimated annual cost: £5,802.29 •The estimated drug cost for a 5-day iloprost infusion (1 treatment cycle) is approximately £375, excluding VAT and associated hospital costs. On average, patients at SASH have 2-4 series of infusions of iloprost per year depending on the severity of their RP. After speaking to the rheumatology team, most patients receive 4 infusions per year. Iloprost (as Iloprost trometamol) 100 microgram per 1 ml (BNF October 2020) •1 ampoule NHS indicative price = £75 •5 ampoule NHS indicative price = £300 The cost SASH pays for 5 ampoules is £360 If repeated every 3 months, the estimated annual cost: £1,440 PLUS associated hospital costs. The associated hospital costs are usually around £450 per day, equivalent to £2250 per treatment cycle. For a patient who receives 4 treatment cycles per year this equates to £9000 just for the hospital costs. At present some patients at SASH are still on epoprostenol for RP, and have not yet been switched over to iloprost. Epoprostenol is not paid for by the CCG, so once all of the patients have been transferred to iloprost this will come as an additional cost to the CCG.
Other financial considerations (if relevant)	Iloprost would also attract costs associated with additional appointments at the trust, infusion costs and nursing care.
Health economic data (if available)	

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Declaration of Interest: None

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Reviewed by:

Jane Allen, Associate Chief Pharmacist, Surrey and Sussex Healthcare NHS Trust

Declaration of Interest: None

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VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	*27/10/20*	*Gemma Sharp*	*Draft*	*Out for consultation*
v.2	*19/11/20*	*Gemma Sharp*	*Final*	