Scottish Paediatric & Adolescent Rheumatology Network (SPARN)

Bisphosphonates Protocol

NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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Contents

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Stakeholders involved	Consultant Paediatric Rheumatologists, Consultant Paediatricians, Rheumatology Nurse Specialists, Occupational Therapist, Lead Pharmacist, Highly Specialist Physiotherapist
Methodology used	• Literature search • Review of evidence • Review of available national and international guidance including UK Paediatric Rheumatology guidance (BSPAR) • Engagement with key stakeholders (see above) • Guidelines drafted with review date • Submitted to Steering Group (see appendix) for comment then approval
Rationale	Bisphosphonates are used in paediatric rheumatology in the treatment of Chronic Non-Infective Osteitis. They are not used for this indication in general paediatric care. This guideline is helpful and useful as a reference to support staff around SPARN network treat children and young people with rheumatological conditions.
Scope	For rheumatology specialists including hospital staff involved in the prescribing and administration of bisphosphonates (Zoledronate[1] and Pamidronate[2] infusions) to Paediatric Rheumatology patients. The decision to commence bisphosphonate therapy will primarily be made by consultants in the Paediatric Rheumatology team who are managing patients with Chronic Non-Infective Osteomyelitis (CNO), SAPHO – synovitis, acne, pustulosis hyperostosis, osteitis; or severe Osteoporosis associated with active inflammatory disease or prolonged steroid use.
Approval process	The guideline was approved by the SPARN Steering Group on 20/08/2025. See appendix for list of Steering Group members.

[1] See Appendix 2 for more information
[2] See Appendix 2 for more information

Background

CNO is a rare condition in which sterile inflammation occurs in and around bones. Onset of symptoms usually occurs in childhood and can include episodes of bony pain, swelling, arthritis, rashes and intermittent fever.
SAPHO is a rare condition explained by its acronym as stated above. The osteitis with this disorder most often affects the axial skeleton whereas CNO is more commonly (but not exclusively) in the extremities.

Bisphosphonate

Zoledronate and Pamidronate are bisphosphonate drugs. This group of drugs bind strongly to bone mineral and interfere with bone remodelling by slowing the process of osteoclastic bone resorption and bone turnover.

Bisphosphonates offer symptomatic relief in CNO and SAPHO by reducing pain and inflammation. In osteoporosis, these drugs improve bone health and reduce long term fracture risk.

These drugs are not licensed for use in children but are currently used off-label for a number of conditions associated with increased bone inflammation and fragility.

Zoledronate can be given on a single day as a short infusion at intervals of 3-12 months, most typically every 6 months.
Pamidronate is generally given over 3 consecutive days at 3 monthly intervals. It can also be given as a single daily infusion monthly.
Decision regarding frequency is at the discretion of the prescribing clinician.
To date, evidence suggests no difference in the desired treatment effect, or side effects, between Pamidronate and Zoledronate.

In advance of the first planned admission

(Checklist in Appendix 1)

1. Children and young people should always have an adequate Vitamin D level (>50 nmol/l) prior to receiving their first infusion.
   25(OH) Vitamin D must be checked and low levels corrected, prior to booking the admission for infusion. PTH and 1, 25(OH) Vitamin D levels are also useful.
2. Hypophosphatasia can mimic CRMO and can be exacerbated by Bisphosphonates. Always ensure Alkaline Phosphatase is not below normal limits for age.
3. An overnight admission to a paediatric medical ward should be considered following the FIRST infusion to monitor for and treat any acute phase reactions, particularly in younger patients. This is not required for subsequent infusions.
4. Calcium supplementation is essential pre-infusion – commence 3 days pre-infusion and continue for 7 days (10 days total including the infusion day(s)). This

should be documented in the patient's clinical notes/letter alongside a request for the GP to prescribe – see BNFc for available preparations.

The doses of oral calcium supplementation in the BNFc are a useful guide:
2 to 4 years: 0.25mmol/kg (10mg/kg) four times daily
5 to 12 years: 0.2mmol/kg (8mg/kg) four times daily
12 to 18 years: 10mmol (400mg) four times daily

The following preparations are suitable:
Cacit 500mg (12.5mmol) effervescent tablets
Adcal 600mg (15mmol) chewable tablets
Calcichew 500mg (12.5mmol) chewable tablets
Calvive1000 (25mmol) effervescent tablets
Alliance Calcium syrup 20.4mg/ml (0.51mmol/ml)

The dose should be revised according to patient's weight, as required.

5. Prescribe the infusion on the patient's fluid prescription chart. The concurrent calcium supplementation and 'as required' paracetamol should also be prescribed on the patient's medication prescription record if it is the first infusion, and the patient is staying overnight.
6. Patients receiving Bisphosphonate for Osteoporosis should have a baseline DEXA.
7. All children should be registered with a dentist. If a child has severe dental problems, they should have a dental assessment before first dose of Bisphosphonate. Significant caries or dental abscess should be treated and be resolved prior to Bisphosphonate infusion due to the potential risk of osteonecrosis of the jaw.

At first admission

1. Children and young people should have a review at admission including ensuring enteral calcium supplements have been taken for the three days prior to and the day of admission. Ideally, growth parameters should be plotted on a growth chart (however this may have been completed recently in clinic).
2. Girls of childbearing potential should have a pregnancy test before the administration of Bisphosphonate.
3. An intravenous cannula will be inserted and bloods taken for U&Es and creatinine, LFTs, PTH, calcium, magnesium and phosphate. A blood gas for ionised calcium can be taken prior to first infusion as a baseline, in order to compare results post-infusion if the patient is symptomatic.
4. **Bloods should be sent urgently to the laboratory and the results reviewed prior to commencement of infusion –** unless normal renal function and a Calcium result of >2.2mmol/L have been confirmed in the preceding four weeks.

See 'Hypocalcaemia' section below for further information. **Bloods should be taken and results reviewed before each dose of Bisphosphonate.**

5. Some children experience 'flu-like symptoms' as a side effect of the infusion. Fever, aching muscles and vomiting can occur, most often after the first infusion. Paracetamol may be beneficial.
6. Following the first infusion, patients require four-hourly observations of heart rate, respirations, blood pressure and temperature until discharge which should be documented on the patient's PEWS (Paediatric Early Warning Score) chart.

   For the first cycle, it is advisable for younger children to stay overnight on Day 1 to monitor for an acute phase reaction, but they can go home after Day 2. Older children (>10yrs) can go home on Day 1 of the infusion if it is in the morning and the patient is observed on the ward until late afternoon. Parents should be advised of symptoms to expect, and Paracetamol use if required. Subsequent cycles do not need overnight admission. This can be discussed with the Paediatric Rheumatology team and decided upon for each individual case if required.
7. Post-bisphosphonate hypocalcaemia is usually mild, transient and asymptomatic. Clinicians may consider checking an ionised calcium on a blood gas if hypocalcaemia is suspected. If hypocalcaemia occurs, doses of oral calcium, in addition to pre-prescribed calcium, can be given. Alfacalcidol could also be considered if calcium remains low (doses as per BNFc).
8. Hypocalcaemia can be avoided in future by giving a higher dose of calcium supplementation prior to subsequent infusions and ensuring that the patient is not Vitamin D deficient

Hypocalcaemia

Hypocalcaemia is defined as a corrected calcium level or an ionised calcium level below normal values for age.
It can be regarded as:

- biochemical/Asymptomatic
- mildly symptomatic (e.g. distal paraesthesia)
- severely symptomatic (e.g. tetany, arrhythmia, seizures)

Corrected Calcium

Serum calcium exists in an ionised form (50%) or is bound to albumin and other ions. Many medical conditions can cause a decrease in albumin. The serum calcium must be interpreted in relation to serum albumin and can be corrected using the following formula:

Corrected Calcium mmol/L	**=**	Measured serum calcium mmol/L	**+**	(40 – serum albumin mmol/L x 0.02)

Ionised Calcium
Ionised calcium is the most accurate assessment of serum calcium concentration and should be measured if available (blood gas analyser).

Calcium Values:

		Normal value	Mild Hypocalcaemia	Severe hypocalcaemia
Child	Corrected Calcium	2.2-2.7 mmol/L	< 2.0 mmol/L	< 1.8 mmol/L
Child	Ionised calcium	1.15-1.29 mmol/L	< 1.0 mmol/L	< 0.9 mmol/L

Treatment of Hypocalcaemia

Biochemical/Asymptomatic – *Extra doses of oral calcium supplementation*

Symptomatic hypocalcaemia - *Treat any value of symptomatic hypocalcaemia (tetany/seizures/arrhythmia/stridor) with IV bolus calcium gluconate followed by IV calcium infusion.*

Severe biochemical hypocalcaemia (corrected Ca < 1.8 mmol/L or ionised Ca < 0.9 mmol/L)

- perform ECG and measure QTc. QTc interval prolongation is directly proportional to the degree of hypocalcaemia
- if prolonged QTc (>0.44 seconds) or history of sudden drop in Ca treat with calcium infusion as above
- if asymptomatic with normal QTc (likely in chronic hypocalcaemia) use oral treatment (see below)
- continuous ECG monitor is recommended until corrected Ca+ > 1.8 mmol/L
- if symptoms develop or a sudden further drop in Ca while on oral supplement, start on intravenous Ca infusion as above
- if vomiting/not tolerating oral intake consider switching to IV treatment without a bolus

For subsequent admissions

1. Ensure that calcium supplements have been taken for the 3 days prior to, and the day(s) of admission – with a plan for a total of 10 days as above.
2. Girls of childbearing potential should have a pregnancy test before the administration of Bisphosphonate.
3. Patients should have urgent bloods sent for U&Es and creatinine, LFTs, calcium, magnesium and phosphate, as well as vitamin D if not measured within the last year. **Results must be reviewed prior to commencement of infusion to**

ensure normal renal function - unless normal renal function has been confirmed in the preceding four weeks.

4. Provided the infusion is well tolerated, patients can go home straight afterwards. Patients having Pamidronate will attend as a day case for the further 2 infusions.

Pamidronate dosing

The dose and frequency of Pamidronate should always be discussed with a consultant. Rheumatology consultants treating CNO may choose a different dosing frequency depending on the clinical situation:

- regular treatment with 3 consecutive daily doses every 3 months for a total of 9 or 12 doses
- a single dose of Pamidronate 1mg/kg given each month until symptoms controlled with a maximum of 12 doses
- a "watch and wait" approach after initial good response to above treatment plan with a further dose (either a single 1mg/kg dose or 3 consecutive daily 1mg/kg doses) of Pamidronate given in the event of clinical flare

Indication	Pamidronate Dose	Suggested Frequency
CNO/SAPHO	1mg/kg over 2-4 hours Up to maximum 90mg (Option to use 0.5mg/kg in first dose for younger children to reduce side effects)	3 consecutive days. Repeat if beneficial and clinically indicated. (No more often than 3 monthly)
Osteoporosis	1mg/kg over 2-4 hours Up to maximum 90mg	Monthly OR 3 consecutive days every 3 months

Maximum yearly dose 12mg/kg (maximum 12 x 90mg total). Use ideal body weight if child obese.

Preparation: Pamidronate is available in 3 different sized vials:

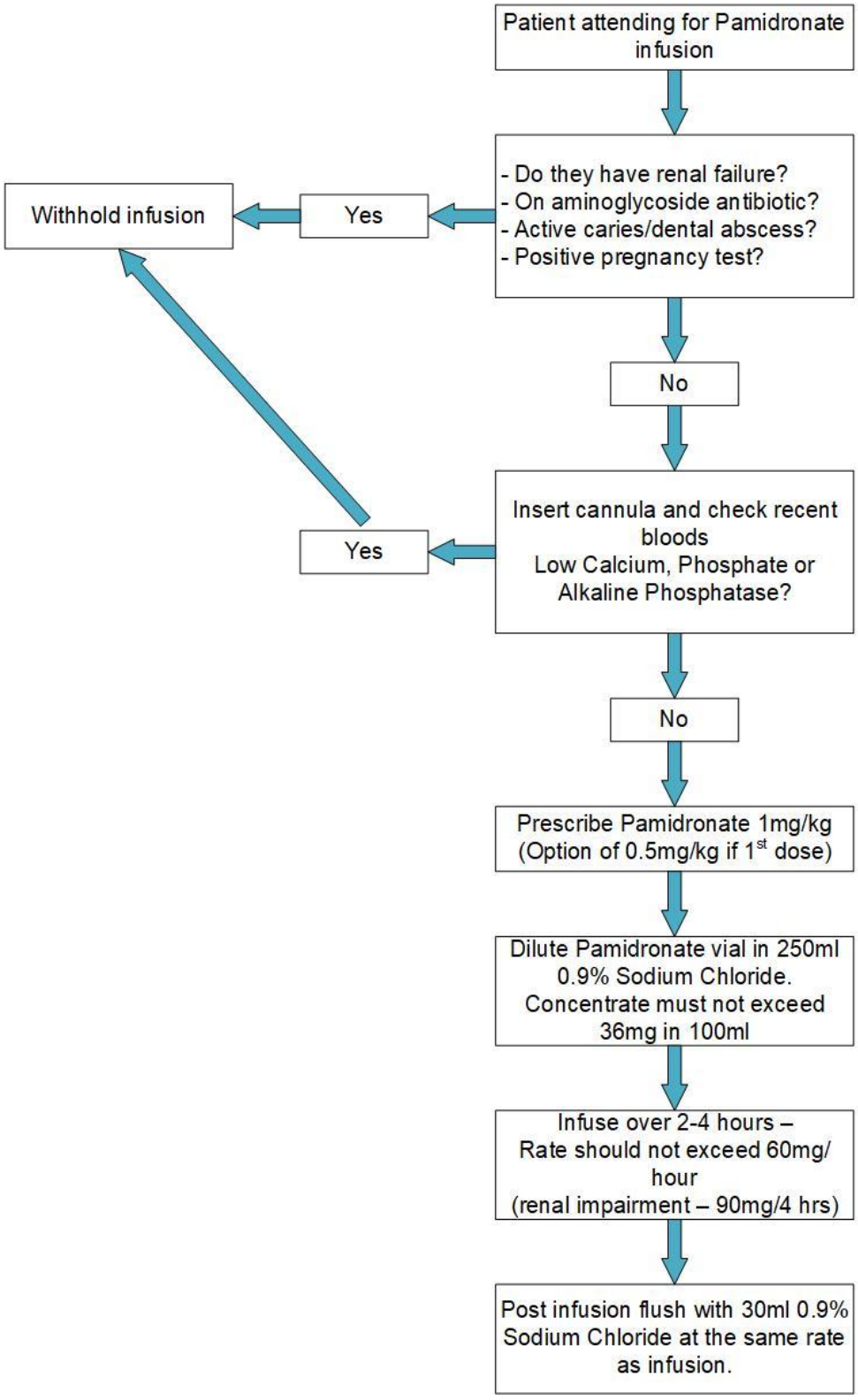
- 15mg in 5ml - 30mg in 10ml - 90mg in 10ml

Dilute with 250mls of 0.9% sodium chloride (or if renal impairment dilute with 500mls of 0.9% sodium chloride).

The final concentration of Pamidronate in the infusion solution should not exceed *36mg/100ml* of diluent or *18mg/100ml* in renal impairment.

Infusion rate should not exceed 60mg/hour or 1mg/minute. If creatinine clearance 30-90ml/minute, infusion rate should not exceed 90mg/4 hours. Do not give if creatinine clearance <30ml/min/1.73m2.

Flush cannula with 30ml 0.9% sodium chloride – **at the same infusion rate as the Pamidronate infusion ran.**



Zoledronate dosing

The dose and frequency of Zoledronate should always be discussed with a consultant rheumatologist. Starting doses are detailed below. Some children and young people will be on a reduced infusion frequency after the first two years.

Age	**Dose *(maximum dosage)***	**Volume of sodium chloride 0.9% infusion bag**	**Duration of infusion**	**Suggested frequency of infusions**
< 2 years	25micrograms/kg (max. 2mg)	50ml	30 minutes	3 monthly
2-3 years	35micrograms/kg (max. 2mg)	50ml	30 minutes	4 monthly
3-5 years	35micrograms/kg (max. 4mg)	100ml	30 minutes	4 monthly
>5 years	50micrograms/kg (max. 4mg)	100ml	30 minutes	6 monthly

Preparation: Zoledronate is available as a concentrate of 4mg/5ml.

This MUST be diluted prior to administration.

To do this, withdraw the required volume of Zoledronate from the vial and add the dose to the infusion bag (see table for volume).

Mix well and then infuse over the required time (see table for duration).

For doses less than 1mg, please prescribe in micrograms. For doses of 1mg or over, please prescribe in milligrams.

Example: For a 12 year old patient weighing 43 kg, the dose would be 50 micrograms/kg = 2,150 micrograms = 2.15 mg Zoledronate. 4mg/5ml concentrate = 0.8 mg in 1 ml solution. Therefore 2.7 mls (= 2.15 ÷ 0.8 milligrams) of Zoledronate 4mg/5ml concentrate should be withdrawn from the vial and added to a 100 ml infusion bag of sodium chloride 0.9%. This should be then infused over 30 minutes.

Appendix 1 - Pre-admission checklist

Action	Complete pre-admission	First admission	Subsequent admissions
Is dental assessment required?			
Vitamin D level checked and optimised			
Alkaline Phosphatase normal?			
Consider booking bed for 1st infusion			
Calcium supplements prescribed			
Calcium supplements commenced			
Infusion and PRN Paracetamol prescribed			
If osteoporosis indication, has patient had DEXA			
Pregnancy test for girls of childbearing potential			
Cannulation and bloods - **Are U&Es and bone profile normal? Consider blood gas for ionised calcium**			

Appendix 2 – Off label drugs statement

Prescribing of medicines outwith their marketing authorisation
Recommendations within this pathway are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use. Medicines may be prescribed 'off-label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration, via a different route
- for administration
- for a different dose for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans. Generally, 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".

The General Medical Council (GMC) recommends that when prescribing a medicine 'off-label', doctors should:

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so.

Make a clear, accurate and legible record of all medicines prescribed and when not following common practice, the reasons for prescribing an unlicensed medicine. Non-medical prescribers should ensure that they are familiar with the legislative framework and Royal Pharmaceutical Society's Competency Framework for all Prescribers.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.

Appendix 3 – Steering Group membership

Name	Designation	Role	Area representing
Andrew Fell	Paediatric Rheumatology Nurse Specialist	Data Lead	NHS Greater Glasgow & Clyde
Angela Cruickshank	Paediatric Rheumatology Nurse Specialist	Former Nurse Lead	NHS Fife
Catriona Anderson	Consultant Paediatric Rheumatologist	Education Lead	NHS Lothian
Elaine Wallace	Senior Child Health Physiotherapist	Physio Lead	NHS Tayside
Emma Carson	Paediatric Rheumatology Nurse Specialist	Working with Families Lead	NHS GGC
Imogen Kelly	Rheumatology Nurse Specialist	Working with Families Lead	NHS Lothian
Jane Adam	Paediatric Rheumatology Nurse Specialist	Nurse Lead	NHS Grampian
Julie Duncan	Consultant Paediatrician	Clinical Guidelines Lead	NHS Lothian
Karen Lapsley	Highly Specialist Physiotherapist	Physio Lead	NHS Forth Valley
Kirsten Healy	Consultant Paediatrician	Paediatrician with an interest	NHS Fife
Kirsty McLellan	Paediatric Rheumatology Consultant	Clinical Guidelines Lead	NHS Greater Glasgow & Clyde
Klaire Connor	Young People and Families Manager Scotland	Third Sector Representative	Versus Arthritis
Lindsay Robertson	Consultant Rheumatologist	Transition Lead	NHS Grampian
Lois Freeland	SNAC Chair	Third Sector Representative	SNAC
Mairi Dunbar	Lead Pharmacist – Paediatrics	Pharmacy Lead	NHS Tayside
Mandy Fanning	Occupational Therapist	Occupational Therapy Lead	NHS GGC
Mary Brennan	Consultant Paediatric Rheumatologist	Chair	NHS Lothian
Neil Martin	Consultant Paediatric Rheumatologist	Lead Clinician	NHS Greater Glasgow & Clyde

References

Scottish Paediatric & Adolescent Rheumatology Network – Protocol for the Administration of Pamidronate Infusion in paediatric Rheumatology

Pamidronate Therapy for Chronic Non-Bacterial Osteomyelitis, NHS University Hospitals Bristol and Weston

Pamidronate Infusions: Paediatrics, NHS Leeds Children's Hospital

Guideline for administration of Intravenous Zolendronic Acid (Zolendronate) in children, NHS Brighton and Sussex University Hospitals

Acute Investigation and Management of Hypocalcaemia in Children and Neonates, NHS Lothian Guideline

Scottish Paediatric and Adolescent Rheumatology Network

Checklist for clinical guideline development, review, approval and posting on SPARN website

Process	Done	N/A	Date	Initials
Literature search and review of available evidence	☒	☐	Ongoing Oct 2022 - 25/3/24	LW/CA
Review national and international guidance	☒	☐	Ongoing Oct 2022 - 25/3/24	LW/CA
Review previous guidelines/ask other centres if appropriate	☒	☐	Ongoing Oct 2022 - 25/3/24	CA
Consult key stakeholders: Medical staff Specialist Nurses Physiotherapists Pharmacy Patients and Families Other	 ☒ ☒ ☒ ☒ ☐ ☐	 ☐ ☐ ☐ ☐ ☐ ☐	Ongoing Oct 2022 - 25/3/24	
Collate information and produce draft guideline	☒	☐	18/10/22	LW
Ensure guideline contains review date (max 3 years hence)	☒	☐	August 2025	JN
Submit to SPARN steering group for review (see Appendix 1)	☒	☐	31/5/23	CA/LW
Decision made by SPARN steering group	☒	☐	12/6/23	CA
Guideline re-drafted and submitted to SPARN steering group	☒	☐	8/10/24	CA
Final guideline accepted	☒	☐	4/2/25	CA
Guideline posted on SPARN website & review date noted	☐	☐	Pending	CA

Date: 11/8/25 Signature: C Anderson

Section	Question	Yes	No	N/A	Date	Signature
Scope and Purpose	1) Has the author demonstrated a need for a clinical guideline adequately? 2) Are the overall objectives specifically described? 3) Are the clinical question(s) covered specifically described? 4) Are the patients to whom it is meant to apply specifically described? 5) Does the title accurately reflect the content and scope?	☒ ☒ ☒ ☒ ☒	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	11/8/25	CA
Stakeholder Involvement	6) Is there a clearly defined authorship? 7) Did the guideline development group include individuals from all relevant professional groups? 8) Are the target users of the guideline clearly defined?	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	11/8/25	CA
Costs	9) Have the potential cost implications of applying the recommendations been considered?	☒	☐	☐	11/8/25	CA
Clarity and Presentation	10) Are the recommendations specific and unambiguous? 11) Are the key recommendations easily identifiable?	☒ ☒	☐ ☐	☐ ☐	11/8/25	CA

Review	12) Does the guideline contain a review date?	☒	☐	☐	11/8/25	CA

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