Scottish Paediatric & Adolescent Rheumatology Network (SPARN)

Chronic Non-Infective Osteitis (CNO): Diagnosis & Management

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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boundaries, National Networks support the delivery of safe, effective healthcare that's designed around patients, carers and families.

Contents

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Stakeholders involved	Consultant Paediatric Rheumatologists, Consultant Paediatricians, Paediatric Rheumatology Clinical Nurse Specialists, Occupational Therapist, Lead Pharmacist, Highly Specialist Paediatric 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 1) for comment then approval
Rationale	This guidance was produced as there was no guidance available in Scotland. Extrapolated from consensus treatment plan by north American group CARRA. To improve and standardize diagnosis and management of this condition across the SPARN network and support colleagues in DGH settings managing these patients. This guideline is helpful and useful as a reference to support staff around SPARN network treat children and young people with rheumatological conditions.
Scope	This guideline is for children presenting with suspected or confirmed CNO. This guideline will be useful for all clinicians who encounter children and young people.
Approval process	The guideline was approved by the SPARN Steering Group on 02/02/2026. See appendix for list of Steering Group members.

Objectives

To provide guidance on the assessment, diagnosis and management of children with suspected or confirmed Chronic Non-Infective Osteitis (CNO), previously Chronic Recurrent Multifocal Osteomyelitis (CRMO). This autoinflammatory condition of the bony skeleton can cause significant morbidity. It is treatable and referral to Paediatric Rheumatology is recommended in all cases. This guideline aims to facilitate earlier diagnosis and treatment to promote improved outcomes for patients.

Introduction

Chronic Non-Infective Osteitis (CNO) is a rare autoinflammatory condition which results in sterile inflammatory lesions of the bony skeleton. The most common presenting complaints are bony pain and swelling. Clinical course varies and diagnostic delay is common, often resulting in significant pain for those affected. The differential diagnosis is wide, including infective and neoplastic lesions. Therefore, it is a diagnosis of exclusion. Detailed history and examination will facilitate preliminary diagnosis and guide further investigation, management and referral.

Clinical Features

• Bony pain
  Most common presenting complaint
  Can be single site or multifocal
  Can occur anywhere
  Back, lower limbs, pelvis and clavicle often affected
  Night pain common – need to exclude malignancy

• Bony swelling
  Tends to be single site
  Can occur anywhere
  Clavicle, tibia and mandible often affected

• Associated Features
  Fever - can be present, but not often – If present consider infection
  Arthritis - may be present
  Rash/Psoriasis – Look for/ask about family history (SAPHO syndrome – Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis)

Diagnosis

CNO is a diagnosis of exclusion. Important exclusions include infection, malignancy and Langerhans Cell Histiocytosis (LCH). Diagnosis is based on a combination of clinical and radiological features; namely sterile bony inflammatory lesions affecting one or more site, where other pathologies have been excluded. Diagnostic criteria

have been proposed but not yet validated. Validation of such criteria could help achieve an earlier diagnosis and avoid unnecessary investigation.

Investigations

Imaging

- Plain X-ray of affected site – can be normal
- Localised MRI of affected site • Baseline whole body MRI at diagnosis to look for asymptomatic lesions/determine extent of disease/type of lesions (hyperostotic/osteitic)
- No place for nuclear medicine bone scans

Bloods (not diagnostic)

- FBC & film – To look for infection/malignancy.
- ESR & CRP – To look for inflammation/infection. Beware - both may be normal or elevated. Most common finding is moderately raised ESR (10-50) with normal CRP.
- Bone profile (Ca, PO4 , alk phos, PTH) – Often normal. Beware - A low ALP can sometimes indicate hypophosphatasia, a rare genetic condition of bones and teeth which can be misdiagnosed as CNO
- Vitamin D – Deficiency may contribute to bony pain.
- HLA B27 – Associated with SAPHO syndrome.
- Bone Biopsy & Culture - Should be done if felt necessary to exclude malignancy or infection e.g. atypical features, very high inflammatory markers. The most common histopathological finding in CNO is that of chronic inflammation/osteomyelitis. Culture will be sterile in CNO. Note – clavicular biopsies frequently result in keloid scars
- Bone biopsy - send histopath, MC+S, 16S, and consider mycobacterial culture if appropriate

Clinical Pathway

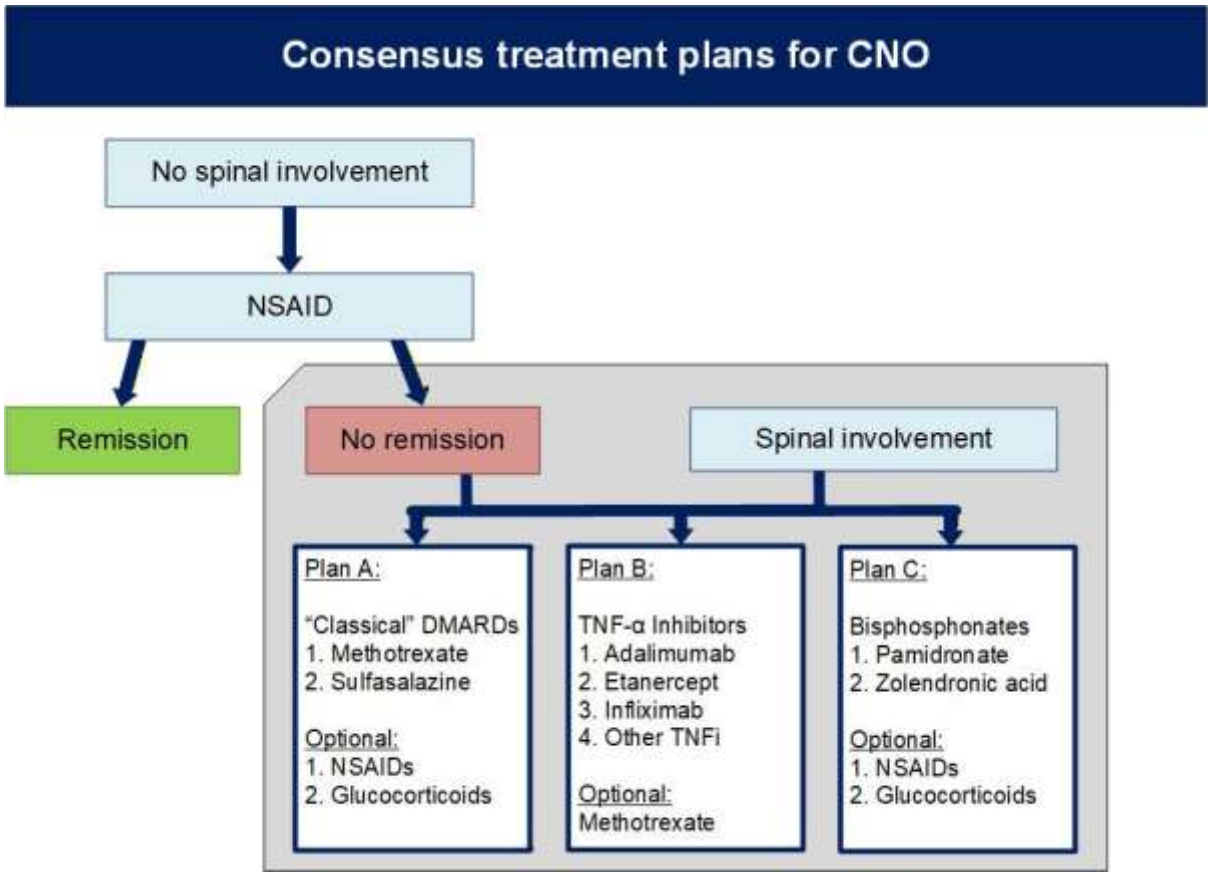
All children with suspected or confirmed CNO should be referred to a Paediatric Rheumatologist for assessment, management and monitoring. Children with CNO may develop significant chronic pain and early, appropriate management may reduce this.

Management

There is no clear evidence base regarding management of CNO and there is an absence of high quality randomised controlled trials due to its rarity. In the absence of this, treatment recommendations are often empiric and in the main based on consensus opinion or small retrospective case series. Treatment practice varies worldwide. Treatment is given for those who are symptomatic or have spinal lesions (due to risk of fracture). Patients may have a relapsing and remitting course and should have regular clinical review 3-4 monthly to assess progress (interval can be extended in periods of quiescence).

Treatment Options

In 2018, CARRA published Consensus Treatment Plans for children with CNO who were refractory to NSAIDs or had active spinal lesions[1] (below). These were based on a survey sent to members of CARRA, 95% of treating physicians who responded (41% response rate) use NSAIDs as first-line treatment in children with a new diagnosis of CNO (24). For patients who failed NSAID treatment, the most commonly used treatments were reported as methotrexate (67%), TNFi (65%), and bisphosphonates (46%) (24). These results guided the development of consensus treatment plans (CTPs). While no clear evidence re treatment of active spinal lesions in CNO, consensus was to escalate treatment rather than give NSAID monotherapy in these patients given perceived risk of vertebral fracture.



Each of these treatment options will be discussed in turn with evidence base.

NSAIDS

Available Evidence:

A prospective study of 37 children with CNO on naproxen[1] found 43% of them to be symptom free at 6-months[2]. Mean disease activity estimated by the patient/physician and the physical aspect of health-related quality of life including functional ability (global assessment/childhood health assessment questionnaire and childhood health assessment questionnaire) and pain improved significantly. Forty-one percent of our patients showed radiological relapses, but 67% of them were clinically silent.

A retrospective case series including 56 patients suggested NSAIDs work in the majority of patients (2/3), but there was > 50% failure after 2-3 years[7].

Recommendation:
Non-steroidal anti-inflammatory drugs (NSAIDS) should be the first step in patients **without spinal involvement.**

High-dose Ibuprofen or Naproxen as per Children's BNF can be given with gastroprotection.

Suggest give 3 months of treatment and assess response (clinically +- radiologically at clinician's discretion)

Good response to NSAIDS – observe and review.

Poor response to NSAIDs or spinal involvement – consider change of treatment.

DMARDS

Methotrexate[2] and Sulfasalazine[3]

Evidence:
There are a few small studies that mention Methotrexate use in CNO, with remission rates varying from 20-24% [3-6]. In a study where patients on methotrexate had a 44% remission rate, 67% of patients had a concomitant rheumatological condition rather than CNO alone.

A couple of studies mention sulfasalazine use in CNO. One showed involving 22 patients showed an 18% complete remission rate, similar to that seen with Methotrexate[6]. Another larger study with 47 patients, showed 38% complete remission rate[5].

Most literature reported variable success of methotrexate (MTX) and sulfasalazine (SSZ) in patients with poor responses to NSAIDs or frequent relapses. Other DMARDs were rarely used. Five articles have reported treatment of DMARDs in CNO with level

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[1] See appendix 2 for more information
[2] See appendix 2 for more information
[3] See appendix 2 for more information

IV evidence. Jansson et al. (19), Catalano et al. (23), and Kaiser et al. (20) documented poor responses to SSZ, MTX, and azathioprine[4] in children with CNO. Borzutzky et al. (17) and Wipff et al. (18) showed relatively lower remission rates (18–20%) and efficacy (38–41%) in children treated with MTX or SSZ. There was poor tolerance of MTX and dosing was not reported in most studies.

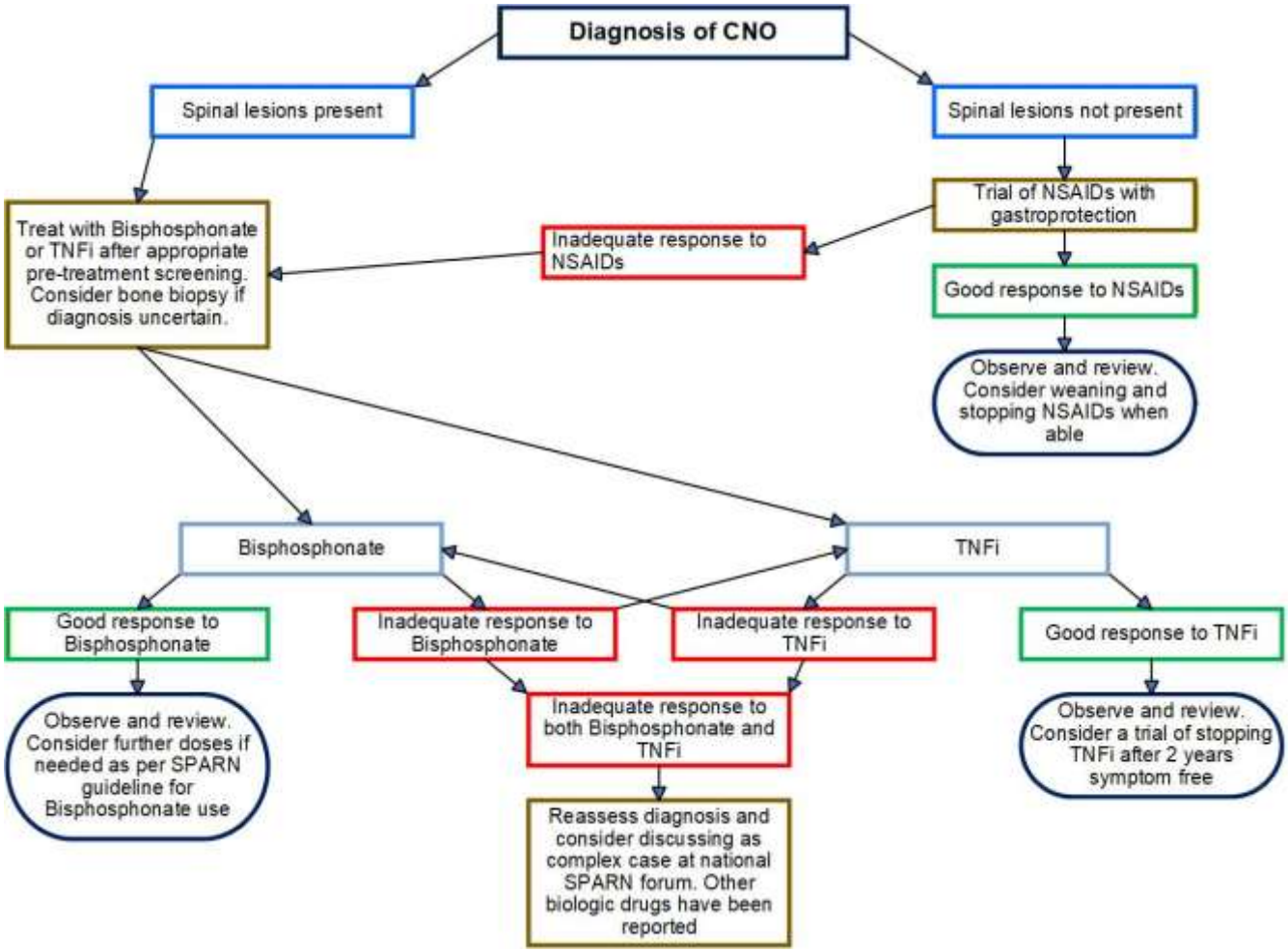
Recommendation:
Methotrexate is a treatment option for CNO, but may be especially useful for those with associated arthritis or other rheumatological conditions (suggested dosing as per children's BNF JIA dose).

Both will require regular blood monitoring as per local protocols.
Sulfasalazine is a treatment option for CNO (suggested dosing as per children's BNF JIA dose).

Both will require regular blood monitoring as per local protocols.

SPARN Treatment Flowchart

[4] See appendix 2 for more information



Bisphosphonates and TNF Inhibitors

Pamidronate[5] and Zolendronic Acid[6]

Bisphosphonates inhibit osteoclast activity, thereby likely stopping inflammatory bone loss. Pamidronate furthermore has inhibitory effects on pro-inflammatory cytokine expression [68].

Different treatment regimens have been reported and are commonly used in clinical practice: 1 mg/kg/dose (max. 60 mg/dose) every month, or 1 mg/kg/dose (max. 60

[5] See appendix 2 for more information
[6] See appendix 2 for more information

mg/dose) on 3 consecutive days every 3 months for 9–12 months. Another approach is to implement these on an ad hoc/as required basis, rather than giving regularly. Treatment regimen is at the discretion of the responsible clinician.

Because of potential side-effects and the long biological half-life of bisphosphonates, they should only be considered in otherwise treatment refractory cases or in individuals with primary vertebral involvement and structural damage [55,68].

We would recommend a dental check prior to bisphosphonate treatment. This is due to theoretical risk of osteonecrosis of the jaw associated with receiving bisphosphonates in the context of dental abscess. Extensive caries or dental abscess should be treated first before commencing bisphosphonate.

Evidence:
A small number of articles have reported treatment of CNO with Pamidronate.

Kerrison and colleagues reported significant pain relief and improved activity and well-being with pamidronate use in seven children (three with spinal lesions) who failed NSAIDs[10].

Simm et al.[11] and Miettunen et al[12] demonstrated the effectiveness of Pamidronate in children with CNO refractory to NSAIDs. Over 80% of patients had pain relief and more than 90% of patients in Miettunen's study showed resolution of bone lesions on MRI after six months of treatment. Gleeson and colleagues reported pain relief with pamidronate in six of seven children who failed NSAIDs[13]. Of five children with spinal fractures, three had follow-up x-rays showing regression of height loss in affected vertebrae in response to pamidronate therapy. Hospach et al.[14] reported complete resolution of hyperintensity signal of active spinal lesions after three to six cycles of pamidronate and a median interval of 13 months follow-up with MRI in eight of nine children with CNO refractory to NSAIDs. Roderick et al. treated 11 children with CNO refractory to NSAIDs with four cycles of pamidronate at 1 mg/kg/day on three consecutive days every three months[15]. Two patients showed a good response, six a moderate response, one a mild response, while two failed to respond based on repeated whole body MRIs. Schnabel et al. described pamidronate to be highly effective in CNO patients refractory to standard treatment with NSAIDs and/or glucocorticoids[16].

A small, randomized double-blinded, placebo-controlled pilot trial of 14 patients by Andreasen et al, investigated the efficacy of Pamidronate in reducing radiological and clinical disease activity in CNO. From baseline to week 36, the radiological disease activity score (using CT of anterior chest wall) decreased from 5 [4-7] to 2.5 [1-3] in the pamidronate group, but did not change in the placebo group ($p = 0.04$). From baseline to week 36, VAS pain and VAS global health tended to decrease more in the pamidronate than in the placebo group ($p = 0.11$, $p = 0.08$). Physical functioning (HAQ) and health-related quality of life (EQ-5D, SF-36) did not change. Biomarkers of bone turnover decreased only in the pamidronate group ($p \leq 0.02$). The authors concluded that Pamidronate may improve radiological and clinical disease activity in CNO[8].

A single-centre retrospective study including 51 patients, treated children with multifocal or spinal bone inflammation and clinical disease activity not responding to NSAIDs with an early onset 2-year Pamidronate regimen[9]. Whole body MRI was performed at time of diagnosis, and at years 1 and 2 in 88%, 84%, and 91% of cases, respectively. During the first year, the total number of radiologically active lesions and number of spinal lesions per patient declined ($p = 0.01$). Clinically inactive disease was recorded in 12/32 children (38%). However, 8/12 children (67%) experienced clinical relapse. The authors concluded that Pamidronate might contribute to improvement in clinical and radiological disease activity in such patients, especially after 1 year of treatment. However, children with continuously active disease after 2 years of pamidronate treatment were seen.

Zhao et al. reported rapid response to treatment with zoledronic acid in combination with the TNF inhibitor infliximab. While very promising and effective in a small cohort, the combination of zoledronic acid and infliximab does not allow an assessment of the exact contribution of each therapeutic [39].

Some paediatric centres use Zolendronic acid for their CNO patients with reported good effect, though no formal evidence as yet.

Recommendations:
Bisphosphonates are an appropriate treatment choice for patients with CNO refractory to NSAIDs or those with spinal involvement.

There is more evidence in the literature relating to Pamidronate, however Zolendronic acid is used in some paediatric centres and may be particularly advantageous in those patients in whom cannulation is difficult as it can be given less often.

Ensure patients have up to date dental review prior to starting

See separate SPARN Protocols for further details – patients will need calcium supplementation/bloods pre-treatment.

TNF Inhibitors

Evidence:

Published data on the use of tumour necrosis factor (TNF)-alpha inhibitors (TNFi) in CNO are more limited. Eight articles have reported treatment of TNFi in CNO with level IV evidence. A small cohort study (n=4) reported by Eleftheriou et al. showed decreased pain in children with CNO after infliximab treatment (n=3) and anakinra (n=1, later switched to adalimumab) (16). Borzutzky et al. (17) and Wipff et al. (18) observed the highest rates of clinical remission (46%) or efficacy (89%) from TNFi compared to glucocorticoids, methotrexate, sulfasalazine, and NSAIDs. Jansson et al. (19), reported disease remission induced by infliximab in two patients who failed NSAIDs, glucocorticoids, DMARDs, and pamidronate. Recently, a combination of

infliximab and methotrexate with or without zolendronic acid significantly improved clinical, laboratory, and imaging results in 9 children with CNO (8). However, Kaiser et al. showed poor response to TNFi in children with CNO in that only two of seven patients achieved remission (not defined) (20). On the other hand, etanercept was effective in all five patients in a small childhood series (21). Anti-interleukin (IL)-1 has been reported in fewer paediatric cases (20). In an adult cohort (n=6), anakinra improved the patient global assessment of disease activity within one month in five patients (22).

Recommendations:

CXR[7] and Quantiferon[8] before starting

Will require regular blood monitoring as per local protocols.

Consider monitoring adalimumab[9] and infliximab[10] levels/antibodies if available.

Consider addition of a co-medication (can be low dose) such as Methotrexate, sulfasalazine, MMF to reduce risk of antibody formation with Adalimumab and Infliximab

Pamidronate Vs TNF Inhibitors

An international multi-centre retrospective study by Schnabel et al, looked at 91 patients who received Pamidronate alone, TNF inhibitors alone, or a combination of both sequentially[9]. Both therapies were associated with clinical remission at 6 months, and reduction of bone lesions on MRI at 12 months. While not reaching statistical significance, pamidronate resulted in faster resolution of MRI lesions. Fewer flares were observed with TNFi. Failure to respond to pamidronate was associated with female sex [p = 0.027], more lesions on MRI [p = 0.01] and higher CRP levels [p = 0.03].

Other

Evidence base is limited but other treatments such as anakinra[11] or secukinumab[12] may be considered at the clinician's discretion.

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[7] See appendix 2 for more information
[8] See appendix 2 for more information
[9] See appendix 2 for more information
[10] See appendix 2 for more information
[11] See appendix 2 for more information
[12] See appendix 2 for more information

Appendix 1 – 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 Highland
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

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.

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