NHS Dorset

SHARED CARE PROTOCOL - METHOTREXATE (ORAL AND SUBCUTANEOUS) FOR PATIENTS IN ADULT SERVICES (EXCLUDING CANCER CARE)

As well this protocol, please ensure that summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.

Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. If the drug is being initiated in patients of childbearing potential, there should be documented evidence that they have been informed of the risks, and they are aware of the requirement to use effective contraception during treatment and for a period after stopping the drug as advised by the specialist. Starting methotrexate in patients with known fatty liver (alcohol related or Metabolic dysfunction-associated steatotic liver disease (MASLD) should be carefully risk assessed. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Explain where drugs are used outside their license.
- Ensure the patient and/or carer understands and can follow the once-weekly dose regimen.
- If prescribing subcutaneous methotrexate, ensure the patient/carer is trained to administer safely. Ensure that there are local arrangements for safe supply and disposal of ancillary products e.g. provision of purple lidded sharps bins. Make sure the brand of subcutaneous methotrexate initiated is communicated to primary care to ensure continuation of the same brand.
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Conduct required baseline investigations and initial monitoring (see section 8). Arrange and review the results of any blood tests for the first 12 weeks of treatment
- Initiate, assess response and optimise treatment as outlined in section 5. Transfer to primary care is normally after the patient has been treated for 3 months and with satisfactory investigation results for at least 4 weeks.
- Explain the intention to share care for drug prescribing and monitoring to the patient. Explain the process and the potential timescales for this.
- Prescribe sufficient medication taking into account any delays in communication to general practice to enable transfer to primary care, including where there are unforeseen delays to transfer of care.

- Once treatment is established and stabilised request shared care from the primary care provider either using the documentation in Appendix 1 or by clinic letter detailing the diagnosis, current and ongoing dose of methotrexate and folic acid, any relevant test results, which day of the week the patient takes their methotrexate and folic acid, and when the next monitoring is required. Include contact information (section 13). If subcutaneous methotrexate is prescribed, include the brand.
- Conduct the required monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Ensure there is a mechanism to receive rapid referral of a patient from primary care in the event of deteriorating clinical condition, non-adherence to monitoring requirements or need for further advice and support
- Review treatment and provide advice if a patient becomes or wishes to become pregnant (See section 12)
- Provide advice to primary care on the management of adverse effects if required
- Patients should be regularly reviewed, and the risk benefit re-assessed as patients get significantly older and frail with increasing co-morbidities and polypharmacy. Dose optimisation and/or dose tapering should be considered if clinically appropriate aiming for the lowest effective dose.
- Advise primary care if treatment should be discontinued.

Primary care responsibilities

- Respond to the request from the specialist for shared care if further clarification or a refusal is intended. Acceptance of shared care is implied by nil response. It is asked that this be undertaken within 14 days of the request being received, where possible.
- If accepted, prescribe methotrexate and folic acid as detailed in the specialist's request and as per section 5, taking into any account potential drug interactions in section 7.
- Assess for interactions with methotrexate when starting any new medicines see section 7. It is recommended to add Trimethoprim and Co-trimoxazole as an allergy warning to the patient’s record to alert for any co-prescribing.
- Adjust the dose of methotrexate and folic acid prescribed as advised by the specialist.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist.
- Manage adverse effects as detailed in section 10 and discuss with specialist team when required.
- Stop methotrexate and discuss urgently with the specialist if the patient develops signs of severe infection, liver or respiratory disease, unexplained bleeding, or bruising, becomes pregnant, or if immunosuppressed patients are exposed to chickenpox or shingles.
- Discuss with the specialist if the patient plans to become pregnant. See section 12.
- Stop treatment as advised by the specialist. If the decision to stop treatment is made in primary care e.g. due to increased frailty index, to let the specialist team know so they can arrange a review as needed.

Patient and/or carer responsibilities

- Take or administer methotrexate as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- Maintain engagement with specialist and primary care; attending regularly for monitoring and review appointments as requested, keeping contact details up to date with both teams. Be aware that medicines may be stopped if they do not attend for blood monitoring or the review appointments
- Advised to take part in all national screening programmes e.g. for breast, bowel, and cervical cancers.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in section 11.
- Report the use of any over the counter (OTC) medications to primary care and specialist and be aware they should discuss the use of methotrexate with their pharmacist before purchasing any OTC medicines.
- Tell anyone who prescribes them a medicine that they are taking methotrexate
- Moderate their alcohol intake as advised by their specialist team – the Versus Arthritis leaflet suggests no more than 14 units per week. Methotrexate | Versus Arthritis Leaflet.
- Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely.

Patients of childbearing potential should use effective contraception during treatment and for a period afterwards as advised by the specialist team. Those of childbearing potential should take a pregnancy test if they think they could be pregnant and inform the specialist or GP immediately if they become pregnant or wish to become pregnant. See section 12.

1. Background

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This shared care protocol has been prepared to support the transfer of responsibility for prescribing from secondary to primary care. Shared care is only appropriate if it provides the optimum solution for the patient.

Methotrexate is a cytotoxic folic acid antagonist used to treat chronic inflammatory conditions and certain cancers. It inhibits the enzyme dihydrofolate reductase and inhibits synthesis of DNA, RNA, and proteins.

Methotrexate is licensed for the treatment of certain cancers, as well as some chronic inflammatory disorders. It is not licensed for all the conditions it is used to treat. However, its use for the indications below are well established and supported by clinical specialists.

This shared care protocol does not cover treatment of cancer, or treatment of people less than 18 years old.

Methotrexate may be used as monotherapy or in combination with other DMARDs including leflunomide and sulfasalazine. Note the frequency of blood monitoring requirements are different if methotrexate is used in combination with leflunomide. (see leflunomide shared care protocol)

2. Indications

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The licensed indications for methotrexate include:

- Active rheumatoid arthritis
- Mild to moderate Crohn's disease in patient's refractory or intolerant to thiopurines (licensed indication of subcutaneous preparations)
- Severe psoriasis
- Severe psoriatic arthritis

Licensed indications vary with brand. See relevant see SPC for full details.

This shared care protocol also includes treatment of chronic inflammatory conditions where off-label use of methotrexate is appropriate, including, but not limited to, the following specialities and conditions:

- Rheumatology (e.g. inflammatory arthritis, connective tissue disease, vasculitis)
- Dermatology (e.g., severe eczema, bullous conditions)
- Gastroenterology (e.g. severe Crohn's disease or other inflammatory bowel disease e.g. collagenous and lymphocytic colitis)
- Neurology (e.g. myasthenia gravis, inflammatory neuropathies)
- Ophthalmology (e.g. uveitis, scleritis)
- Respiratory disease (e.g. sarcoidosis, interstitial lung disease)

These indications are off label. The specialist must specify the indication for each patient when initiating shared care and clearly state when use is off label.

This shared care protocol applies to adults aged 18 and over. It does not include use of methotrexate for cancer indications.

3. Locally agreed off-label use

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Nil further identified- see above

4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

Contraindications:

- Hypersensitivity to methotrexate or any excipients.
- Significant hepatic impairment.
- Ascites or pleural effusion: drain prior to treatment to reduce the risk of methotrexate accumulation.
- Significant renal impairment – creatinine clearance (CrCl) less than 30 mL/min.
- Severe infections (acute or chronic) or immunodeficiency syndromes.
- Known active peptic ulceration.

- Pregnancy and breast-feeding.
- Vaccination with live vaccines during treatment with methotrexate at immunosuppressive doses. See section 7 for further detail.
- Concomitant use of medicines with anti-folate properties, e.g. trimethoprim, co-trimoxazole (see section 7). It is recommended to add Trimethoprim and Co-trimoxazole as an allergy warning to the patient's record to alert for any co-prescribing.

Cautions:

- Renal impairment: dose reduction required (section 5).
- Alcohol dependence.
- Hepatic impairment, particularly if due to alcohol use.
- Pre-existing blood dyscrasias or disorders, including bone marrow hypoplasia, leucopenia, thrombocytopenia, or significant anaemia. Confirm to primary care that any underlying dyscrasias have been considered, and whether any change to standard monitoring in section 9 is required.
- Respiratory disease.
- Concomitant use with hepatotoxic or haematotoxic medicines (see section 7).
- History of ulcers of the oral cavity, ulcerative stomatitis, gastrointestinal ulcers, or ulcerative colitis.
- History of chronic or recurrent infection (e.g. frequent infective COPD exacerbations, or recurrent urinary tract infection).
- Frail or elderly – consider reduced/ minimum effective dose.
- Conditions which increase the risk of dehydration (e.g. vomiting) may increase the risk of toxicity. Consider interrupting treatment until symptoms cease.

5. Initiation and ongoing dose regimen

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- Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient's dose has been optimised and with satisfactory investigation results for at least 4 weeks.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician
- Termination of treatment will be the responsibility of the specialist.

There is a wide dose range depending on the indication. The selected dose of methotrexate, and the folic acid regimen, will be tailored to the individual patient and decided by the specialist.

The initial stabilisation period must be prescribed by the initiating specialist.

Transfer of monitoring and prescribing to primary care is usually after 3 months. The duration of treatment will be determined by the specialist based on clinical response and tolerability.

Maintenance dose (following initial stabilisation):

Usual dose range**: 7.5 mg – 25 mg weekly**, adjusted according to response. Please note for rheumatology conditions a patient may be initiated on more than one DMARD. To reduce dosing errors **only the 2.5 mg methotrexate tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient.

All patients should be prescribed folic acid at a dose of 5 mg at least once weekly, to be taken on a different day than their methotrexate dose. The specialist should include clear details of the folic acid regimen in their communication with the patient and primary care.

The initial maintenance dose must be prescribed by the initiating specialist.

Conditions requiring dose adjustment:

- Renal impairment: in patients with CrCl less than 60 mL/min the dose should be reduced by 50%. If CrCl is less than 30mL/min discontinuation may be indicated. See section 10.

6. Pharmaceutical aspects

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Route of administration:	Oral tablets, or subcutaneous injections

Formulation:	**Methotrexate 2.5mg tablets** Other strengths are available but, to reduce dosing errors, **only the 2.5 mg tablets should be prescribed**. The dose should be taken **once weekly** on the same day each week, and that day should be clearly communicated to the patient. **Methotrexate subcutaneous injection** Solution for injection available in 2.5 mg increments ranging from 7.5 mg – 30 mg and varying with brand: • 50 mg/mL in pre-filled injector or syringe (Methofill®): 7.5 mg to 30 mg • 50 mg/mL in pre-filled pen (Metoject®): 7.5 mg to 30 mg • 25 mg/mL in pre-filled pen (Nordimet®): 7.5 mg to 25 mg • 25 mg/mL in pre-filled syringe (Zlatal®): 7.5 mg to 25 mg If subcutaneous methotrexate is prescribed, secondary care must specify the brand, and the patient should be maintained on that brand due to device familiarity and training provided. Brand should be specified on clinical systems. See SPCs for full details of available products. Local, pre-existing arrangements for the supply of methotrexate injection and ancillary products, and for the disposal of cytotoxic waste, should be observed. When deciding which formulation to prescribe, the specialist should consider the patient's circumstances and overall polypharmacy burden, especially for patients with a high pill burden. See MHRA advice on preventing inadvertent daily dosing. Converting from an oral to a subcutaneous dosage form may be appropriate where patients experience intolerable gastrointestinal adverse effects and should only be undertaken by a specialist.
Administration details:	Tablets should not be split or crushed for administration. Review formulation if patient is unable to swallow tablets. Carers should wear single-use gloves to handle methotrexate tablets. Anyone handling the tablets should wash their hands immediately afterwards. Pregnant people, including patients and carers, should avoid handling methotrexate. Avoid skin or mucosa contact with methotrexate solution for injection. Spillage advice should be provided to patients on subcutaneous methotrexate. If a dose of methotrexate is missed it should be taken as soon as remembered, within one or two days. Doses which are three or more days late should be skipped entirely. Take the next dose as scheduled, on the usual day. A double dose should not be taken to make up for a missed dose.

Other important information:	Methotrexate is taken once weekly, and there is a significant risk of toxicity if it is taken more frequently. Prescribers should follow the MHRA advice on preventing inadvertent daily dosing, including ensuring that the patient and/or carer understands the dosing schedule and is able to follow it. All patients should be prescribed folic acid at a dose of at least 5 mg once weekly, to be taken on a different day than their methotrexate dose. The specialist should include clear details of the folic acid regimen in their initial communication with primary care. In areas where methotrexate monitoring booklets are in use, the patient should receive a monitoring booklet from the specialist upon initiation of treatment. They should bring this booklet to all specialist and GP appointments where it will be updated by the health professional conducting the appointment. The patient should also produce the booklet to any health professional involved in other aspects of their care e.g. pharmacists and dentists.

7. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

Methotrexate is associated with many interactions, some of which are significant enough to contraindicate concurrent use, require dose adjustment and/or additional monitoring (see section 4). Additional interactions which become relevant at higher doses (e.g. those used in oncology) are not included.

- Co-administration of medicinal products which cause folate deficiency (e.g. **trimethoprim** and **co-trimoxazole**) can lead to increased methotrexate toxicity and is contraindicated (see section 4). Particular caution should therefore also be exercised in the presence of existing folic acid deficiency. It is recommended to add Trimethoprim and Co-trimoxazole as an allergy warning to the patient's record to alert for any co-prescribing.
- NSAIDs, COX-2 inhibitors, aspirin: may reduce excretion of methotrexate, increasing risk of toxicity. These drugs are frequently used with methotrexate without incident, and aspirin at antiplatelet doses is unlikely to interact to a significant degree. Be aware of trends in monitoring parameters.
- **Alcohol:** consumption of alcohol increases the risk of hepatotoxicity. Patient should moderate their alcohol intake as advised by their specialist team – the Versus Arthritis leaflet suggests no more than 14 units per week. Methotrexate | Versus Arthritis Leaflet.
- **Antibiotics** may alter methotrexate levels. Methotrexate should be interrupted during periods of acute infection (see section 10).
- **Leflunomide and Sulfasalazine**: increased risk of bone marrow and liver toxicity; these combinations are used in clinical practice without incident. Be aware of trends in monitoring parameters; increased monitoring and vigilance required.
- **Ciclosporin**: increased risk of nephrotoxicity and methotrexate toxicity.
- **Azathioprine and mercaptopurine:** not advised due to increased risk of toxicity.

- **Live vaccines** (e.g. oral polio, oral typhoid, MMR, BCG, Zostavax®) are advised in line with the national schedule for all patients, unless the patient is taking a dose of methotrexate or other immunosuppressive drug that exceeds those specified in the Green Book. Doses below this level are not considered sufficiently immunosuppressive and these patients can receive live vaccines. Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice.
- **Proton Pump Inhibitors:** potentially decreases the clearance of Methotrexate when high doses are used (Doses used for inflammatory diseases are considered low dose compared to the higher doses used in cancer treatments). Manufacturer advises use with caution or avoid if possible.
- Drugs with hepatotoxic, haematotoxic or nephrotoxic effects: Increased frequency of monitoring may be recommended.
- Avoid concomitant use of **cytotoxics, clozapine, and olanzapine:** increased risk of agranulocytosis.
- Levetiracetam: may increase plasma levels of methotrexate.
- **Retinoids**: increased risk of hepatotoxicity and may increase plasma levels of methotrexate.
- **Nitrous oxide and pyrimethamine**: increased antifolate effect of methotrexate.
- **Lomitapide:** increased risk of hepatotoxicity.
- **Probenecid:** excretion of methotrexate reduced.
- **Phenytoin:** possible increased methotrexate toxicity, and decreased phenytoin effect.
- **Theophylline and other methylxanthines:** may reduce methotrexate efficacy. Methotrexate may reduce theophylline clearance.
- **Anticonvulsants:** may reduce methotrexate levels.
- **Colestyramine**: may increase elimination of methotrexate.

8. Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations:

- Height and weight
- Blood pressure
- Full blood count (FBC)
- Urea and electrolytes (U&Es) including creatinine and creatinine clearance (CrCl)
- Alanine aminotransferase (ALT) and albumin
- Screening for viral infections as per local policy e.g. HIV, Hepatitis B and C, Varicella Zoster, Epstein Barr virus, Cytomegalovirus
- Screening for lung disease, including interstitial lung disease and tuberculosis, should be undertaken at clinician discretion on a case-by-case basis
- Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g. pneumococcal, shingles, influenza, COVID-19)
- Consideration for regular monitoring of liver fibrosis using FIB4 scores in patients at increased risk

Initial monitoring and at dose change:
To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for 3 months. After which, the transfer of prescribing to primary care should normally only take place when the patient has received a stable dose for at least 4 weeks and their blood and physical tests results have been satisfactory. It is anticipated that this should be around 12 weeks after initiation of the medicine.

- FBC
- U&Es, including creatinine and CrCl
- ALT and albumin (LFTs)
- Rheumatology patients: CRP &/or ESR (for monitoring disease activity/outcomes rather than for safety- this may continue to be monitored by the rheumatology team but will not be part of the primary care safety monitoring parameters)

Following a dose increase repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule.

More frequent monitoring is appropriate in patients at higher risk of toxicity, e.g. concurrent use of more than one DMARD. This is particularly important for patients co-prescribed methotrexate and leflunomide. The combination is highly effective but potentially synergistically toxic to liver and bone marrow and increase monitoring frequency is recommended. (see Leflunomide shared care protocol)

Ongoing monitoring:
The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. This should usually be undertaken annually unless the patient has been stabilised on treatment for a long time and considered suitable for patient initiated follow up (PIFU). Rapid access to the specialist team for advice and guidance should still be available if the patient is enrolled with PIFU.

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

9. Ongoing safety monitoring requirements to be undertaken by primary care

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See section 10 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring	Frequency
• FBC • U&Es including creatinine and CrCl • ALT and albumin (LFTs)	Every 12 weeks. Where necessary seek advice on increased frequency of monitoring on a case-by-case basis. **The exact frequency of monitoring to be communicated by the specialist in all cases**.

• Immunocompromised patients aged 50 years and over are eligible for the shingles (herpes zoster) vaccine (Shingrix®). • The eligible age for Immunocompetent patients will change in a phased implementation over a 10-year period. • . Refer to Green Book Chapter 6 (Contraindications and special considerations) and Green Book Chapter 28a (Shingles) for further details. • **Annual** influenza (The Green Book, Chapter 19) vaccinations are recommended. • COVID-19 vaccination (The Green Book, Chapter 14a) is safe and recommended. • Repeat pneumococcal vaccine may be indicated. See Green Book Chapter 25 for advice.	• Shingles vaccination: one-off. • Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. • Other vaccinations as per national schedule.
(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.	

10. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Result	Action for primary care
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance	
• Full blood count: • White blood cells less than $3.5x10^9$/L • Lymphocytes less than $0.5x10^9$/L • Neutrophils less than $1.6x10^9$/L • Platelets less than $140x10^9$/L • Eosinophilia greater than $0.5x10^9$/L	Withhold and discuss with specialist team.

Mean cell volume >105 fL	Consider interruption in treatment if there is a significant increase from baseline. Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently.
Signs or symptoms of bone marrow suppression, e.g. unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers.	Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above.
Infections: Systemic infection requiring antibiotics	Temporarily withhold methotrexate until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate. Contact specialist for advice as needed
Liver function tests: ALT >100 units/L, or any sudden increases (e.g. double of baseline), OR Unexplained fall in serum albumin <30g/L Jaundice	Withhold and discuss with specialist team. Assess for other causes of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Renal function: Creatinine increase of greater than 30% from baseline in the last 12 months, or if CrCl reduces to <60ml/min	Use clinical judgement and repeat in 1 week. Rule out other causes. If still more than 30% from baseline withhold and discuss with specialist team.
Gastrointestinal disorders: Nausea	Review for reversible causes and treat as appropriate. Enquire which day of the week the patient takes their methotrexate, and which day(s) they take folic acid and confirm against the patient's records. Discuss with specialist team if persistent or severe. Switch to subcutaneous therapy may be indicated, under specialist advice.

Diarrhoea, ulcerative stomatitis, haematemesis, black or bloody stools, or suspected pancreatitis	Withhold and discuss with specialist team.
Symptoms of interstitial lung disease e.g. persistent cough, dyspnoea, fever	If methotrexate-induced lung disease is suspected, discuss with specialist team urgently and withhold treatment. Treat with corticosteroids as directed by a specialist and do not restart methotrexate.
Photosensitivity	Continue methotrexate. Reinforce appropriate self-care e.g. sun avoidance and purchasing of a broad-spectrum sunscreen (at least SPF30).
Pregnancy	In pregnant patients, stop methotrexate immediately and prescribe folic acid 5 mg/day. Discuss with specialist team urgently. See section 12. In pregnancies with paternal exposure, see section 12.

11. Advice to patients and carers

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The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Symptoms of chickenpox or contact with a person with chickenpox or shingles.
- Persistent cough, shortness of breath, or any other problems with breathing.
- Sore throat, mouth ulcers, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection
- Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting.
- Swelling of the hands, feet, or ankles
- Unexplained bleeding or bruising, black stools, or blood in the vomit or stools.
- Suspected or confirmed pregnancy.

The patient and/or carer should be advised:

- What shared care means for their treatment, what to expect, and their responsibilities under shared care.

- During a serious systemic infection methotrexate should be temporarily discontinued until the patient has recovered from the infection.
- That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended.
- Methotrexate is taken **once weekly** and taking it more frequently can be dangerous. If a patient thinks they have taken too much methotrexate they should immediately seek advice from their prescriber, or NHS 111.
- For patients taking tablets, that they will only ever be prescribed methotrexate 2.5 mg tablets. **Patients who receive 10 mg tablets should always question the discrepancy and not take the higher strength tablets**.
- Which day or days they should take their folic acid, with emphasis that methotrexate and folic acid should not be taken on the same day.
- To moderate their alcohol intake as advised by their specialist team – the Versus Arthritis leaflet suggests no more than 14 units per week. Methotrexate | Versus Arthritis Leaflet.. More information can be found at https://www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/. Taking alcohol and methotrexate together increases the risk of liver injury.
- Tell anyone who prescribes them a medicine that they are taking methotrexate. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- Skin may be more sensitive to exposure to UV light while taking methotrexate. If this occurs use appropriate self-care: e.g. sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use a broad-spectrum sunscreen (at least SPF30).
- To use effective contraception, and to take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant. All patients, both men and women, should inform their specialist well in advance if they are planning a pregnancy so that changes can be made to their treatment regime.
- Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely, e.g. due to fatigue or dizziness.
- For patients taking 20mg/week or more: to avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see:
    - the Green Book (Chapter 34)
    - Guidelines on post exposure prophylaxis (PEP) for varicella or shingles (October 2024) - GOV.UK

Patient information:

General information: https://www.nhs.uk/medicines/methotrexate/

Dermatology: Methotrexate patient information leaflet Methotrexate - BAD Patient Hub

Rheumatology: Versus Arthritis patient information leaflet Methotrexate Versus Arthritis

Gastroenterology: Crohn's and Colitis UK patient information Methotrexate

12. Pregnancy, paternal exposure, and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

Pregnancy:

Methotrexate is contraindicated in pregnancy. It is cytotoxic and is used for termination of pregnancy and to treat ectopic pregnancy. Pregnancy should be excluded prior to starting treatment.

Patients of childbearing potential should use effective contraception during treatment and for a period afterwards as advised by the specialist team. If a patient becomes pregnant whilst taking or within the defined period by the specialist, folic acid 5 mg daily should be continued throughout the pregnancy. Those who wish to become pregnant should speak to their prescriber to discuss the possibility of switching to an alternative medicine.

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids | Rheumatology | Oxford Academic 2022 advises that Methotrexate at any dose should be avoided in pregnancy and stopped at least one month in advance of planned conception, when it should be switched to another pregnancy-compatible drug to ensure maintenance of maternal disease suppression.

In women treated with low-dose (<25 mg/week) Methotrexate within one month prior to conception, folic acid supplementation (5 mg/day) should be continued up to 12 weeks of pregnancy

In unintended pregnancy on low-dose (<25 mg/week) Methotrexate there is minimal risk to the foetus; the drug should be stopped immediately, folic acid supplementation (5 mg/day) continued and a careful evaluation of foetal risk with early referral to a foetal medicine department considered

Information for healthcare professionals: https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-METHOTREXATE-IN-PREGNANCY/

Information for patients and carers: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Methotrexate/

Breastfeeding:

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids | Rheumatology | Oxford Academic 2022 advises although only minute amounts of methotrexate are excreted into breastmilk, methotrexate cannot be recommended in breastfeeding because of theoretical risks and insufficient data on outcomes

The manufacturers contraindicate use of methotrexate while breastfeeding. The UK Drugs in Lactation Advisory Service recommends caution and advises that breastfeeding should be avoided until at least 24 hours after a weekly dose not exceeding 25 mg. Infant blood counts

should be monitored. Limited evidence indicates that small amounts are found in breast milk after weekly administration.

Paternal exposure:

There are hypothetical risks of genetic abnormalities in sperm which could potentially affect offspring conceived during treatment. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). Where a couple wishes to attempt conception and the male partner's condition is well-controlled with methotrexate, the UK Teratology Information Service recommends an assessment and discussion of the potential benefits and risks of continuing paternal treatment vs. discontinuation. This should be undertaken by the specialist, using a shared decision-making approach. The risks to the foetus are theoretical rather than established.

Paternal methotrexate use at the time of conception is not an indication for additional foetal monitoring. However, other risk factors may be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids | Rheumatology | Oxford Academic 2022 advises paternal exposure to low dose methotrexate (<25mg/week) is considered compatible with pregnancy

Information for healthcare professionals:
https://www.medicinesinpregnancy.org/bumps/monographs/PATERNAL-USE-OF-METHOTREXATE/

Fertility:

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects are reversible after discontinuation of therapy in most cases.

13. Specialist contact information

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Please approach the patient's named secondary care clinician via the usual method of communication, this may be via letter or if more urgent via advice and guidance

Respiratory disease (e.g. sarcoidosis, interstitial lung disease)

Rheumatology

- Advice and Guidance.
- Consultant Connect - during office hours

- UHD switchboard – on-call rheumatologist during office hours
- Rheumatology advice line: This is not a direct connection (answerphone service) and is not for emergency calls. It requires patients/clinicians to leave a message via the answerphone service. The messages will be logged, triaged and answered in order of need.

Gastroenterology (UHD and DCH)

- Advice and Guidance
- Consultant Connect- during office hours
- IBD advice line: This is not a direct connection (answerphone service) and is not for emergency calls. It requires patients/clinicians to leave a message via the answerphone service. The messages will be logged, triaged and answered in order of need.

Neurology

- Advice and Guidance
- Consultant Connect- during office hours
- UHD Switchboard- on-call neurologist during office hours

Dermatology (UHD and DCH)

- Advice and Guidance (please mark as urgent)
- Via switchboard to the on-call dermatology doctor

Respiratory (UHD and DCH)

- Advice and Guidance

14. Additional information

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It is anticipated that each area will continue to adhere to pre-existing local arrangements for the supply of methotrexate injection and ancillary products, and for the disposal of cytotoxic waste.

Where patient care is transferred from one specialist service or GP practice to another the GP is responsible for letting the specialist team know if they are unhappy with continuing the shared care. All involved healthcare professionals should ensure a prompt transfer of care that includes effective information sharing and continued access to the medicines by the patient during the transition.

15. References

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- eBNF. Methotrexate. Accessed via https://bnf.nice.org.uk/drug/methotrexate.html on 13/08/2021.
- Methotrexate 2.5 mg tablets (Maxtrex®). Date of revision of the text 12/2020. Accessed via https://www.medicines.org.uk/emc/product/1376/ on 13/08/21.

- Methotrexate 10 mg solution for injection in pre-filled injector (Methofill®). Methofill Self dose Healthcare Professional Guide
- Methotrexate 10 mg solution for injection in pre-filled pen (Metoject®). Date of revision of the text 07/2020. Accessed via https://www.medicines.org.uk/emc/product/11351/ on 13/08/21.
- Methotrexate 10 mg solution for injection in pre-filled pen (Nordimet®). Date of revision of the text Dec 2020. Accessed via https://www.medicines.org.uk/emc/product/7721/ on 13/08/21.
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- British Society of Rheumatology and British Health Professionals in Rheumatology. 2017. Guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Accessed via https://academic.oup.com/rheumatology/article/56/6/865/3053478.
- British Society of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016. Accessed via https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.14816.
- British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids | Rheumatology | Oxford Academic 2022
- . MHRA Drug Safety Update. Methotrexate once weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing. September 2020. Accessed via https://www.gov.uk/drug-safety-update/methotrexate-once-weekly-for-autoimmune-diseases-new-measures-to-reduce-risk-of-fatal-overdose-due-to-inadvertent-daily-instead-of-weekly-dosing.

16. Other relevant national guidance

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- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/
- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

Via the usual methods

Appendix 1: Shared Care Request letter (Specialist to Primary Care Prescriber)

Dear *[insert Primary Care Prescriber's name]*

Patient name: *[insert patient's name]*
Date of birth: *[insert date of birth]*
NHS Number*:* *[insert NHS Number]*
Diagnosis: *[insert diagnosis]*

As per the agreed *[insert APC name]*shared care protocol for *[insert medicine name]* the treatment of *[insert indication],* this patient is now suitable for prescribing to move to primary care.

The patient fulfils criteria for shared care, and I am therefore requesting your agreement to participate in shared care. Where baseline investigations are set out in the shared care protocol, I have carried these out.

I can confirm that the following has happened regarding this treatment:

	Specialist to complete
The patient has been initiated on this therapy and has been on an optimised dose for the following period:	
Baseline investigation and monitoring as set out in the shared care documents have been completed and were satisfactory	*Yes / No*
The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care	*Yes / No*
The risks and benefits of treatment have been explained to the patient	*Yes / No*
The roles of the specialist/specialist team/ Primary Care Prescriber / Patient and pharmacist have been explained and agreed	*Yes / No*
The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments	*Yes / No*
I have enclosed a copy of the shared care protocol which covers this treatment/the SCP can be found here (insert electronic/ web link)	*Yes / No*
I have included with the letter copies of the information the patient has received	*Yes / No*
I have provided the patient with sufficient medication to last until	
I have arranged a follow up with this patient in the following timescale	

Treatment was started on, *[insert date started]* and the current dose is *[insert dose and frequency]*.

If you agree, please undertake monitoring and treatment from *[insert date]* NB: date must be at least 1 month from initiation of treatment.

The next blood monitoring is due on *[insert date]* and should be continued in line with the shared care guideline.

Please respond to this request for shared care, in writing, within 14 days of the request being made where possible.

Appendix 2: Shared Care Agreement Letter (Primary Care Prescriber to Specialist) Not routinely used in the Dorset system; acceptance of shared care is implied by a nil return.

Primary Care Prescriber Response

Dear *[insert Doctor's name]*
Patient *[insert Patient's name]*
NHS Number *[insert NHS Number]*
Identifier *[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient under a shared care agreement and to provide the following treatment

Medicine	Route	Dose & frequency

I can confirm that I am willing to take on this responsibility from *[insert date]* and will complete the monitoring as set out in the shared care protocol for this medicine/condition.

Primary Care Prescriber signature: _____Date: _____

Primary Care Prescriber address/practice stamp

Appendix 3: Shared Care Refusal Letter (Primary Care Prescriber to Specialist)

Re:

Patient *[insert Patient's name]*

NHS Number *[insert NHS Number]*

Identifier *[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient.

In the interest of patient safety NHS *[insert CCG name]***,** in conjunction with local acute trusts have classified *[insert medicine name]*as a Shared Care drug and requires a number of conditions to be met before transfer can be made to primary care.

I regret to inform you that in this instance I am unable to take on responsibility due to the following:

		Tick which applies
1.	**The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care** As the patient's primary care prescriber, I do not feel clinically confident to manage this patient's condition because *[insert reason]*. I have consulted with other primary care prescribers in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice. **I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given above.**	
2.	**The medicine or condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement** As the medicine requested to be prescribed is not included on the national list of shared care drugs as identified by RMOC or is not a locally agreed shared care medicine I am unable to accept clinical responsibility for prescribing this medication at this time. **Until this medicine is identified either nationally or locally as requiring shared care the responsibility for providing this patient with their medication remains with you**	

3.	**A minimum duration of supply by the initiating clinician** As the patient has not had the minimum supply of medication to be provided by the initiating specialist, I am unable to take clinical responsibility for prescribing this medication at this time. Therefore, can you please contact the patient as soon as possible to provide them with the medication that you have recommended. ***Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.***	
4.	**Initiation and optimisation by the initiating specialist** As the patient has not been optimised on this medication, I am unable to take clinical responsibility for prescribing this medication at this time. Therefore, can you please contact the patient as soon as possible to provide them with the medication that you have recommended. ***Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.***	
5.	**Shared Care Protocol not received** As legal responsibility for clinical care lies with the clinician who signs the prescription, I need to ensure that I am in possession of sufficient clinical information for me to be confident to prescribe this treatment for my patient and it is clear where each of our responsibilities lie to ensure the patient is safely managed***.*** For this reason, I am unable to take clinical responsibility for prescribing this medication at this time, therefore would you please contact the patient as soon as possible to provide them with the medication that you have recommended. ***Until I receive the appropriate SCP, responsibility for providing the patient with their medication remains with you.***	
6.	**Other (Primary Care Prescriber to complete if there are other reasons why shared care cannot be accepted)**	

I would be willing to consider prescribing for this patient once the above criteria have been met for this treatment.

NHS England ‘Responsibility for prescribing between Primary & Secondary/Tertiary care’ guidance (2018) states that “when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs

would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs." In this case we would also see the term GP being interchangeable with the term Primary Care Prescriber.

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible

Yours sincerely

Primary Care Prescriber signature: _____

Date: _____

Primary Care Prescriber address/practice stamp