1. **Aim/Purpose of this Guideline**
   1.1. This guideline applies to medical, nursing and pharmacy staff in the safe and appropriate prescription and administration of methotrexate when used in rheumatological and dermatological conditions.

2. **The Guidance**
   2.1. See below for the Shared Care Guideline.
**ORAL AND SUBCUTANEOUS METHOTREXATE**

- This shared care guideline sets out details for the sharing of care of patients with inflammatory joint disease and psoriasis prescribed methotrexate orally or subcutaneously. These guidelines provide additional limited information necessary to aid in the treatment of rheumatology and dermatology patients. As with all shared care guidelines they highlight significant prescribing issues but should be used in conjunction with the BNF, ABPI summary of product characteristics and do not replace them.

**BACKGROUND INFORMATION**

The National Patient Safety Authority (NPSA) has highlighted the risks when prescribing methotrexate including failings from poor monitoring of therapy, which have led to fatalities. This Shared Care Guideline reflects these recommendations.

**Methotrexate must be administered as a WEEKLY dose.**

Serious errors have occurred as a result of ambiguous instructions.

**INDICATIONS FOR THE PURPOSES OF THIS GUIDELINE**

Treatment of adults with inflammatory joint disease or connective tissue disease, and treatment of adults with psoriasis and other rare skin diseases.

Methotrexate requires careful monitoring to avoid toxicity. It is recommended that it is initiated in primary care only after consultant diagnosis and under consultant supervision. Patients may be switched from oral to subcutaneous methotrexate due to poor tolerance, particularly gastrointestinal side effects, or to improve efficacy.

**DOSE**

Usual oral dose range 2.5mg – 25mg once weekly. Methotrexate should be prescribed as multiples of 2.5mg tablets.

The label on prescribed/dispensed methotrexate should state the instructions clearly, for example: 'methotrexate 2.5mg tablets: (number of tablets) to be taken as a single dose ONCE A WEEK on XXXDAY'.

Usual subcutaneous dose 7.5mg – 25mg once weekly. Methotrexate should be prescribed as complete pre-filled pens by brand name. The majority of patients will use Metoject but a small number may be on alternative brands if they are unable to operate the device.

The label on prescribed/dispensed methotrexate should state the instructions clearly, for example: 'methotrexate .............injection: (dose) to be injected subcutaneously ONCE A WEEK on XXXDAY'.

To limit the side effects of methotrexate, all patients should receive folic acid 10mg once a week on the day after they take/administer methotrexate. Higher doses (e.g. 5mg daily omitted on the day of methotrexate) may sometimes be used on the advice of the specialist team.

**CONTRAINDICATIONS – methotrexate should not be used in patients:**

- With severe / significant renal or hepatic impairment
- Active acute infectious disease, evidence of immunodeficiency syndrome
- With serious cases of anaemia, leucopenia, thrombocytopenia
- Receiving drugs with antifolate properties e.g. cotrimoxazole, trimethoprim, sulphonamides
- Who are breastfeeding
- Pregnancy – Methotrexate can reversibly affect the fertility of men and women. It can also affect the development of the unborn child so women of childbearing potential should use a reliable method of contraception to avoid the risk of an unplanned pregnancy during treatment and for at least three months after discontinuing methotrexate. When planning a pregnancy it is important that women on this drug discuss their medication with the relevant clinical team. They will need to stop treatment with methotrexate for at least three months before attempting to conceive.

**PRECAUTIONS - caution is advised in patients:**

- Who are elderly (consider reduction in dose)
- With haematological depression
- Renal impairment (reduce dose)
- Diarrhoea, ulcerative disorders of GI tract
- Psychiatric disorders
- Radiotherapy
- Alcohol consumption increases the risk of liver fibrosis so it is advisable not to drink. However an occasional drink will not usually cause significant side effects.

**MONITORING**

PRIOR TO STARTING THERAPY - THE RHEUMATOLOGY / DERMATOLOGY TEAM TO UNDERTAKE AND COMMUNICATE TO GP, RESULTS OF:

- Chest x-ray
- Baseline assessment of renal and liver function, and FBC
- Pulmonary function tests in selected patients.
- Then FBC. Electrolytes & LFTs every 2 weekly until on stable dose for 6 weeks the dose is stabilised) then monthly thereafter for 3 months, then at least every 12 weeks unless advised otherwise.
ONGOING MONITORING - GENERAL PRACTICE:
It is recommended that all blood counts are monitored and recorded in the patient record and patient booklet to comply with NPSA and GMS. The patient may be asked to show their methotrexate booklet when collecting prescriptions from a community pharmacy; this is an additional check to ensure that appropriate monitoring is being undertaken. DO NOT issues further prescriptions unless the patient is attending for the required blood monitoring.

- FBC, LFTs, Electrolytes fortnightly until dose is stable for 6 weeks, then monthly for three months, then at least once every 12 weeks. Some patients at increased risk of toxicity may be advised to have monthly blood tests for longer by their specialist team.
- FBC, U&Es and LFTs should be measured one week after any increase in dose.
- In order to monitor disease activity a 3 monthly CRP/ESR would be helpful.
- Always look at the mean corpuscular volume (MCV). A rising value may precede marrow dysplasia BUT check for other causes before stopping treatment (eg B12, TFT, Folate and alcohol consumption).
- Note that Dermatology also request pro-collagen III (PIIINP) test at regular intervals – this will be carried out by secondary care if indicated.

IF ANY OF THE FOLLOWING OCCUR, REPEAT THE TEST, CONSIDER INTERRUPTING TREATMENT AND IF REQUIRED CONTACT THE SPECIALIST TEAM FOR ADVICE:

- WCC < 3.5 x 10^9/L – particularly if falling trend
- Neutrophils < 1.6 x 10^9/L – particularly if falling trend
- Mean Cell Volume > 105 – particularly if rising trend
- Unexplained eosinophilia > 0.5 x 10^9/L
- Platelet count < 140 x 10^9/L
- ALT and/or AST > 100
- Unexplained reduction in albumin (below 30 g/L)
- Creatinine increased > 30% over 12 months
- eGFR decreases < 60mL/min/1.73m² and there is a significant falling trend
- Severe nausea or diarrhoea
- Severe mouth or genital ulceration

NB: Do not routinely stop treatment prior to surgery or if the patient has an infection, unless hospital admission or parenteral antibiotics are required.

SIDE EFFECTS
Patients must report mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, and any unexplained illness / infection and should be seen urgently for full blood count and liver function tests.

If pulmonary symptoms are reported, these should be investigated urgently with a chest x-ray to exclude pneumonitis.

Beware of patients attending GP surgeries or pharmacies presenting with other symptoms; signs of methotrexate toxicity may present as, for example, breathlessness, dry persistent cough, vomiting and diarrhoea.

Very common/Common:
- Mouth ulcers, nausea and diarrhoea, hair loss

Uncommon:
- Headaches, bone marrow suppression, lung inflammation, liver inflammation, clinically significant renal failure

Very rare:
- Drowsiness

COMMON/SIGNIFICANT DRUG INTERACTIONS
- Folate antagonists should be avoided – nitrous oxide, co-trimoxazole, trimethoprim, sulphonamides, phenytoin and some antimalarials.
- NSAIDs – This is not considered to be a problem in patients with inflammatory arthritides as the doses used take this interaction into account. However it may be an issue with Dermatology patients and advice should be sought from the Dermatology Team
- Ciclosporin
- Actretin
- Clozapine: increased risk of agranulocytosis
- Leflunomide: increased risk of liver toxicity
- Drugs affecting transport function of renal tubules – ciprofloxacin, penicillins, probenecid, aspirin (though low-dose aspirin can be used safely)
- Caution is needed when co-prescribing hepatic or nephrotoxic drugs

VACCINATIONS
The Green Book should be regarded as the definitive source of information regarding vaccination; chapter 7 deals specifically with immunosuppressed patients. Recommended vaccines for all patients include influenza (annually) and pneumococcus, as a single dose of Pneumovax. Ideally this should be administered before starting treatment, but if this is not possible it should be administered as soon as practicable.

Live vaccines are not recommended for patients on immunosuppression, including those on methotrexate. Low levels of immunosuppression are not considered an absolute contraindication to the shingles vaccine (Zostavax) and the Green Book recommends that low-dose (≤ 25mg/week) methotrexate is not a contraindication in most patients, though clinician discretion is advised.

Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles.
PRODUCT INFORMATION

- Methotrexate 2.5mg tablets
- Methotrexate Pre-Filled Pen – the Metoject brand is the preferred product that patients are trained to administer; there are differences in the preparation and administration technique between brands. Please prescribe by brand name
- If Metoject is prescribed generically, the concentration will be 50mg/mL with different volumes used depending on the dose required:
  - 7.5mg/0.15mL
  - 10mg/0.2mL
  - 12.5mg/0.25mL
  - 15mg/0.3mL
  - 17.5mg/0.35mL
  - 20mg/0.4mL
  - 22.5mg/0.45mL
  - 25mg/0.5mL
  - 27.5mg/0.55mL
  - 30mg/0.6mL
- Parallel-Imported Metoject Pre-Filled Syringes are available and can be supplied against prescriptions that do not specify pens - this may cause difficulties for patients who have only been trained to administer from the pen.

HANDLING AND DISPOSAL

- The patient will be trained in safe self administration of subcutaneous methotrexate by one of the lead nurses in an outpatient setting. When the patient feels confident, and the nurse is convinced that the patient is able to self administer, they can start to self administer at home. The hospital will supply the first cytotoxic sharps bin.
- Should a nurse administer subcutaneous methotrexate, then it is advised they follow accepted good practice as described in the RCN guidance (see reference). Gloves and apron should be worn and methotrexate should not be administered by anyone who is, or suspects they may be, pregnant.
- METOJECT is manufactured such that an air bubble facilitates full discharge of the syringe contents. All waste contaminated with methotrexate is classed as a cytotoxic waste and therefore should be disposed in accordance with local policy for the disposal of hazardous waste. Disposal of full sharps bins is via Cornwall Council (see http://ow.ly/IU8m30ds1ST or call 0300 1234 141 for details).
- For home use, purple lidded cytotoxic sharps bins can be prescribed on an FP10 as: Sharpsguard (Daniels) or Sharpsafe (Frontier) Cyto/Purple, 1 Litre. NB. Not all practice computer systems list the

colour of the container and so prescribers may need to manually add the word ‘purple’ to the prescription to ensure a cytotoxic one is supplied.

References

- Summary of Product Characteristics.

Request for other formats

Please ask if you would like to receive this leaflet in large print, braille, on CD or in any other languages. If you would like the leaflet in an alternative format please contact the NHS Kernow Communications Team at communications@kernowccg.nhs.uk or call 01726 627800.
AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

These are suggested ways in which the responsibilities for the management of patients with rheumatoid arthritis or psoriasis and other rare skin disorders who are prescribed oral or subcutaneous methotrexate can be shared between the specialist and the general practitioners. GPs are invited to participate. The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing these drugs. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them. In its guidelines on responsibility for prescribing (circular EL(91)127) between hospitals and GPs, the DH has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Specialist:

- Decision to prescribe methotrexate.
- Discussion with the patient regarding the benefits and side effects of treatment and gain consent to treatment. Refer patient to specialist nurse service where appropriate (e.g. new patient) for advice on taking/administering the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom.
- A patient information leaflet and booklet for recording test results must be issued.
- To remind patients to bring their monitoring booklet with them each time they see a healthcare professional (so results can be recorded appropriately) and each time they collect a prescription from the community pharmacy.
- Either start oral methotrexate treatment by providing the first prescription and ensuring the patient’s condition is stabilized (usually requires two to three month’s treatment prescribed by the specialist), or, if appropriate, ask the GP whether they are willing to participate in shared care and initiate treatment. In general, Rheumatology ask primary care to initiate oral treatment, whereas Dermatology ask primary care to take over after about one to two months. Subcutaneous treatment should always be initially prescribed by the specialist.
- Prompt communication with GP of any changes in treatment, results of monitoring undertaken and assessment of adverse events.
- Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- Advice to GPs on when to stop treatment.
- Ensure clear arrangements for back-up advice and support.
- Reporting adverse events to the MHRA.

General Practitioner:

- If the GP disagrees to undertake shared care he/she will notify the consultant in writing without undue delay.
- Prescribing of oral or subcutaneous methotrexate after communication with specialists regarding the need for treatment.
- If relevant, taking note of National Patient Safety Advice on methotrexate and on injectable medicines
  http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800&q=0%C2%ACmethotrexate%C2%AC
  http://www.nrls.npsa.nhs.uk/resources/?entryid45=59812&q=0%C2%ACinjectable+medicines%C2%AC
- Monitoring as outlined in the shared care guideline.
- Recording of the results of monitoring in GP system and encouraging the recording of results in the patient booklet.
- Ensure that the GP computer system has an alert flag in accordance with NPSA guidance.
- Prompt referral to a specialist if there is a change in the patient's status.
- Reporting to and seeking advice from a specialist on any aspect of patient care which is of concern to the GP and may affect treatment.
- Reporting adverse events to specialist and MHRA.
- Stopping treatment in the case of a severe adverse event or as per shared care guideline.

Patient:

- Report any adverse effects to their GP and/or specialist whilst being treated with methotrexate.
- Ensure that they have a clear understanding of their treatment. The patient may need support from an appropriate health professional on how to complete the patient held record.
- Ensure they attend for monitoring requirements as per shared care guideline.
- Aware that treatment will be stopped if patient does not attend for monitoring
- Aware that a record of monitoring results should be entered in their booklet, and that they may be asked to show this record when collecting prescriptions from their pharmacy.
- Disposes of used syringes and full sharps bins appropriately and safely.

BACK-UP ADVICE AND SUPPORT IS AVAILABLE FROM THE RELEVANT CLINICAL TEAM
3. Monitoring compliance and effectiveness

<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Compliance with prescribing and administration in accordance with this guideline (or other safe practice)</th>
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<td>Tool</td>
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<tr>
<td>Frequency</td>
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<td>Reporting arrangements</td>
<td>Via Medicines Practice Committee</td>
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<tr>
<td>Acting on recommendations and Lead(s)</td>
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<tr>
<td>Change in practice and lessons to be shared</td>
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4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Diversity & Human Rights Policy' or the [Equality and Diversity website](http://example.com).

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.
# Appendix 1. Governance Information

<table>
<thead>
<tr>
<th>Document Title</th>
<th>Shared care guideline for oral and subcutaneous methotrexate</th>
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<tbody>
<tr>
<td>Date Issued/Approved:</td>
<td>January 2018</td>
</tr>
<tr>
<td>Date Valid From:</td>
<td>January 2018</td>
</tr>
<tr>
<td>Date Valid To:</td>
<td>January 2021</td>
</tr>
<tr>
<td>Directorate / Department responsible (author/owner):</td>
<td>M Wilcock, Head of Prescribing Support Unit, Pharmacy Department, RCHT</td>
</tr>
<tr>
<td>Contact details:</td>
<td>01872 253548</td>
</tr>
<tr>
<td>Brief summary of contents</td>
<td>Some clinical issues and details of prescribing responsibilities for GP and specialists</td>
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<tr>
<td>Suggested Keywords:</td>
<td>Shared care</td>
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<td>Target Audience</td>
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<tr>
<td>Executive Director responsible for Policy:</td>
<td>Medical Director</td>
</tr>
<tr>
<td>Date revised:</td>
<td>January 2018</td>
</tr>
<tr>
<td>This document replaces (exact title of previous version):</td>
<td>Shared care guideline for oral and subcutaneous methotrexate v2.0</td>
</tr>
<tr>
<td>Approval route (names of committees)/consultation:</td>
<td>Cornwall Area Prescribing Committee</td>
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<tr>
<td>Divisional Manager confirming approval processes</td>
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<tr>
<td>Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings</td>
<td>{Original Copy Signed}</td>
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<tr>
<td>Name and Post Title of additional signatories</td>
<td>Not required</td>
</tr>
<tr>
<td>Signature of Executive Director giving approval</td>
<td>{Original Copy Signed}</td>
</tr>
<tr>
<td>Publication Location (refer to Policy on Policies – Approvals and Ratification):</td>
<td>Internet &amp; Intranet</td>
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Version Control Table

<table>
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<th>Version No</th>
<th>Summary of Changes</th>
<th>Changes Made by (Name and Job Title)</th>
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<td>19 Sept 12</td>
<td>V1.0</td>
<td></td>
<td>M Wilcock, Head of Prescribing Support Unit</td>
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<tr>
<td>Nov 2015</td>
<td>V2.0</td>
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All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.

This document is only valid on the day of printing

Controlled Document
This document has been created following the Royal Cornwall Hospitals NHS Trust Policy on Document Production. It should not be altered in any way without the express permission of the author or their Line Manager.
Appendix 2. Initial Equality Impact Assessment Form

<table>
<thead>
<tr>
<th>Name of the strategy / policy / proposal / service function to be assessed (hereafter referred to as policy)</th>
<th>Provide brief description: Shared care guideline for oral and subcutaneous methotrexate</th>
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</thead>
<tbody>
<tr>
<td>Directorate and service area: Pharmacy</td>
<td>Is this a new or existing Policy? Existing</td>
</tr>
<tr>
<td>Name of individual completing assessment: Dan Thomas, Pharmaceutical Services Contracting Team, NHS Kernow</td>
<td>Telephone: 01726 627953</td>
</tr>
</tbody>
</table>

1. Policy Aim* Who is the strategy / policy / proposal / service function aimed at? To provide information on prescribing of oral and subcutaneous methotrexate to enable General Practitioners to take over prescribing responsibility from secondary care.

2. Policy Objectives* To promote a consistent level of shared care between primary and secondary care (in relation to RCHT catchment area)

3. Policy – intended Outcomes* Confident and competent prescribers, enabling medicines to be access in a primary care setting.

4. *How will you measure the outcome? If the guideline is not well received, publicised and adopted, then some GPs may not enter into shared care arrangements.

5. Who is intended to benefit from the policy? General practitioners, hospital specialists and community pharmacists – from understanding local guidance around use of these medicines. Patients/carers, from being able to access medicines from their GP.

6a) Is consultation required with the workforce, equality groups, local interest groups etc. around this policy? No

b) If yes, have these *groups been consulted? Cornwall & IoS Area Prescribing Committee

6c) Please list any groups who have been consulted about this procedure.

7. The Impact

Please complete the following table.

<table>
<thead>
<tr>
<th>Equality Strands:</th>
<th>Yes</th>
<th>No</th>
<th>Rationale for Assessment / Existing Evidence</th>
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<td>Age</td>
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<td><strong>Sex</strong> (male, female, transgender / gender reassignment)</td>
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<td><strong>Race / Ethnic communities /groups</strong></td>
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<td><strong>Disability - learning disability, physical disability, sensory impairment and mental health problems</strong></td>
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<td><strong>Religion / other beliefs</strong></td>
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<td><strong>Marriage and civil partnership</strong></td>
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</table>

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:

- You have ticked “Yes” in any column above and
- No consultation or evidence of there being consultation- this excludes any policies which have been identified as not requiring consultation. or
- Major service redesign or development

8. Please indicate if a full equality analysis is recommended. No

9. If you are not recommending a Full Impact assessment please explain why.

Signature of policy developer / lead manager / director

Date of completion and submission

Names and signatures of members carrying out the Screening Assessment

1. Dan Thomas
2. Mike Wilcock

Keep one copy and send a copy to the Human Rights, Equality and Inclusion Lead, c/o Royal Cornwall Hospitals NHS Trust, Human Resources Department, Knowledge Spa, Truro, Cornwall, TR1 3HD

A summary of the results will be published on the Trust’s web site.

Signed ___________________________

Date ___________________________