Royal College of Nursing

Administering Subcutaneous Methotrexate for Inflammatory Arthritis

Fourth edition

CLINICAL PROFESSIONAL RESOURCE

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Foreword

Having been project lead and lead adult author of the previous two editions of this document – I am both delighted and proud to welcome you to this, the fourth edition of the RCN's guidance on *Administering Subcutaneous Methotrexate for Inflammatory Arthritis*. It is extremely evident from the number of page views (3,264) and downloads (1,341) of the last edition (2016), how clinically and professionally important and supportive clinical practice guidance documents are in promoting evidence-based best practice.

In our continual aim to promote and apply evidence-based best practice, I strongly recommend you read this version. Since the last publication there have been significant and important changes to clinical practice; further licensed products of methotrexate are now available; and the document is now digital, to help facilitate more timely updates

The RCN Rheumatology Nursing Forum is best placed to update this document as all members are rheumatology clinical practitioners, working either in adult or paediatric nursing, and use methotrexate in their daily practice. The publication contains the latest evidence-based guidance to support adult and paediatric practitioners in the safe and confident administration of subcutaneous methotrexate in a variety of primary and secondary care settings, including community and managed care environments.

The publication also, and very importantly, promotes and supports clinical competence and continuous professional development – in line with the RCN's *A Competency Framework for Rheumatology Nurses* (2020), which is a very important framework and pivotal for the ongoing training and development needs of rheumatology nurses.

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Introduction

This is a brief introduction to the RCN's fourth edition of *Administering Subcutaneous Methotrexate for Inflammatory Arthritis*, highlighting the key issues for practitioners.

Updated guidance is necessary as further methotrexate preparations become available to practitioners and new evidence needs to be incorporated. Due to the differences in the current preparations, this guidance does not advise on how to administer a subcutaneous injection, so please refer to the respective summary of product characteristics (SPC), medication information leaflets, educational booklets and videos available for the different preparations.

This guidance provides the background information regarding subcutaneous methotrexate as an educational resource for practitioners, with particular reference to safety and best practice; and incorporates new sections on treat-to-target and medication optimisation.

Whilst the guidance has been developed for rheumatology practitioners, some aspects may also be of value to health care colleagues working in other specialties including dermatology, gastroenterology and ophthalmology.

At the time of writing, there are a number of commercially available pre-filled methotrexate autoinjector PENs and pre-filled injector devices which fully comply with EU directives (2013). The risk of needlestick injury and cytotoxic spillage using either a PEN or injector device is minimal throughout the injection process as the needle is not exposed and pressure is needed after skin insertion, so accidental spillage is reduced.

However, licensed and EU compliant pre-filled methotrexate syringes are also commercially available for use from some manufacturers. There is anecdotal evidence that some patients prefer these syringes, as they can control the speed of administration. However, practitioners do need to carry out a risk assessment as there is an increased risk of needlestick injury due to needle exposure prior to administration and a risk of accidental cytotoxic spillage when using a syringe device.

In some areas of the UK, practitioners are still using unlicensed pharmacy-prepared pre-filled syringes of methotrexate – these have an even greater risk of needlestick injury and cytotoxic exposure as the needle does not retract post-injection and some preparations require a needle to be attached. In acknowledgement of these concerns, this guidance strongly recommends the use of subcutaneous methotrexate autoinjector pre-filled PENs or pre-filled injector devices over pre-filled syringe preparations and, in particular, any unlicensed pre-filled syringe preparations.

The guidance covers aspects of both adult and children/young people's care, including:

- methotrexate use
- risk management
- supply, storage, protective clothing and disposal
- home administration
- practitioner training and competence
- patient education and training
- audit trail and data collection.

Practitioners will find that key issues relating to the specific needs of children and young people can be found in the Paediatric guidance located in Section 2 of this document.

The term practitioner is used throughout this document and relates to nurses or allied health care professionals who have been trained and demonstrate competence in administering subcutaneous therapies.

The terms autoinjector pre-filled PEN and pre-filled injector devices are used to signify any manufactured designed administration device, excluding pre-filled syringes.

Risk management

The use of autoinjector pre-filled PENs/pre-filled injector devices

This guidance strongly supports and recommends the use of licensed methotrexate via the subcutaneous route, for instance, an autoinjector pre-filled PEN or a pre-filled injector device, NOT the pre-filled syringes or vials.

Under the Control of Substances Hazardous to Health (COSHH) Regulations 2002 and COSHH (NI) 2003, methotrexate remains listed as a cytotoxic agent; risk assessment and management should always be in the context of managing potential low-dose long-term exposure (COSHH, 2002; COSHH(NI), 2003; HSE, 2002, 2003 and 2009). The administration and handling of injectable methotrexate should be undertaken safely and in line with the EU and Health and Safety Executive's *Health and Safety (Sharp Instruments in Healthcare Regulations)* 2013 and the RCN's *Sharps safety guidance* (2013).

The training and administration of methotrexate in autoinjector pre-filled PENs and pre-filled injector devices should be undertaken in accordance with manufacturer and/or local policies. This document should not be considered definitive on all issues related to treatment with methotrexate, but should be read alongside key texts recommended in Appendix 4.

Protective clothing/spillage

It is standard clinical practice for health care professionals and carers to wear gloves (ideally latex free) and observe good hand washing protocols when administering methotrexate. They should also be aware of local policies and, where locally agreed, have access to spillage kits; this should include knowledge of how to deal with all types of accidental spillage of methotrexate.

Although the risk of spillage with the subcutaneous methotrexate autoinjector pre-filled PEN and pre-filled injector device is negligible, advice should be given to patients and carers on how to deal with an accidental spillage at home.

Patient education and training

Patients and carers should receive adequate information (verbal and written) to enable them to make an informed, shared decision about methotrexate therapy. For further guidance refer to NICE guidance (NICE CG138, 2014) and the Department of Health's *Equity and excellence: Liberating the NHS* (2010).

Patients may elect to self-administer methotrexate injections (or elect a carer), prior to which the necessary training needs to be provided and undertaken. Whilst some training can be provided remotely, best practice is to meet the patient and carers face to face and

spend time ensuring they understand the methotrexate specifics, as documented in this guidance, and that they can be observed safely administering the methotrexate. Patients (and carers where appropriate) should be aware of their responsibilities when giving methotrexate injections.

For example, they must:

- participate in a training programme and be prepared to demonstrate that they are competent in the safe administration of subcutaneous methotrexate
- attend blood tests as per agreed monitoring schedule
- know how to store and dispose of methotrexate and equipment safely
- be aware of the need to use effective means of contraception (where appropriate)
- be fully informed of all aspects relating to sexual health
- be aware of implications from alcohol consumption
- be aware of implications for overseas travel
- understand how and when to seek advice or guidance on treatment and related issues that may require prompt medical opinion.

(Butler, 2011; BSPAR, 2020; Dougherty and Lister, 2018; Ledingham et al, 2017; McInnes et al., 2012).

1. Adult guidance

Methotrexate use in adult rheumatology

History of methotrexate use

Methotrexate was developed in the 1940s as a specific antagonist of folic acid. It is classed as a cytotoxic drug because, in high doses, it inhibits the proliferation of malignant cells and has teratogenic properties and irritant effects to the skin (Butler, 2011; Dougherty and Lister, 2018; McInnes et al., 2012).

In recent years research has highlighted the need for more robust management of inflammatory joint diseases such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). For example, we know that early treatment with methotrexate should be increased rapidly until clinical indicators of disease control demonstrate an optimum therapeutic dose (Bakker et al., 2011; Braun, 2010; BSPAR, 2010; Gullick and Scott, 2012; Jacobs, 2012a, 2012b; McInnes et al., 2012; NICE, 2009; NICE, 2018; Smolen et al., 2010a, 2012b; Smolen et al., 2013).

Current evidence base

Over the past 30 years methotrexate has become the standard of care in the treatment of adults with rheumatoid arthritis (Weinblatt, 2013).

There has been debate about the extent of the drug's cytotoxic nature when used in low weekly doses for rheumatic diseases. For example, Cutolo (2001) states that the cytotoxic mechanism of action might be more anti-inflammatory, while Wong et al., (2009) assert that the risk relating to the low dosages used in the management of inflammatory arthritis is minimal.

Methotrexate should be considered as part of the first line treatment for patients with inflammatory conditions (unless contra-indicated) and remains the anchor drug in the treatment of rheumatoid arthritis (RA) (EULAR, 2019). Methotrexate is generally a safe and well-tolerated drug in the treatment of certain autoimmune diseases (Teitsma et al., 2018). It is efficacious, with good evidence supporting a slowing down of radiological disease progression and preservation of function. There is good evidence detailing the part methotrexate plays in combination therapy with other disease-modifying anti-rheumatic drugs (DMARDs) as well as the role it plays when used together with biologic therapies (Taylor et al., 2019).

Treat-to-target

During the last decade, the approach to treating inflammatory arthritis has changed significantly with growing evidence supporting a treat-to-target approach in patient care (Singh et al., 2015; EULAR, 2019). Early diagnosis and optimal treatment (the optimal dose to ensure your patient achieves remission) to 'switch off' the inflammatory process in the shortest period of time are critical to ensure the best outcome for the patient.

With the emergence of the treat-to-target approach, more emphasis is put on rapidly introducing disease modifying drugs like methotrexate and escalating doses to induce low disease activity or remission (Bello et al., 2017).

Taylor et al., (2019) identify the approach as encompassing five overarching principles:

1. defining the treatment goal. *The National Clinical Audit for Rheumatoid Arthritis and Early Inflammatory Arthritis* (BSR, 2016) indicated that health care professionals set a treatment target for about 90% of their patients
2. close and regular monitoring of disease activity using validated tools such as the DAS28 for rheumatoid arthritis
3. regular changes to treatment if active disease persists. Although there are different approaches to this, NICE (2009) identified monthly monitoring is appropriate as this was used in some of the studies of the treat-to-target strategy
4. consideration of patient preference
5. evidence of shared decision-making with the patient.

Methotrexate plays a key role in the treat-to-target process. The approach is supported by national charities such as the National Rheumatoid Arthritis Society (NRAS, 2018) as, although it is a formulated step-by-step process, it treats the patient as an individual and takes into account their views and preferences when selecting medication to get the disease under control.

Medicines optimisation

The rheumatology community has become much better at treating inflammatory arthritis and the care of patients has greatly improved in the last decade due to the availability of more medications to suppress active disease.

Treating inflammatory arthritis well can reduce the economic burden on individual patients, their families and on the communities where they live. EULAR (2019) identifies that the economic burden and cost of poorly controlled disease may not just include direct medical costs associated with a medical admission, but also accounts for the indirect costs associated with ill health (eg, sick leave, work disability and premature retirement due).

NICE (2015) identifies it is important to ensure we get the greatest possible benefit from all the medications we use before moving onto more expensive drugs for treatment. Working in a cost-effective way is an important point to consider as it will ensure financial sustainability of the National Health Service and enable access to medication for all those that need it.

Taylor et al., (2019) recognise that if patients are struggling to tolerate oral methotrexate, optimising an increased dose of folic acid or switching to the subcutaneous injection route are more cost-effective solutions than considering biologic medication as soon as a patient starts to encounter problems with treatment.

Rationale for the use of subcutaneous methotrexate

Methotrexate is recognised as the most effective of the traditional (non-biologic) DMARDs in current use for inflammatory arthritis (Bijlsma, 2012; Bijlsma and Jacobs, 2009; Jacobs, 2012a, 2012b; Smolen et al., 2010a, 2010b; Smolen, et al., 2013). It is recognised as the gold standard for treating people with rheumatoid conditions (BSPAR, 2020; EULAR, 2013; Ledingham et al., 2017; NICE, 2009).

The rationale for considering the administration of methotrexate using subcutaneous routes has been driven by the need to increase the therapeutic dose, ensure the maximum bioavailability and reduce symptomatic side effects for some patients (Bakker et al., 2010; Bijlsma and Jacobs, 2009; Braun, 2010; Braun et al., 2008; BSPAR, 2020; McInnes et al., 2012; Ortiz et al., 2009; Taylor et al., 2019; Visser et al., 2009).

With the development and availability of the licensed autoinjector pre-filled PEN and pre-filled injector devices, the ease and safety of the administration of subcutaneous methotrexate has been further enhanced, in line with the various national safety regulations/guidance.

In recent years, the development of biologic therapies has added another dimension. The effectiveness of some biologic therapies is enhanced by the co-administration of a DMARD (usually methotrexate), while also reducing the potential for antibodies to develop against the biologic agent.

Practitioners using this guidance should refer to additional key documents (see Appendix 4 and References).

Therapeutic indications and dosage

Subcutaneous methotrexate usage for rheumatic conditions include:

- active rheumatoid arthritis
- severe psoriatic arthritis in adults
- polyarthritic forms of severe juvenile idiopathic arthritis.

Intramuscular administration is not recommended due to increased injection pain.

Subcutaneous methotrexate injection doses for adults range from 7.5mg to 30mg **once weekly**, depending on the brand please note not all companies may supply this full range. Paediatric doses are often calculated using body surface area and only licensed for those aged three years and over (see Paediatric guidance).

Folic acid supplementation

Ledingham et al., (2017) identify co-prescribing folic acid alongside methotrexate significantly reduces the risk of abnormal liver biochemistry, gastrointestinal side-effects (e.g., nausea, vomiting, abdominal pain and diarrhoea). Therefore, prescribing folic acid at a minimal dose of 5mg once weekly, taken on a different day of the week to methotrexate – to a maximum dose of 5mg x six days a week (excluding the methotrexate day), is strongly recommended. Due to the lack of evidence available, there is no recommendation on which day of the week folic acid should be taken, although the overwhelming majority of clinical trials have avoided folic acid supplementation on the day of the methotrexate dose.

Risk management

Risk assessment and management is an integral aspect of providing safe and effective health care. This guidance recommends that practitioners should consult and be aware of the local risk management policy and guidelines and be able to demonstrate that all potential areas of risk have been addressed.

The evidence shows that the cytotoxic risk relating to the low dosages used in the treatment of inflammatory arthritis is small (Wong et al., 2009) and since the development and availability of licensed autoinjector pre-filled PEN and pre-filled injector devices for the administration of subcutaneous methotrexate, the cytotoxic risks have been reduced even further, making the administration of subcutaneous methotrexate even safer.

It is vitally important to ensure that the handling, administration and disposal of subcutaneous methotrexate injections is safe and that the appropriate risk assessments have been completed in line with local policy and procedures, including accidental needlestick injury.

Practitioner responsibilities

Practitioners should undertake a risk assessment. In addition, practitioners should:

- ensure a robust blood monitoring system is in place – see Ledingham et al (2017), and BSPAR (2020) guidelines, and ensure NPSA (2006) advice is followed. Although the NPSA ceased to exist as an organisation in 2012, and its patient safety responsibilities transferred to NHS Improvement (NHSI), the information relating to methotrexate is still relevant and considered best practice.
- ensure any risk assessment produced is reviewed and tailored in accordance with individual needs or risks relating to individual patients/carers undertaking subcutaneous administration in the home, including ensuring patients are aware of the once-weekly dosing regime
- report any errors, new risks, near misses or adverse events promptly, according to local policy.

Drug interactions

A number of drugs have the potential to interact with methotrexate. Drug interactions can enhance the action of methotrexate, resulting in an increased risk of methotrexate toxicity. Some of these drugs include salicylates, hypoglycaemics, sulfonamides, phenytoin, and trimethoprim. For a comprehensive list, please refer to the most up-to-date copy of the *British National Formulary* (BNF) (BMA and RPS) and/or the summary of product characteristics (SPC) for subcutaneous methotrexate.

Advice on the handling and administration of subcutaneous methotrexate; conceiving, pregnancy and breastfeeding

Methotrexate can impair the fertility of those using it and is embryotoxic, which means it can cause abortion or fetal defects, particularly during the first trimester of pregnancy (Flint et al., 2016; Jensen et al., 2018; Ostensen and Förger, 2009; Temprano, 2018).

Best practice advocates women of childbearing potential must not be treated with methotrexate until pregnancy has been excluded (please see summary of product characteristics (SPC) for further details: **medicines.org.uk**).

The current BSR/BHPR (Flint et al., 2016) recommendations state that:

- methotrexate, at any dose, should be avoided in pregnancy and stopped a minimum of three months prior to conceiving
- in women who have been on methotrexate, folate supplementation (5mg/day) should be continued three months prior to, and throughout, pregnancy
- in the case of pregnancy whilst taking methotrexate, the drug should be stopped immediately, folate supplementation continued and a careful evaluation of fetal risk carried out by local experts
- methotrexate is not recommended for breastfeeding women because of theoretical risks and insufficient outcome data.
- based on limited evidence, low-dose methotrexate may be compatible with paternal exposure however men taking methotrexate should talk to their health care professional team for advice about trying for a family (Flint et al., 2016; Jenson et al, 2018).

Contraceptive measures are essential and should be used by men, women and young people during treatment with methotrexate and for at least three months following cessation of treatment before actively trying to conceive (Dougherty and Lister, 2018; Flint et al., 2016; McInnes et al., 2012).

In addition, carers who are pregnant and administering to someone else, should be aware of the risks of handling methotrexate, although these are much reduced in the autoinjector pre-filled PEN and pre-filled injector devices. Practitioners are advised to adhere to their local policy regarding this.

It is the responsibility of the physician and nurse to educate their patients, promote shared decision-making and consider an alternative DMARD if family planning is still a consideration.

It is the responsibility of the physician and nurse to have these conversations with patients prior to commencing any treatment and promote shared decision-making. Having been informed of the potential risks, the final decision of individuals in relation to the handling and/or administration of methotrexate is a personal one, but one that should be well documented.

Supply, storage, protective clothing and disposal

Supply, preparation and delivery

Due to an increase in preparations of methotrexate being available, those who self-administer or carers who administer for others, must be informed of the specific requirements for their particular preparation prescribed. Any change in preparation prescribed must be accompanied with an update on the new preparation and any changes to storage, administration or disposal must follow the manufacturer's guidelines.

Packaging and transport systems should ensure that adequate protection and storage instructions are adhered to during delivery. Practitioners should be guided by local policies and the manufacturer's guidance.

Storage and drug stability

Methotrexate is a clear yellow-ish solution and is stable if stored out of direct sunlight. The shelf life and storage conditions of autoinjector pre-filled PEN and pre-filled injector devices should be carefully checked and reviewed on a regular basis and prior to each administration of the drug.

Storage at home

The storage of methotrexate and clinical waste bins should be out of the reach and sight of vulnerable adults, children and pets.

Practitioners and patients/carers who undertake self- administration should be trained and competent in all aspects of safe storage. This will include awareness that storage will vary according to the product used (see Supply, preparation and delivery above).

Personal protective equipment (PPE)

The cytotoxic nature of methotrexate means that it could potentially pose a risk to those staff and patients that handle it. However, due to the low doses used in rheumatology, and if licensed autoinjector pre-filled PENs and pre-filled injector devices are used, this risk is considered relatively low.

This guidance suggests that aprons, goggles, masks or armlets no longer need to be worn by practitioners when administering autoinjector pre-filled PENs and pre-filled injector devices.

In promoting good clinical practice, this guidance recommends that practitioners and carers should always use gloves (latex free, ideally) and observe good hand washing protocols when administering subcutaneous methotrexate (Crauste-Manciet et al., 2005; Dougherty and Lister, 2018).

It is not necessary for patients administering their own therapy to wear gloves. The key element for practitioners is documenting that the individual is aware of the risks and has made an informed choice.

If pre-filled syringe injections are used, practitioners are strongly advised to refer and adhere to local policy and procedures, as the risk of cytotoxic spillage/exposure is/will be increased with such preparations and the procedures and policy on use of PPE may be very different.

Disposal of sharps and clinical waste

Local policy should dictate the storage, collection, handling and disposal of methotrexate clinical waste/sharps.

Practitioners should receive regular training and be up to date on policies in relation to dealing with hazardous waste and sharps safety. Purple lidded clinical waste bins should be used for the disposal of methotrexate injections (as opposed to yellow sharps bins seen elsewhere) and patients should be informed of this difference.

Patients should be aware of the need to ensure the safe disposal of equipment using a clinical waste bin, and that the bin itself also constitutes a risk and should be safely

stored when not in use. The bin should never be filled more than two-thirds of its total capacity and should be securely sealed during transportation.

Spillage

Based on the recommendation and assumption that methotrexate will be administered using a licensed autoinjector pre-filled PEN or pre-filled injector device (not syringe) containing a small volume of methotrexate, the risk of exposure is very small and a spillage kit is unlikely to be necessary. Please refer to your local policy for guidance.

Although a spillage is unlikely when using an autoinjector pre-filled PEN or pre-filled injector device, patients and carers should also be aware of what to do in case of a spillage. A small spillage kit may be provided to the patient if felt necessary.

Liquid spillage on clothing

Wear protective gloves and blot dry with a paper towel or kitchen roll (and dispose of in a cytotoxic bin). As a precaution, clothing should be removed immediately (Dougherty and Lister, 2018) and washed separately from other items. Wash hands thoroughly.

Liquid spillage directly onto the skin

Wong et al., (2009), found poor dermal methotrexate penetration from deliberate contamination. However, if methotrexate is accidentally spilt onto the skin, the area should be washed 'liberally with soap and cold water' (Dougherty and Lister, 2018; Weinstein and Plumer, 2007). Methotrexate is not a vesicant (blister agent).

Liquid spillage directly into the eye

The eye should be washed out using plenty of water (Dougherty and Lister, 2018; Weinstein and Hagle., 2014) for a few minutes. A doctor should be contacted if any side effects are experienced. Some care settings may have eye wash kits available, if needed.

Liquid spillage on floors or work surfaces

Wearing gloves, cover the spillage with absorbent paper and clean with soap and water. Paper tissue should be bagged and disposed of in the bin.

Practitioner training and competence

No specialist training is required for the administration of subcutaneous methotrexate by practitioners; however, all practitioners should be competent in the administration of the subcutaneous injection technique.

Ideally, specialist practitioners should undertake appropriate training in the administration and management of methotrexate (see Appendix 3).

Considerations before commencing home administration for patients

Home administration requires effective communication and good collaboration between patient and carers, plus health care providers from all sectors. A training programme is required to assess the patient's/carer's ability to undertake the methotrexate injection safely and competently at home.

Patients should be advised that they can elect not to self-administer methotrexate and can opt out of treatment. However, should they choose this course of action they MUST inform their health care team promptly, so their records can be appropriately updated.

Following training and risk assessment, a decision will be made about whether the patient or carer:

- is competent and wishes to proceed with home administration
- has a clear understanding of their responsibilities in the safe management of methotrexate (including correct dose and frequency), the use of additional equipment and safe waste disposal
- can adhere to regular blood monitoring as per BSR guidelines /local practice. Ensure shared care agreements between primary and secondary care are in place for prescribing and monitoring bloods, and the patient agrees to attend blood monitoring and clinic appointments
- recognise that a risk assessment must support home administration and that this will be subject to review
- understands the back-up plan in the event of being unable to self-administer.

Patient information leaflets on subcutaneous methotrexate injections are available from a number of organisations and drug manufacturers.

Pre-treatment checklist for adults

The following pre-treatment checks should be undertaken for adults (please see Section 2 for Paediatric guidance).

Baseline clinical assessment should include:

- height
- weight
- blood pressure.

When commencing patients on methotrexate Ledingham et al., (2017) advise checking:

- full blood count (FBC)
- creatinine/calculated glomerular filtration rate (GFR)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- albumin.

These should be checked every two weeks until the patient has been on a stable dose for six weeks. Once stable, monthly full blood count, creatinine/calculated GFR, ALT and/or AST and albumin are advised for three months. Thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin can be undertaken every three months.

More frequent monitoring such be considered in patients at higher risk of toxicity such as those on combination therapy.

When increasing the dose of methotrexate, blood monitoring should be increased and FBC, creatinine/calculated GFR, ALT and/or AST and albumin every two weeks until on a stable dose for six weeks again.

A past medical history of lung disease is not a specific contraindication to methotrexate therapy; however, caution is advised when using methotrexate in patients with respiratory conditions which can be associated with pneumonitis. Therefore, respiratory history should always be noted and in addition to thorough clinical assessment and baseline chest X-rays, spirometry may be useful. If there is a significant reduction in spirometry, then further evaluation would be required and alternatives to methotrexate should be considered (Ledingham et al., 2017).

In patients who developed methotrexate-related pulmonary toxicity, clinical symptoms of shortness of breath, coughing, fever and dyspnoea can be seen.

During a serious infection, methotrexate should be temporarily discontinued until the patient has recovered from the infection. For clinically urgent abnormalities, emergency access to specialist rheumatology advice, with a response within one working day, should be available (Ledingham et al., 2017).

Pregnancy testing

Pregnancy testing is recommended for all women of childbearing potential prior to the commencement of methotrexate. Please see local policy for further guidance and the summary of product characteristics (SPC) at: **medicines.org.uk**

Vaccinations

EULAR (2019) recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases highlights the need for annual vaccination status assessment following the initiation of any immune-modulating therapy. Non-live vaccines can be safely administered to patients regardless of the underlying treatment used for their inflammatory arthritis. Live attenuated vaccines are generally not advisable but may be considered with caution after weighing up the risks and benefits to the individual. As the administration of vaccinations are likely to take place in primary care, health care professionals should advise patients to check with their rheumatology teams if they are unsure as to which vaccination they can safely receive.

Varicella immune status

Chickenpox infection is a concern in any non-immune immunosuppressed patient with a significant exposure to either chicken pox or shingles.

Checking varicella immune status (VZV IgG) prior to starting methotrexate has been identified as an important aspect of patient care, especially in those who have

autoimmune inflammatory disease and require immunosuppressant medication, as it has been reported that this group of patients are at greater risk of infection and/or reactivation of latent disease/shingles (Butler, 2008; DH, 2006; McCarthy et al., 2011).

This can be checked via history taking and/or varicella zoster (VZV IgG antibody) blood test screening if clinically indicated.

If varicella immune status (VZV IgG) is not performed at this stage, then it should be urgently performed within seven days of a significant exposure to either chicken pox or exposed shingles.

If chickenpox/shingles develops, the patient should be urgently assessed for acyclovir treatment; methotrexate should be discontinued until the last spot has crusted over and the patient is clinically well.

The risk and severity of shingles is higher amongst immunosuppressed individuals, therefore, individuals should be assessed for shingles vaccine eligibility (based on age) prior to starting treatment. At least 14 days, preferably one month, is required prior to starting methotrexate. For further information see the Green Book, available at: **gov.uk/government/publications/varicella-the-green-book**

Some patients may be eligible for the shingles vaccine while on methotrexate therapy. Patients on long-term stable low-dose corticosteroid therapy (defined as 20mg prednisolone per day for more than 14 days), either alone or in combination with low dose non-biological oral immune modulating drugs (eg, methotrexate 25mg per week or less), are not considered sufficiently immunosuppressive and these patients can receive the vaccine after weighing up the risks and benefits in each individual case. In these cases, live vaccines should be considered with caution and in discussion with their rheumatologist. If there is any doubt between the risk of shingles versus the benefit of immunisation, specialist advice should be sought (BSR, 2013).

Influenza vaccination

The EULAR (2019) and Ledingham et al., (2017) guidelines states that the influenza vaccination should be strongly considered for most adult patients with autoimmune inflammatory rheumatic diseases, in line with national guidance – these patients have a higher risk of contracting influenza compared with the general population. Although temporary discontinuation of methotrexate was shown in clinical trials to provoke a better immune response to the vaccine, it is currently not recommended to stop methotrexate before or after vaccinating for influenza due to the risk of flare. The effectiveness of the vaccine whilst on treatment should therefore be discussed with patients.

Pneumococcal vaccination

EULAR (2019) and Ledingham et al., (2017) recommended that patients with autoimmune inflammatory rheumatic diseases should be offered pneumococcal vaccination as the risk of pulmonary infection is particularly high in this patient group.

Full advice on varicella, influenza and pneumococcal vaccination can be found in the Green Book at: **gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book**

Alcohol history

Patients should be informed of the importance of restricting alcohol intake when receiving methotrexate treatment as the liver metabolises both alcohol and methotrexate, however, there is some evidence that <14 units weekly does not appear to be associated with an increased risk of transaminitis. The risk of transaminitis (liver damage) for patients on methotrexate does increase with raised levels of alcohol consumption. In patients with impaired liver function, DMARD therapy should be used with extreme caution (Humphreys et al., 2017; Ledingham et al., 2017). Please refer to the summary of product characteristics (SPC).

More information about the impact of alcohol on health can be found at:
drinkaware.co.uk/facts/alcoholic-drinks-and-units

Concomitant medications

All concomitant medications (including proton-pump inhibitors, statins and analgesics) need to be considered and reviewed prior to and during methotrexate treatment, as several agents have the potential to cause independent hepatotoxicity.

A careful and detailed review of concomitant medications must be undertaken to exclude any potential drug interactions or absolute contraindications, such as trimethoprim and co-trimoxazole. Refer to the current version of the BNF or the BNFC and the manufacturer's specific summary of product characteristics (SPC). For further advice, contact the local prescriber.

Practitioners should also be aware of, and exercise caution, in relation to patient use of over-the-counter (OTC) medications and complementary/herbal remedies, as such agents, when taken with methotrexate, might confuse and potentially compromise a patient's clinical management.

To promote patient safety and best practice, practitioners need to ask patients specifically about their use of complementary and alternative medicines and be aware of the potential these may have for hepatotoxicity and interactions (Fogden and Neuberger, 2003; Gonzalez-Stuart, 2011; Joshi and Medhi, 2008; Leung, 2006; Liu et al., 2011; Toselli et al., 2009; Ulbricht et al., 2008; Yang et al., 2006).

Contraindications to treatment with methotrexate

The following are contraindications to treatment with methotrexate:

- renal or liver impairment/failure (or recent hepatitis)
- blood dyscrasias/abnormalities
- alcoholism
- planned conception, pregnancy or breast feeding
- immunodeficiency syndromes
- active chickenpox/shingles
- recent live vaccines (within two weeks).

Over-the-counter (OTC), complementary and alternative medications (including herbal remedies) should be treated with caution. In promoting and improving patient safety and self-management, patients should be advised to check with pharmacists when buying OTC or herbal medicines.

Checklist for practitioners

All practitioners should adhere to the following checklist prior to administering a pre-filled, methotrexate PEN or autoinjector device to a patient:

- check the methotrexate dose and frequency prescribed (remember, methotrexate should only be prescribed once weekly), and expiry date of the licensed autoinjector pre-filled PEN or pre-filled injector device
- ensure blood monitoring (including the monitoring of trends) is in place as per Ledingham et al., (2017), DMARD monitoring guidelines and local protocols are followed. Ensure that blood results are satisfactory, and patients know when they need to attend for their next blood test
- check there are no contraindications to administration (as per the SPC)
- ensure the patient has consented to have the injection
- ensure the patient knows the advice line telephone number (or any other relevant contact numbers) for support or concerns
- document the injection and the site used
- be aware of protocols relating to the safe disposal of sharps
- note the date and time of next injection.

Specialist practitioner training and competence (see Appendix 3)

- Practitioners should be knowledgeable and competent in all aspects of methotrexate administration and risk management and stay up to date with the latest evidence in relation to the drug's indications and side effects.
- Practitioners should have undertaken appropriate training to educate, support and teach patients in the self-administration of subcutaneous methotrexate, and ensure their own training is regularly updated.
- Practitioners should ensure appropriate communication and support are available for primary health care teams and patients self-administering in their own homes.
- Practitioners should be aware of clinical governance and local policies in relation to the management of patients receiving methotrexate.
- Documentation and audit should be an integral aspect of developing a service for patients receiving subcutaneous methotrexate.

Patient education and training

The practitioner's role is to teach the patient how to administer their methotrexate safely, using the correct technique for the appropriate subcutaneous pre-filled injection device prescribed.

Please refer to the specific manufacturer's guidance for preparation and administration.

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Points to consider

Skin preparation

There remains debate around the use of alcohol-impregnated swabs to clean subcutaneous injection sites.

The World Health Organization (2010) suggested that if a patient is physically clean and generally in good health, swabbing of the skin before injection is not required.

In older patients and those who maybe immunocompromised, skin preparation using an alcohol-impregnated swab (70% isopropyl alcohol) may be recommended (Dougherty and Lister, 2015).

The patient's condition should always be individually assessed and local policies followed.

The importance of rotating injection sites

If giving two injections (such as methotrexate and a biologic therapy) these should be given in different sites. For example, one should be given in the right thigh and the other in the left thigh. The injections should be at least 3cm apart, if given in the same limb. If injecting in the abdomen, injections should be in a 5cm radius away from the navel.

Local variations and further advice

The arrangements for the prescribing, distribution of prescriptions and collection of clinical waste will vary according to local policies and arrangements between primary care organisations. It is essential that the patient and carer are provided with information about their prescriptions and have clear guidance on the support they can access in the case of concerns. This should include information on a telephone or electronic repeat prescription, blood monitoring and/or advice line services.

Safe disposal of sharps

Local policy should dictate the storage, collection, handling and disposal of methotrexate clinical waste/sharps.

Practitioners should receive regular training and be up to date on policies in relation to dealing with hazardous waste and sharps safety. Purple lidded clinical waste bins should be used for the disposal of methotrexate injections.

Documentation following the injection

It is recommended that the patient should keep a record of their injections.

Patient competency

Patients and carers should be provided with adequate information (verbal and written) about the treatment and understand the contraindications, the potential risks and side effects to enable them to make an informed decision about methotrexate therapy. They should also be given the opportunity to discuss any concerns they may have.

Training the patient or carer

The patient or carer should be able to access training sessions if necessary, and as required. It is best practice to undertake an annual review of patient or carer skills (for example, practise in injecting and management of their prescription), where possible.

Patients and carers should also be encouraged to watch online patient education videos from all licensed providers of subcutaneous methotrexate.

Patients may elect to self-administer methotrexate injections (or elect a carer), provided they undertake the necessary training.

The patient or carer should have a training plan that provides them with a clear understanding of the process and responsibilities required for home administration.

For example, they must:

- participate in a training programme and be prepared to demonstrate that they are competent in the safe administration of subcutaneous methotrexate using the prescribed device and, also know when not to administer the methotrexate (for example, when only part of a dose has been administered for some reason – a device failure or technique)
- be aware of the need to use effective means of contraception (where appropriate) and be fully informed of all aspects relating to sexual health (Flint et al., 2016; Butler, 2011; BSPAR, 2020; McInnes et al., 2012)
- know how to store and dispose of methotrexate and equipment safely
- understand the importance of remembering to attend for blood tests and monitoring regularly, as agreed with the local team and protocol
- understand how and when to seek advice or guidance on treatment and related issues that may require prompt medical opinion
- be aware of their responsibilities when giving methotrexate injections.

To minimise reactions and promote and maintain good injection technique, practitioners should routinely ask patients/carers if they are experiencing any problems and arrange an appropriate assessment if this is required. This approach will help maintain a thorough audit trail and ensure the maintenance of safe practice by patients/carers.

In addition, patients and carers should be made aware and have a clear understanding of the aim, purpose and importance of the NPSA (2006) methotrexate monitoring booklet (or equivalent local methotrexate monitoring book). Although the NPSA ceased to exist as an organisation in 2012 and its work incorporated into NHSI patient safety improvement work, many rheumatology departments still issue patients with this booklet as its content is still relevant for patients commencing methotrexate.

The role of practitioners is to recognise the individual needs of patients and provide support in administering the most appropriate treatment for that patient. Patient preferences will vary depending on:

- the patient's medical history and general health status
- social and psychological factors that affect their treatment options.

Best practice is to meet each patient face to face to ensure training is safe and the patient is assessed as competent. The time taken to train each patient or carer, together with the number of practice sessions that require supervision, will vary. Following an initial assessment and discussion with the patient and carer, a mutually agreed training

package should be provided and tailored to meet the patient and/or carer's individual learning needs. The practitioner, patient and/or carer, where appropriate, will determine the number of training sessions necessary to achieve competency.

Travelling with methotrexate

The autoinjector pre-filled PEN and pre-filled injector devices should be stored as per the manufacturer's recommendations. Make sure that they check the injection box for instructions on how to store.

They should seek specific advice on storage at high temperatures and note that extra caution needs to be exercised in hot climates/environments over 25°C, when it is recommended to place the methotrexate injection in the fridge and warm to room temperature (approximately 30 minutes) prior to injection. If they have any questions or concerns about this, ask them to discuss the details of storage with their GP, nurse, practitioner or pharmacist.

Advise patients of the options available to them if going away, for example:

- tablets instead of an injection
- an injection just before they travel and then one as soon as they return. And to discuss this with their GP or rheumatology department.

If they are flying, they may need a letter from their rheumatology team to be able to carry their PEN or pre-filled injector device with them. This should be discussed with their rheumatology team before they go away.

It is recommended that they always keep their medication in their hand/cabin luggage in case the bags get mislaid, but also rough handling of luggage could damage the medication, plus it may freeze in the hold.

Patients should see their practice nurse or doctor to arrange any vaccinations they need well in advance of their travel. Live vaccines are contraindicated in patients receiving methotrexate and so it is important that they are aware of this and inform their nurse or doctor they are receiving methotrexate.

Rheumatology advice line

Ensure patients and carers are made aware of an advice line they can call and how and when they should use this.

Audit trail and data collection

If a unit or department wishes to collect additional data that contains personal or clinical details of an individual or a group of individuals, staff must seek the advice and gain permission from the respective local ethics and audit departments to ensure that national data protection legislation and information on governance guidance and local policies are adhered to (Data Protection Act, 2018).

In addition, nurses have a professional responsibility to adhere to the NMC guidance for good record keeping (NMC, 2015).

It is important that practitioners audit the service and include the value of the educational programme. Your local audit department will provide guidance and support.

Conclusions

This document has been developed to inform practitioners on the key issues relating to the administration of subcutaneous methotrexate.

Subcutaneous methotrexate has an important part to play in the treatment of inflammatory arthritis and should be considered as an option before considering more expensive treatment for adult patients with rheumatic conditions.

Pre-filled PENs and injector devices simplify the self-administration process for patients over methotrexate syringes.

The increase in licensed pre-filled PENs and injector devices of methotrexate for use in the UK gives more choice of products.

Home administration of methotrexate using these devices is easy and safe.

2. Paediatric guidance

Introduction

This paediatric guidance should be used for children, young people and their families receiving subcutaneous methotrexate treatment.

Paediatric rheumatic diseases are different from their adult counterparts. The umbrella term juvenile idiopathic arthritis (JIA) covers a heterogeneous group of conditions that combines arthritis with onset before the age of 16 years with unknown aetiology (Cassidy and Petty, 2011; Foster and Brogan, 2012; Ruperto and Martini, 2011).

In addition:

- pharmacokinetic and toxicity profile of medications are different in adults and paediatrics
- indications for medications differ, for example, chronic anterior uveitis can be a devastating complication of JIA (not seen with adult RA), warranting methotrexate treatment to prevent blindness, despite mild arthritis (Weiss et al., 1998; Cassidy and Petty, 2011)
- children and young people have fewer complicating risk factors (for example, alcohol consumption and pre-existing lung and liver disease) compared to adults.

Methotrexate use in paediatric rheumatology

History of methotrexate use

Over the last 40 years of clinical use, methotrexate has transformed the outlook for children with JIA and is considered the gold standard for patients that require a second line therapy (NICE, 2002; Ramanan et al., 2003; Foster and Brogan, 2012). Methotrexate is also widely used in other paediatric rheumatological conditions such as juvenile dermatomyositis (JDM), scleroderma (particularly localised), juvenile systemic lupus erythematosus (JSLE), idiopathic chronic anterior uveitis, and some vasculitides (Cordeiro and Isenberg, 2006; Hedrich et al., 2011).

Subcutaneous administration of methotrexate in children has a 10-12% increased absorption rate compared with oral preparation (Tukova et al., 2009).

Alsufyani et al. (2004) retrospectively studied children who failed oral methotrexate. They found that changing to subcutaneous methotrexate had a high likelihood of success, with more than 70% of patients with JIA achieving significant improvement. In clinical practice, subcutaneous administration is often used as first line, compared to oral, due to the higher bioavailability and less gastrointestinal upset (BSPAR, 2020). Adherence is often an issue, with children and young people not liking the taste of oral preparations or struggling to swallow the tablets, and thus, preferring the subcutaneous route.

Subcutaneous methotrexate treatment can be self-administered at home, giving the patient and family a greater degree of independence and comfort.

Rationale for the use of subcutaneous methotrexate

Subcutaneous methotrexate is currently available from a number of pharmaceutical companies, either as an autoinjector pre-filled PEN or pre-filled injector device, pre-filled

syringes or vials. This document recommends either the pre-filled PENs or the pre-filled injectors – both have fewer risks from potential spillage than either of the other two preparations (pre-filled syringes or vials).

Subcutaneous methotrexate in an autoinjector pre-filled PEN or a pre-filled injector device are licensed for polyarthritic forms of JIA in children over three years of age who have failed to respond adequately to non-steroidal anti-inflammatory drugs (NSAIDs). These are easy to obtain and safer to administer to paediatric patients and ideally should be administered at home (Livermore, 2014).

These commercially available licensed autoinjector pre-filled PENs or pre-filled injector devices have reduced volumes of drug and, in contrast to hospital-manufactured methotrexate syringes, the needle is attached and non-visible – so, not only safer but preferred by the paediatric population. The licensed autoinjector pre-filled PEN or pre-filled injector device are easier to administer (especially by young people), easier to store and transport, and with a decreased risk of spillage. Also, they have recently been shown to be less painful in comparison than prefilled syringes (Roszkiewicz, 2020).

Best practice, as advised by the ARMA standards of care for JIA (2010), involves developing shared care between a paediatric rheumatologist (who regularly sees children with rheumatic conditions) and the local health care team, supported by a paediatric rheumatology nurse specialist. Ideally, the family should be taught how to administer the methotrexate.

The advantages of using subcutaneous methotrexate therapy at home for children, young people and their families include:

- not missing school/work, spending less time travelling to and waiting at GP surgeries or the local hospital
- a more consistent approach to care (normalises treatment)
- the child or young person can self-administer, thereby increasing independence and concordance
- children may get car sick on journeys to hospital or GP for injection, coupled with methotrexate anticipatory nausea, may increase the chance of vomiting (Bultovic et al., 2011; van der Meer et al., 2007)
- it may prevent the build-up of negative anticipation in the child because the methotrexate can be administered when desired and is not dependent on other health professionals.

In recent years, the development of biologic therapies has added another dimension. The effectiveness of some biologic therapies is enhanced by the co-administration of a DMARD (usually methotrexate) to enhance the action of the biologic agent, but also reduce the potential for antibodies to develop against the biologic agent.

Dosage

Unlike adult care, methotrexate use in paediatrics is usually calculated by body surface area (BSA) rather than weight alone as this gives a more accurate calculation in growing children (see Paediatric resources 1: how to calculate body surface area).

The recommended licensed dose is 10 to 15mg/m^2 body surface area (BSA) once weekly, in children over three years of age. In therapy-refractory cases, the weekly dose may be increased by up to 25mg/m^2 BSA once weekly (BNFC) (British Medical Association and Royal Pharmaceutical Society, 2020b).

Commercially available PEN and autoinjector devices currently come in gradients of 2.5mgs, in a dose range of 7.5mg to 30mg per week. If a patient is prescribed a dose smaller than 7.5mg (i.e., off-label dose), this dose would need to be specially made in a local hospital pharmacy. This has implications for weaning doses in patients in remission; due to the available syringe doses it is good practice to reduce in 2.5mg steps.

It is also important to be aware that two of the currently available (at time of publication) commercial PEN/device preparations have different concentrations, so the volume of methotrexate may be different, but the dosage the same.

Folic acid supplementation

Folic acid supplementation is used as standard practice by most paediatric rheumatologists to reduce methotrexate side effects and there are variations in its prescribing. However, the BSPAR methotrexate guidance (2020) states that if folic acid is prescribed, it can be given as 5mg orally, weekly; 1mg daily or 5mg daily administration, but not on the day methotrexate is given. Folic acid supplementation can be initiated at the start of methotrexate therapy or added in if needed due to adverse effects.

Risk management

Risk assessment and management is an integral aspect of providing safe and effective health care and this guidance recommends that practitioners should consult and be aware of their local authority risk management policy and guidelines, and be able to demonstrate that all potential areas of risk have been addressed.

Evidence shows that the cytotoxic risk relating to the low dosages used in the treatment of inflammatory arthritis is small (Wong et al., 2009) and since the development and availability of pre-filled PEN and pre-filled injector devices for the administration of subcutaneous methotrexate, the cytotoxic risks have been reduced even further, making the administration of subcutaneous methotrexate even safer.

Advice on the handling and administration of subcutaneous methotrexate and pregnancy

Methotrexate has the ability to impair the fertility of those using it and is embryotoxic, which means it can cause abortion or fetal defects, particularly during the first trimester of pregnancy (Ostensen and Förger, 2009).

Best practice advocates that those who are pregnant (and particularly those who are in the first trimester of pregnancy) do not handle or administer methotrexate (BSPAR, 2020; Dougherty and Lister, 2018). Practitioners are advised to adhere to their local policy regarding this.

Methotrexate can cause embryotoxicity and teratogenicity and, therefore, should not be handled by pregnant health care professionals, carers or young people who are pregnant, breastfeeding or men/women trying to conceive (BSPAR, 2020).

Therefore, it is essential that young people are counselled about the risks relating to pregnancy and contraception is discussed by a clinical nurse specialist prior to commencing on methotrexate and for at least six months following cessation of treatment (Flint, 2016).

Supply, preparation and delivery

Methotrexate is available in licensed, pre-filled PENs and pre-filled injector devices. Packaging and transport systems should ensure that adequate protection and storage instructions are adhered to during delivery. Practitioners should be guided by local policies and the manufacturer's guidance.

Patients or carers whose self-administer must be told about any changes of manufacturer, volume or dose change, storage conditions, expiry date or change in appearance of their methotrexate. They must also be informed of the potential change in administration technique according to the manufacturer's guidelines and be appropriately retrained.

Storage and drug stability

Methotrexate is a clear yellowish solution and is stable if stored out of direct sunlight. The shelf life and storage conditions of pre-filled PENs and pre-filled injector devices should be carefully checked and reviewed on a regular basis and prior to each administration of the drug.

During the teaching programme, families are taught what information to check on the label (such as the child's name and drug dose). When considering families for home administration, thoroughly discuss with the family the facilities needed for safe home storage of the pre-filled PEN and pre-filled injector device and clinical waste bins.

Storage at home

The storage of methotrexate and clinical waste bins should be out of the reach of vulnerable adults, children and pets.

Practitioners and patients/carers who undertake self-administration should be trained and competent in all aspects of safe storage. This will include awareness that storage will vary according to the product used.

Personal protective equipment (PPE)

In promoting good clinical practice, it is recommended practitioners and carers should use gloves (latex free, ideally) and observe good hand washing protocols when administering subcutaneous methotrexate (Crauste-Manciet et al., 2005; Dougherty and Lister, 2018). It is not necessary for a child or young person administering their own therapy to wear gloves. Parents should be taught safe hand washing techniques and be helped to reach an informed decision about wearing gloves.

Disposal of sharps and clinical waste

Local policy should dictate the storage, collection, handling and disposal of methotrexate clinical waste/sharps.

Practitioners should receive regular training and updates on policies in relation to dealing with hazardous waste and sharps safety.

When methotrexate is administered in any community setting, issues relating to the management of clinical waste need to be considered (please refer to your local policy). In some circumstances, companies that deliver the methotrexate to patients' homes are also responsible for the collection and disposal of sharps and clinical waste. Purple lidded clinical waste bins should be used for the disposal of pre-filled PENs and pre-filled injector devices.

The bin should never be filled more than two-thirds of its total capacity or transported if not securely sealed.

Spillage

Based on the recommendation and assumption that methotrexate will be administered using a licensed, pre-filled PEN or pre-filled injector device containing a small volume of methotrexate, the risk of exposure is minimal and a spillage kit is unlikely to be necessary. (Please refer to your local policy for guidance.)

Practitioner training and competence

No specialist training is required for the administration of subcutaneous methotrexate by practitioners; however, all practitioners should be competent in the administration of the subcutaneous injection technique and be aware of specific issues for methotrexate, as detailed below.

Checklist for practitioners

All practitioners should adhere to the following checklist prior to administering a licensed, pre-dosed, subcutaneous methotrexate injection to a patient:

- check the methotrexate dose, frequency prescribed and expiry date
- ensure blood monitoring (including the monitoring of trends) is in place as per BSPAR (2020) and local protocols, that blood results are satisfactory, and patients know when they need to attend for their next blood test
- check there are no contraindications to administration (as per the SPC)
- ensure the patient has consented to have the injection
- ensure the patient and parent/carer knows the advice line telephone number for support or concerns
- document the injection and the site used
- be aware of protocols relating to the safe disposal of sharps
- note the date and time of next injection.

Specialist practitioner training and competence (see Appendix 3)

- Practitioners should be knowledgeable and competent in all aspects of methotrexate administration and risk management and be up to date with the latest evidence in relation to the drug's contraindications and side effects.
- Practitioners should have undertaken appropriate training to educate, support and teach patients/parents in the self-administration of subcutaneous methotrexate, and ensure their own training is regularly updated.
- Practitioners should ensure appropriate communication and support are available for primary health care teams and patients/parents are supported to administer in their own homes.
- Practitioners should be aware of clinical governance and local policies in relation to the management of patients receiving methotrexate.
- Documentation and audit should be an integral aspect of developing a service for patients receiving subcutaneous methotrexate.

Home administration

Wherever possible, the patient and family should be encouraged to administer methotrexate within their own home as this provides a significant degree of independence for the child/young person and avoids unnecessary hospital attendances and/or the need for direct health care practitioner support.

For home administration to work efficiently, good communication is vital, not only between all care providers and pharmacy services, but also with the family.

The injections may be administered at home by the trained parent, child, young person or responsible adult. If this is not possible, the injections should be administered by an appropriately trained health professional.

Administration by a child or young person

Any child or young person that voices a desire to self-medicate must be individually assessed for his or her level of understanding and compliance. In general, it has been found that encouraging children to self-inject fosters independence and compliance with the treatment programme. If a full injection is a step too far, assisting them to participate in the process – for example, holding the device for the injection process – is a step towards self-administration. The question of whether they would like to self-inject should be revisited in the future as they become more independent.

There is little published evidence on the ideal age for a child or young person to self-administer subcutaneous injections. Livermore (2003) suggests an arbitrary age of ten years; however, there is anecdotal evidence of children younger than this self-administering.

Administering methotrexate with a licensed, pre-filled PEN or pre-filled injector device is also seen as easier than injecting with a syringe and needle. However, some young people may prefer to administer via the licensed syringe as they have some control over

the speed of administration (please ensure you use the licensed syringes rather than those that are unlicensed). If this is the case, please be aware of increased risks of using the syringe (such as an increased risk of needlestick injury and cytotoxic spillage). It is important to stress that there must be ongoing supervision by an appropriately trained adult at all times.

Screening families for home administration

When screening families for home administration the two important requirements (once a training programme is in place) are:

1 a desire from the parent, child or young person to give the injections

2 an assessed level of competence – best practice is to assess this face-to-face with the child and family, however, if this is not possible, the practitioner takes responsibility for doing this over technology. However, it must be highlighted that teaching parents to administer to their child is inherently more complicated than teaching an adult to administer to themselves and the nurse has a duty of care to witness how the child or young person reacts to their parent or responsible adult and whether there are concerns which need addressing.

In addition, following training and risk assessment, a decision will be made whether the patient/carer:

- has a clear understanding of their responsibilities in the safe management of methotrexate, including correct dose and frequency, additional equipment, and waste disposal
- will undertake regular blood monitoring and attend clinic appointments
- recognises that a risk assessment must support home administration and that this will be subject to review
- understands what to do/who to contact in the event of being unable to administer or self-administer.

Patient information leaflets on subcutaneous methotrexate injections are readily available from a number of charity organisations (see **Appendix 4 – useful websites**). Manufacturers also produce illustrated patient guides and online videos.

Suitability of family circumstances

Each family needs to be individually assessed to see whether home administration is appropriate (Livermore, 2003). Practitioners need to assess the family for their understanding of treatments, their ability to recognise and manage side effects, and the safe administration/compliance of medications.

Families need to undertake a training programme and a review of their ability to manage all aspects related to administration in their own home. They have a responsibility in the partnership and should always agree to check with a health care professional before they take any decision to omit an injection.

Consideration of risk-taking behaviours

Practitioners should be aware of using an assessment tool (for example, HEADSSS) to

identify sexually active young people and counsel them about the use of contraception and the prevention of sexually transmitted diseases, as well as the importance of minimising alcohol intake while taking methotrexate.

Further discussion may be needed about planning pregnancy in the future. For example, it is necessary for both male and female patients to stop methotrexate for six months prior to considering starting a family. This should be done with the support and advice from the rheumatology team

Pre-treatment checklist and baseline investigations

The following pre-treatment/baseline investigations must be undertaken for a child or young person:

- full blood count and differential white blood count
- ESR (erythrocyte sedimentation rate) and/or C-reactive protein (CRP)
- liver function tests
- urea and electrolytes
- varicella and MMR titres – if the titres are negative, have the chickenpox and MMR vaccines been offered prior to starting treatment if time allows?
- consider if a pregnancy test is appropriate.

Note: Chest X-rays are not routinely performed prior to starting methotrexate in paediatric rheumatology.

A careful and detailed review of concomitant medication must be undertaken to exclude any potential drug interactions or absolute contraindications. Please refer to the current version of the BNFC (British Medical Association and Royal Pharmaceutical Society, 2020b) and the manufacturer's specific summary of product characteristics (SPC). For further advice, contact the local prescribing doctor.

Administration of subcutaneous methotrexate

At the time of writing, there are numerous preparations available of subcutaneous methotrexate, as either licensed pre-filled PENs or pre-filled injector devices. As the administration techniques differ slightly between devices, please refer to the specific manufacturer's guidelines for the device you are using. Therefore, this guidance will not detail the process for giving a subcutaneous injection, but instead will discuss any important considerations when specifically administering subcutaneous methotrexate.

Rotating injection sites

Patients or carers who self-administer treatment need to ensure that they rotate the injections sites. If giving two injections (such as methotrexate and a biologic therapy) these should be given in different sites. For example, one should be given in the right thigh and the other in the left thigh. The injections should be at least 3cm apart, if given

in the same limb. If injecting in the abdomen, injections should be in a 5cm radius away from the navel.

It is suggested that the patient and/or parent/carer should keep a record of injection sites used.

Review and monitoring

The patient or carer should be able to access additional training sessions if necessary and as required. Although it is best practice to undertake an annual review of patient or carer skills/practice in injecting and managing their prescriptions, this may not always be feasible.

To minimise reactions, promote and maintain good injection technique, practitioners should routinely ask patients/carers if they are experiencing any problems and arrange an appropriate assessment if this is required. This approach will help maintain a thorough audit trail and ensure the maintenance of safe practice by patients/carers.

Patient education and training

Children, young people and their families should be provided with information (verbal and written) about the treatment and understand the contraindications, the potential risks and side-effects to enable them to make an informed decision about methotrexate therapy.

The child/young person and parent should also be given ample opportunity to discuss any concerns they may have after they have been given information about methotrexate.

In addition, the young person and/or parent should have a training plan that provides them with a clear understanding of the process and responsibilities required for home administration. The time taken to train a young person or parent, together with the number of practice sessions, will vary.

When not to administer

As with any medication, the practitioner, parent or young person needs to be aware of the circumstances when they would not administer methotrexate. The two most common reasons for temporarily discontinuing methotrexate in paediatrics include:

- significant deranged blood tests: it is the responsibility of the monitoring physician/nurse to inform families of abnormal blood results that require stopping the treatment
- the child/young person develops chickenpox/shingles; the parent/young person should inform their GP or treatment centre for appropriate advice.

Usual childhood coughs, colds, or minor infections do not warrant stopping methotrexate. However, if there is any suspicion that the child is systemically unwell – for example, a high fever (over 38.5°C) or a rash (that is different to any usual fevers or rashes such as those that accompany systemic onset JIA) – then expert opinion should be sought.

Side effects

The majority of children and young people tolerate methotrexate very well; however,

the main side effects seen in children and young people generally include nausea and vomiting, increases in liver enzymes, abnormal blood results and post-dosing reactions of feeling unwell.

Nausea and vomiting

A considerable number of children/young people suffer from methotrexate-related nausea. Early recognition and intervention can help to avoid this in some patients. There appears to be several types of nausea/vomiting. The first is cumulative, over a period of time, or when the dose is escalated. The other is often described as anticipatory. This is prior to the injection when the child or young person may feel sick or when they see or talk about methotrexate. It is also common to have a negative association to the colour yellow. Anecdotal evidence suggests that nausea, vomiting, and perhaps the more troublesome anticipatory nausea, are hugely underestimated problems for patients (Bultovic et al., 2011; van der Meer et al., 2007). Practice within services differs, but it is worth considering administering an antiemetic and folic acid prophylactically when starting methotrexate to try and prevent nausea and vomiting occurring in the first place.

It is worth ensuring that all steps are fully taken early to try and lessen the side effects before they become troublesome. This is especially importantly because methotrexate is often returned to many times throughout the disease course, often in conjunction with biological therapies. Therefore, gaining compliance from children and their families is key, as is not associating it with negative side effects.

Often the whole family will need support as they are all involved in the preparation for the procedure, including calming and supporting the child with JIA. Although antiemetics are often used, their effects on patients are variable.

There are a number of strategies to try and lessen nausea and vomiting and the disruption it causes:

- giving the injection just before bedtime and on a Friday or Saturday (to avoid school absenteeism)
- folic acid supplementation
- withholding NSAID dosage on the injection day
- administering an antiemetic dose a few hours before and one to two doses after the injection
- eating something during the injection, such as a chewy sweet bar can help (although in some patients this makes it worse).

Non-pharmacological interventions can also be used in conjunction with the above:

- self-hypnosis
- relaxation
- music therapy
- guided imagery.

Abnormal blood results and monitoring

The blood monitoring regime for subcutaneous methotrexate is the same as for oral methotrexate (BSPAR, 2020).

Baseline bloods should be obtained and repeated on a regular basis (Kocharla, 2009). The BSPAR methotrexate guidelines (BSPAR, 2020) state that full blood count and liver transaminase (aspartate transaminase (AST) and/oral alanine transaminase (ALT) levels should be checked:

- every two weeks for the first month after starting methotrexate treatment or after changing the dose of methotrexate
- at one month, if stable, check monthly for three months
- thereafter, every three months.

Also, check creatinine and urine analysis at six monthly intervals. ESR and CRP inflammatory markers should be taken to monitor disease activity.

Blood dyscrasias, such as neutropenia and lymphopenia will often lead to a temporary halt of the methotrexate until blood values have normalised. If the liver enzymes are raised above three times the upper limit of normal, the methotrexate is usually discontinued for one or two weeks and the results rechecked. If these have returned to normal, methotrexate can be restarted at the same dose. If the enzymes are still high, the dose can be discontinued for a further fortnight and then rechecked. There is little evidence of liver damage or long-term toxicity in JIA patients taking methotrexate (Foster and Brogan, 2012; Hashkes et al., 1997; Ramanan et al., 2003). Responsibility for blood monitoring should be agreed locally and a shared care agreement entered into if monitoring is to take place in primary care.

Good practice often involves a patient-held record (such as the NPSA's blood monitoring booklet, which may still be available in some trusts), particularly when the parents or young person administer the injections.

Needle aversion

Strong dislike or 'aversion' of needles can be a major concern in paediatric care. Whilst the pre-filled PENs or pre-filled injector device are preferred by many children and young people as they cannot see the needle, health professionals still need to be alert to any concerns. Some children may benefit from referral to a child psychologist or play therapist, although this may not be available in all local areas.

Topical anaesthetic creams or sprays can be used, or a wrapped frozen bag from the freezer can be used to numb the skin. The use of distraction techniques, bravery certificates and stickers may also prove useful.

Giving the child as much control as possible, for example, in which room they want their injection done and what they want to do (look at a book, watch TV, play a computer game), are often useful strategies. There are some commercially available products which families can buy to aid subcutaneous injections in children and young people by, for example, vibrating on the skin surface and lessening the pain signals to the brain.

Vaccinations

BSPAR (2020) and The Department of Health publication Immunisation against Infectious Disease (the 'Green Book') state that children and young people who are on up to 15mg/m^2 of methotrexate can receive live vaccines, as long as they are not receiving any other DMARDs, such as biologics or high dose steroids. If you are unsure, please check with the local health team. Those on more than 15mg/m^2 should not receive live vaccines.

Inactivated vaccines should be given according to the normal immunisation schedule; however, the child may not build up the appropriate immune response to vaccines while on methotrexate and must have these checked if they discontinue the methotrexate.

It is recommended that all children and young people are brought up to date with the pneumococcal vaccine for those who have not had it previously and annual inactivated flu vaccines should be given while on this treatment.

Chickenpox

Chickenpox is a major concern in paediatric practice, much more so than in adult practice.

The treatment of a child who has been in contact with chickenpox, or who develops chickenpox, differs from area to area and this document advises consultation with local centres.

Measuring chickenpox titres in all children prior to starting methotrexate is now standard practice and some even offer the chickenpox vaccine to those who have negative titres. The vaccine is live and thus this may delay starting methotrexate treatment, depending on local guidance. Consideration should be given to providing immunisation to closer relatives that have not been previously infected with chickenpox.

It is also vital to note that if chickenpox develops, methotrexate should be discontinued until the last spot has crusted over and the child is clinically well. Antiviral drugs such as acyclovir should be given (BSPAR, 2020). Passive protection against chickenpox (or herpes zoster) with VZIG and/or acyclovir should be given in the event of significant contact in non-immune patients. The Department of Health publication *Immunisation against Infectious Disease* (the 'Green Book') is regularly updated and should be considered as the definitive source of information about vaccinations. For an up-to-date definition of 'significant contact' see: **gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book**

Transition to adult care

At least one-third of children with JIA continue to have active inflammatory disease in their adult life and up to 60% of all patients continue to have some limitation to daily living activities (Nigrovic and White, 2006).

Specific figures for many rheumatic diseases that continue into adulthood are harder to find, particularly since conditions such as ankylosing spondylitis (AS) and juvenile systemic lupus erythematosus (JSLE) are primarily presenting in adolescence rather than childhood. Adolescence can be a challenging transitional time (McDonagh and Kaufman, 2009) and the following needs special attention.

- Identification and counselling of risk-taking behaviours, such as alcohol, recreational drugs and unprotected sex.
- Planned transition and transfer to adult care.

Transfer to adult care often does not happen seamlessly and, therefore, needs special consideration – including the development of self-management skills in paediatric care in preparation for adult care. The importance of having similar systems in place between paediatric and adult care are vital. For example, if the young person self-administers, the nurse needs to know whether this can continue in the adult setting. Also, if a paediatric nurse administers the injections in the family home, will there be an adult willing to take over this role?

Travelling away from home

In relation to the storage of injections, caution is recommended when travelling to hot climates over 25°C, and the manufacturer's guidelines/local prescriber should be consulted for advice on storage in high temperatures.

Advice should be given to patients if the injections they receive for travel require different storage to their usual treatment. Options available to patients who cannot take their injections away with them are:

- tablets/liquids instead of an injection
- an injection just prior to travelling and one immediately on return.

There may be an issue with the transportation of pre-filled PENs or pre-filled injector devices when flying and patients may require a supporting letter before they travel.

Patients and parents/carers should be advised to carry the medication in their hand/cabin luggage in case the bags get mislaid, but also as any rough handling of luggage could damage the medication and it may freeze in the hold.

Patients and parents/carers should be advised to arrange any vaccinations they may require well in advance of travel and the importance of informing the vaccination provider that they are receiving regular methotrexate treatment (to ensure they do not receive any live vaccines).

Patients and parents/carers should be advised to use high factor sunscreen as sun sensitivity can be increased whilst receiving methotrexate.

Audit trail and data collection

It is essential that all patients who are self-administering methotrexate, or parents/carers who administer at home, can be identified and traced promptly should the need arise.

Further information relating to data collection and audit trails can be found in the **Adult guidance** section of this document.

Conclusion

The increase in licensed pre-filled PENs and injector devices of methotrexate for use in the UK is great news for our paediatric patients. Offering a choice of preparations, colours, shapes and sizes continues to further normalise treatment for children and young people with rheumatic disease. Home administration of methotrexate is safe and without doubt improves the quality of life of the child or young person and their parents/carers.

Paediatric resources

1: How to calculate body surface area

Body surface area (BSA) is calculated in square metres (the Mosteller formula).

$$\sqrt{\frac{\text{Height (cm) x weight (kg)}}{3{,}600}} = \text{m}^2$$

Example calculation for a patient with a height of 100cm and weight of 30kg:

$$\sqrt{\frac{\text{100 (cm) x 30 (kg)}}{3{,}600}} = 0.91\ \text{m}^2$$

If this patient receives methotrexate 15mg/m^2/week, she/he will receive weekly:

0.91m^2 (BSA) x 15mg = 13.65mg/week

This will be rounded up or down to the nearest 2.5mg by the prescriber.

To calculate the methotrexate dose m^2/week:

$$\frac{1}{\text{BSA}} \text{ x dose (mg) per week = dose m}^2\text{/week}$$

To calculate the methotrexate dose m^2/week if this child receives 10mg methotrexate per week:

$$\frac{1}{0.91} \text{ x dose 10mg per week = 10.99mg/m}^2\text{/week}$$

Appendices

Appendix 1: Glossary of terms and definitions

Bioavailability

The amount of drug that reaches the blood system regardless of how it is given. After an intravenous injection, bioavailability is 100% but the bioavailability of drugs given by mouth is often much less because the drugs are broken down by the digestive enzymes and may be poorly absorbed.

Cytotoxic

Toxic to cells. Any agent or process that kills cells.

DMARD

Disease modifying anti-rheumatic drug

Hazard

The Health and Safety Executive defines a 'hazard' as: 'Anything that may cause harm, such as chemicals, electricity, working from ladders, an open drawer etc' (HSE, 2012).

Risk

'A risk is the chance, high or low, that somebody could be harmed by these or other hazards, together with an indication of how serious the harm could be' (HSE, 2012).

Risk management

'A means of reducing the risk of adverse events occurring in an organisation by systematically assessing, reviewing and then seeking ways to prevent their occurrence. Clinical risk management takes place in a clinical setting' (National Health Service Executive, 2001, cited in Dimond, 2002).

Teratogen

Any substance, agent, or process that induces the formation of developmental abnormalities in a fetus.

Vesicant

An agent that causes blistering of the skin.

Appendix 2: Training checklist for home administration of subcutaneous methotrexate by a patient (adult, young person or child) or carer/parent

Patient name:	
Person taught:	
Assessor:	

Skill	Date shown/ trainer discusses	Date supervised	Date completed/ proved competence by trainee	Patient and/ or carer's signature	Assessor's signature
Understands verbal and written information given on subcutaneous methotrexate, including potential complications/side effects. Can discuss why it's given.		N/A			
Knows how to acquire the methotrexate injections.		N/A			
Understands storage requirements.		N/A			
Knows how to check the equipment and drug.					
Knows the correct hand washing techniques.					
Knows the correct use and disposal of gloves (if using).					
Knows how to deal with a needlestick injury.		N/A			
Can give the subcutaneous methotrexate injection using a safe technique and can identify where the injection can be given.					
Knows how to deal with spillage on surfaces, skin and eyes.		N/A			
Knows how to dispose of used sharps, and any unused methotrexate.		N/A			
Can discuss instances when not to give the injections.		N/A			
Knows who to contact in case of any problems.		N/A			
Can discuss the rationale and arrangements for blood monitoring while on methotrexate therapy.		N/A			
Knows that co-trimoxazole (septrin) and trimethoprim must not be taken with methotrexate.		N/A			
Knows what to do when travelling with methotrexate.		N/A			
Signed certificate of instruction	N/A	N/A			

One copy for patient and one to be retained in patient's notes.

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Certificate of instruction for the home administration of subcutaneous methotrexate by patient or patient's carer

Patient name:	
Address:	
Telephone number/email:	

This is to certify that I have received teaching about subcutaneous methotrexate and how to give the injections. I now feel confident and competent in giving the injectable treatment at home. I understand what problems may arise and what to do if they occur.

Patient/carer name:	
Signature:	
Date:	
Assessor name:	
Assessor signature:	
Date:	

One copy for patient and one to be retained in patient's notes.

Useful information

Date methotrexate therapy commenced:	
Dates and doses of any increases:	
Name and preparation prescribed:	
Name and address of prescribing doctor:	
Telephone number (if appropriate):	
Name of nurse involved in your or your child's care:	
Telephone number (if appropriate):	
Any other telephone numbers/help lines:	

Name and address of supplier, such as local hospital, or pharmaceutical company:	
Telephone number (if appropriate):	
Any other important information:	

Appendix 3: Example of specialist practitioner competence checklist

Name of practitioner:	
Name of supervisor:	

Element of competence to be achieved	Date of achievement	Practitioner signature	Supervisor signature
Discuss the rationale for the use of subcutaneous methotrexate in rheumatic conditions.			
Discuss potential issues related to treatment including: • screening of patients • possible side-effects or adverse events • drug interactions • contraindications to methotrexate therapy.			
Discuss the circumstances when subcutaneous methotrexate should not be administered.			
Describe interventions required to alleviate methotrexate induced side-effects.			
Discuss the process for assessing the patient's suitability for methotrexate therapy. For example, medical history, concomitant medications, allergies, level of disease activity, dexterity and attitude to treatment.			
Demonstrate the ability to check the validity of the current prescription. This includes expiry date, dose, route by which the drug is to be administered and the checking of the patient identification.			
Demonstrate the ability to teach a patient/carer how to administer subcutaneous methotrexate.			
Demonstrate the ability to assess a patient's/carer's suitability for home administration of subcutaneous methotrexate.			
Describe local health and safety guidelines and risk assessment required for providing a subcutaneous methotrexate service in hospital and in the patient's home. With particular relevance to: • safe storage and handling • dealing with disposal and rare situation of spillage • ensuring a quiet and safe environment • preventing unnecessary exposure to other people • travelling and transporting methotrexate.			
Demonstrate the ability to discuss the information/educational needs of the patient/carer in relation to home administration of subcutaneous methotrexate therapy.			
Demonstrate the ability to provide the patient/carer with information about the treatment in order that they are able to give informed consent (written/verbal – in line with local guidelines).			
Describe sites on the body that would be appropriate for subcutaneous methotrexate injection.			
Demonstrate the ability to maintain concise and accurate patient documentation and audit.			
Describe the local monitoring requirements and follow up arrangements for subcutaneous methotrexate therapy and the actions that must be taken in the event of a blood dyscrasia.			
Describe the rationale for the use of folic acid supplementation in patients receiving subcutaneous methotrexate.			
Identify the ways of maintaining current competency.			

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Appendix 4. Useful websites and further reading

Advancing Quality Alliance: aquanw.nhs.uk

British National Formulary (BNF): bnf.nice.org.uk

British National Formulary for Children (BNFC): bnfc.nice.org.uk

British Society for Paediatric and Adolescent Rheumatology (BSPAR): bspar.org.uk

British Society for Rheumatology (BSR) – guidelines and clinical statements: rheumatology.org.uk

Department for Environment, Food and Rural Affairs (DEFRA): defra.gov.uk

Department of Health and Social Care – legislation, reports and guidance: dh.gov.uk

eMC (for summary of product characteristics (SPC)): medicines.org.uk/emc

Environment Agency in England and Wales: environment-agency.gov.uk

Health and Safety Executive – for all health and safety regulations, including information on the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations: hse.gov.uk/reach

Health and Safety Executive (2013) *Health and Safety (Sharps Instruments in Healthcare) Regulations 2013. Guidance for employers and employees:* **hse.gov.uk/pubns/hsis7.htm**

National Rheumatoid Arthritis Society: nras.org.uk

NHS Right Care (for information on shared decision making): england.nhs.uk/rightcare

NHS Quality Improvement Scotland: healthcareimprovementscotland.org

Northern Ireland Environment Agency (NIEA): daera-ni.gov.uk/northern-ireland-environment-agency

Nursing & Midwifery Council (NMC): nmc.org.uk

Paediatric Rheumatology European Society (PRES): pres.eu

Royal College of Nursing (online guidance and RCN member access to rheumatology forum): rcn.org.uk

Royal College of Nursing – A Competency Framework for Rheumatology Nurses: rcn.org.uk/professional-development/publications/pub-009004

Royal College of Nursing – *Sharps safety: RCN guidance to support the implementation of the Health and Safety (Sharps Instruments in Healthcare) Regulations 2013*: **rcn.org.uk/professional-development/publications/pub-004135**

Scottish Environment Protection Agency (SEPA): sepa.org.uk

Subcutaneous injections information: bd.com/uk/diabetes

Versus Arthritis: versusarthritis.org

You can find full texts of all UK government legislation at: legislation.gov.uk

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RCN quality assurance

Publication

This is an RCN practice guidance. Practice guidance are evidence-based consensus documents, used to guide decisions about appropriate care of an individual, family or population in a specific context.

Description

This guidance provides the background information regarding subcutaneous methotrexate as an educational resource for practitioners, with particular reference to safety and best practice; and incorporates new sections on treat-to-target and medication optimisation. Whilst the guidance has been developed for rheumatology practitioners, some aspects may also be of value to health care colleagues working in other specialties including dermatology, gastroenterology and ophthalmology.

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