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BSR Guidelines

British Society for Rheumatology RHEUMATOLOGY OXFORD

BSR Guidelines

The 2025 British Society for Rheumatology guideline for the prescription and monitoring of conventional synthetic disease-modifying anti-rheumatic drugs

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¶See Supplementary Data S1, available at *Rheumatology* online, for a list of the BSR Guidelines Steering Group members.

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Introduction

Disease-modifying anti-rheumatic drugs (DMARDs) are crucial in the management of systemic autoimmune rheumatic diseases (SARDs), helping to control disease activity and preventing long-term joint and tissue damage. Over the past decades, the focus on early intervention and achieving sustained remission has been underpinned using conventional synthetic DMARDs (csDMARDs), often with a treat-to-target approach with tight control, leading to improved patients' clinical outcomes and quality of life [1–3].

csDMARDs carry certain risks alongside their benefits. Appropriate screening prior to initiation, precautions during treatment and regular monitoring are required to mitigate these risks. This updated 2025 guideline supersedes the previous 2017 BSR/BHPR guideline [4], incorporating advances in clinical evidence, emerging treatment strategies and updated best practices to reflect the current standards of care.

A summary infographic is available in Supplementary Data S2.

Purpose and scope

Background and need for guidance

An update of the previous BSR guideline published in 2017 was required due to significant advancements in clinical practices involving csDMARDs and the growing evidence base to support clinical decision-making. This includes new evidence on blood monitoring for long-term use of csDMARDs, updates on vaccination timing and effectiveness in the context of influenza, COVID-19 and shingles, revised hydroxychloroquine dosing and monitoring protocols, and the inclusion of new therapies such as voclosporin. This up-to-date guideline also extends across the whole life course, including the use of csDMARDs in children and adolescents, unlike the previous 2017 version.

Objectives of this guideline

This guideline provides up-to-date, evidence-based recommendations for the safe and effective uses of csDMARDs in children, adolescents and adults with SARDs. It is intended for use across primary, secondary and tertiary rheumatology care settings. This guideline focuses on several domains comprising: (1) pretreatment evaluation prior to csDMARD initiation (including clinical assessment, blood tests, imaging and vaccination status); (2) drug specific recommendations; (3) consideration of comorbidities prior to and during csDMARD prescribing; (4) blood test monitoring during therapy; and (5) shared care agreements.

DMARDs covered by this guideline

The following csDMARDs are covered in this guideline: apremilast (APL), azathioprine (AZA), ciclosporin (CSA), hydroxychloroquine (HCQ), leflunomide (LEF), mepacrine, methotrexate (MTX), minocycline (MCN), mycophenolate (MMF), sulfasalazine (SSZ), tacrolimus (TAC) and voclosporin.

This guideline should be viewed along with each individual drug's Summary of Product Characteristics (SmPC) that are freely available online at the medicines compendium (www.medicines.org.uk). The prescribing clinician is always responsible for evaluating the risks and benefits of treatment for each individual patient and ensuring that the patient is appropriately supported to make a shared decision about treatment, with their parent/guardian/carer if applicable.

The areas the guideline does not cover

The guideline does not cover the indications for csDMARD therapy. This topic is addressed in both national and international disease-specific recommendations, as well as guidance from NICE. The guideline does not cover the use of biologic or targeted synthetic DMARDs (e.g. JAK inhibitors) or prescribing in pregnancy or when breastfeeding. These areas are covered in separate dedicated BSR guidelines [5, 6].

Target audience

This guideline is intended for health professionals in the UK directly involved in managing patients with SARDs, including adult and paediatric rheumatologists, paediatricians, allied health professionals, general practitioners, pharmacists and

specialist nurses, other interested stakeholders including patient organisations and charities, and patients.

Stakeholder involvement

This guideline was commissioned by the BSR Standards, Guidelines and Audit Working Group (now called the BSR Guidelines Steering Group). A guideline working group (GWG) was convened, with Louise Mercer as Chair and James Galloway as Deputy Chair, alongside representatives from relevant stakeholders. In accordance with BSR policy, all members of the GWG made declarations of interest.

Involvement and affiliations of stakeholder groups

The GWG consisted of adult and paediatric rheumatologists from a range of clinical backgrounds, pharmacists, rheumatology specialist nurses, general practitioners, a dermatologist, a hepatologist and experts by experience. All members contributed to the process of agreeing key questions, guideline content, recommendations and strength of agreement (SoA).

The GWG surveyed users of the 2017 guideline in August 2023, to identify areas of the previous guideline that required updating or amending. The survey was promoted by BSR social media channels and e-news, and The Limbic.

Rigour of development

This guideline has been developed in line with the BSR's guideline protocol: Creating Clinical Guidelines v5.4 [7]. It is important to acknowledge that there are no trials comparing different strategies for csDMARD screening and monitoring. Nevertheless, cohort data exist on the risk factors and adverse events associated with csDMARDs, alongside relevant national and international guidelines. For each csDMARD, recommendations were devised based on a review of current guidelines, available evidence on specific drug toxicities, and baseline screening and monitoring information obtained by accessing the current SmPC for each drug, the BNF (British National Formulary), SPS (Specialist Pharmacy Service) and NHSE Shared Care Policy. The current SmPC for each drug was obtained online at www.medicines.org.uk [8], up to date as of December 2024. If multiple SmPCs were available for a drug (in the case of multiple manufacturers), all SmPCs were reviewed.

Recommendations that are new to this BSR 2025 guideline were informed by relevant systematic literature searches. These searches were conducted according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [9]; MEDLINE and Embase databases were searched for articles from inception until 21 March 2024 using key MESH and free text terms. A manual search was also conducted of the reference lists of relevant systematic literature reviews and recently published national and international guidelines.

Two reviewers independently screened the titles and abstracts of the articles identified through the search and then examined the full texts of relevant studies. Studies eligible for inclusion comprised randomized and non-randomized controlled trials, cohort studies, case-control studies and case series with more than 10 participants. Conference proceedings were considered if they provided appropriate data and had no corresponding published article. Exclusions were made for case reports, case series with fewer than 10 participants, animal studies and studies not published in English. Data extraction was conducted by two reviewers, with any disagreements resolved through group discussion and, when needed, a third reviewer.

For recommendations that were unchanged from the 2017 guideline, the evidence surrounding each guideline recommendation was updated, where appropriate, based on new publications identified since September 2015 (the latest month included within the BSR 2017 guideline search strategy) until December 2024. Further publications were also suggested by the GWG, and through searching the reference lists of relevant systematic reviews, national and international guidelines.

Grading of the evidence

This guideline was developed in accordance with BSR's Guidelines Protocol using Grade of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, to evaluate the quality and strength of evidence. Alongside each recommendation in this guideline, in brackets, is the strength of recommendation, quality of evidence and strength of agreement (SoA).

Strength of recommendation

Recommendations were classified as either strong (indicated by 1) or weak (indicated by 2), using GRADE, with evaluation of the respective benefits and risks. For instance, in cases where the benefits were significantly greater than the risks, a strong recommendation was issued. A weak recommendation either indicates that the relative benefits and risks are more balanced, or there is more uncertainty based on the available evidence.

Quality of evidence

Using GRADE, the quality of evidence available was indicated as high (denoted by A), moderate (B) or low/very low (C), reflecting the confidence in the estimates of benefits, harms or burden.

Strength of agreement

Initially, a core group within the GWG met to review the available evidence, resolve disagreements and develop preliminary recommendations. A draft document with these recommendations was shared with the full GWG for review. Subsequently, the GWG met on several occasions and revised the wording of these recommendations further. Every recommendation was then voted upon by each member of the GWG in relation to strength of agreement (SoA) on a scale of 0 (no agreement) to 100 (complete agreement). In this guideline, the strength of agreement is presented as an average (mean) percentage of the scores issued by all the members of the GWG.

Limitations of the guideline

The literature search was conducted until December 2024 and was limited to human studies and articles written in the English language. Notably, some of the systematic reviews supporting new recommendations in the BSR 2025 guideline identified only a limited number of studies, highlighting a current paucity of evidence relating to these areas.

Plan for review

The planned review date for this guideline will be 2028. However, in the interim, significant alterations to this guideline will be updated on the BSR website.

The guideline

The guideline is structured around five key sections: pretreatment evaluation prior to csDMARD initiation; drug-specific recommendations; considerations relating to comorbidities; guidance on blood test monitoring during therapy; and principles for shared care agreements. Recommendations will be listed and followed by explanatory text describing the evidence supporting them.

Pretreatment evaluation prior to csDMARD initiation

Recommendation 1	The decision to initiate csDMARDs should be made in conjunction with the patient/carer (with parent/guardian for paediatric age group) and be supervised by an expert in the management of rheumatic diseases (GRADE 1B, SoA 100%).
Recommendation 2	Education about treatment should be provided to promote self-management (GRADE 1B, SoA 100%).
Recommendation 3	Support should be provided around the time of transition of care from paediatrics to adult services, with an emphasis on continuing developmentally appropriate care (GRADE 1B, SoA 99%).
Recommendation 4	When appropriate, patients should be advised about the impact of csDMARD therapy upon fertility, pregnancy and breastfeeding (GRADE 1B, SoA 100%).
Recommendation 5	At the time any new csDMARD is initiated, the following assessments should usually be conducted: weight and laboratory evaluation (FBC, renal function, ALT/AST, albumin) as well as any of blood pressure, ECG, HbA1C, height, lipid profile and magnesium if relevant to the treatment (GRADE 1C, SoA 97%).
Recommendation 6	In patients with increased risk for latent tuberculosis, test for latent tuberculosis prior to initiating csDMARD therapy (GRADE 1B, SoA 97%).
Recommendation 7	All adults starting csDMARD (except HCQ/Mepacrine) should be screened for chronic infection with hepatitis B virus, hepatitis C virus or human immunodeficiency virus. In the paediatric age group, this is at the discretion of the clinicians, depending on individual case risk (GRADE 1B, SoA 97%).
Recommendation 8	Age-specific vaccination recommendations from the UK Health Security Agency Green Book should be followed. An assessment of the patient's total immunosuppression should be made if live vaccines are being considered (GRADE 1B, SoA 100%).
Recommendation 9	Screen for varicella immunity in all children and in adults with no prior history of chickenpox, shingles or VZV vaccination who are commencing csDMARDs. In the paediatric age group, screening for immunity to measles is also recommended before starting csDMARD therapy (GRADE 1B, SoA 99%).
Recommendation 10	Following influenza or COVID-19 vaccination in adults, methotrexate should be withheld for up to two weeks, assuming disease activity/risk of flare allows. In the paediatric age group, this is up to the discretion of the clinician and an individualized approach is needed (GRADE 1A, SoA 99%).

Evidence supporting recommendations

Recommendation 1: **The decision to initiate csDMARDs should be made in conjunction with the patient/carer (with parent/guardian for paediatric age group) and be supervised by an expert in the management of rheumatic diseases (GRADE 1B, SoA 100%).**

There is strong evidence from cohort studies that patients with SARDs who are managed by a rheumatologist compared with a non-rheumatologist experience better clinical outcomes. Studies have suggested that a lack of access to rheumatologists is linked to a risk of sub-optimal csDMARD prescribing for rheumatoid arthritis (RA) [10, 11]. Patients with RA who visit a rheumatologist (compared with non-rheumatologists) are more likely to have prompt csDMARD initiation and are more likely to receive combination DMARD therapy [12]; moreover, delays in assessment by a rheumatologist are associated with increased radiographic progression and lower rates of disease remission [13]. Whilst data is primarily limited to patients with RA, it is reasonable that this recommendation extends to all patients with SARDs requiring csDMARD treatment.

Shared decision making (SDM) is an essential facet of high-quality patient care. A recent systematic review has demonstrated that SDM in rheumatology improves patients' knowledge, satisfaction and self-efficacy [14]. Whilst further discussion of SDM is beyond the scope of this guideline, a comprehensive review of the evidence supporting SDM is available online at https://www.nationalvoices.org.uk/publication/supporting-shared-decision-making/.

Recommendation 2: **Education about treatment should be provided to promote self-management (GRADE 1B, SoA 100%).**

The importance of patient education for supporting self-management is well-established, with a NICE quality standards guideline advising that patients living with RA should have the opportunity to participate in educational activities that support self-management [15]. Trial data have shown that patient education programmes can: improve drug adherence [16]; increase patients' disease knowledge [17]; and, when combined with pharmacological treatment, improve clinical outcomes [18]. A Cochrane review from 2003 concluded that the clinical benefit of patient education interventions is primarily limited to short-term effects [19]; nevertheless, in subsequent years, strategies and frameworks for patient education have developed considerably. In 2015, eight evidence- and expert opinion-based European Alliance of Associations for Rheumatology (EULAR) recommendations were developed to provide a standardized framework for implementing patient education as an integral part of standard care in inflammatory arthritis [20].

Healthcare professionals involved in initiating csDMARDs should ensure that patients receive appropriate education to support informed decision-making, safe use and long-term adherence. Initiation of csDMARDs should not be delayed by a desire to deliver comprehensive education at the outset, since early treatment is critical for many SARDs. Instead, patient education should be recognized as a longitudinal process as patients build understanding of their disease and treatment overtime.

This education should cover: the purpose and expected benefits of csDMARD therapy; how to take the medication; dosing schedules and what to do if a dose is missed; potential side effects and how to manage them; signs of adverse effects or

toxicity that require urgent medical attention; the importance of regular monitoring and blood tests; interactions with other medications or alcohol; and any necessary precautions such as contraception, vaccination or infection risk. Nurse-led clinics, clinical psychologists and other allied health professionals are playing an increasingly important role in delivering and reinforcing patient education, particularly during transitional care or when initiating treatments associated with significant side effects.

There is a growing role for information and communication technology (ICT) in supporting patient education around csDMARD therapy. ICT-based strategies, such as online peer support communities, digital self-management tools and multimedia learning resources, can enhance disease understanding, promote self-management and improve quality of life [21]. Education on disease and medication should be developmentally appropriate, culturally sensitive and accessible, recognizing the diversity in patients' educational backgrounds, language proficiency, health literacy and digital access. Patient choice should be respected, with opportunities for questions and clarification built into the process. Group education sessions and materials produced by patient organizations may also provide valuable support. Ultimately, the format and content of educational interventions should be determined by the clinician initiating therapy, tailored to individual patient needs and reviewed over time.

***Recommendation 3*: Support should be provided around the time of transition of care from paediatrics to adult services, with an emphasis on continuing developmentally appropriate care (GRADE 1B, SoA 99%).**

The transition from paediatric to adult rheumatology services is a critical period for young people on csDMARD therapy, requiring tailored support to ensure continuity of quality care. There is evidence of worsening disease activity and quality of life during the transition period for patients with SARDs, with a lack of continuity of care thought to be an important factor behind this trend [22]. Previous work has highlighted several limitations of transitional care in juvenile idiopathic arthritis (JIA), including poor coordination and transfer of information between paediatric and adult services; adolescents feeling unable to self-advocate; and a lack of adolescent-focused information [23].

A comprehensive list of recommendations and standards for ensuring high-quality transition care have been developed previously; a EULAR/Paediatric Rheumatology European Society (PReS) task force created tailored recommendations for young people with juvenile-onset rheumatic and musculoskeletal disease [24]. These consensus-based recommendations align with NICE guidance for good transition [25] and cover key domains such as ensuring: multidisciplinary team (MDT) input from early adolescence (or promptly after diagnosis); involvement of a transition co-coordinator; thorough documentation of the transition processes and progress; and the creation of a transfer document for each patient [24].

***Recommendation 4:* When appropriate, patients should be advised about the impact of csDMARD therapy upon fertility, pregnancy and breastfeeding (GRADE 1B, SoA 100%).**

The topic of prescribing csDMARDs in individuals who are (or are planning to become) pregnant and/or breastfeeding is covered in separate BSR guidelines [5, 26]. Aside from the recommendation that this subject is discussed in relevant cases, this guideline will not cover this area further, to avoid duplicating recommendations.

***Recommendation 5:* At the time any new csDMARD is initiated, the following assessments should usually be conducted: weight and laboratory evaluation (FBC, renal function, ALT/AST, albumin) as well as any of blood pressure, ECG, HbA1C, height, lipid profile and magnesium if relevant to the treatment (GRADE 1C, SoA 97%).**

A variety of investigations may be indicated for patients before starting a csDMARD. Relevant investigations may include recording baseline height and weight, blood pressure, performing an ECG, as well as certain baseline laboratory tests.

Patients with SARDs experience a greater burden of cardiovascular disease, compared with the general population [27]. Hypertension is the most commonly observed comorbidity, and there is evidence that the condition is both underdiagnosed and under-treated in inflammatory arthritis [28, 29]. The importance of this finding is exacerbated by the fact that certain csDMARDs can cause an increase in blood pressure [30, 31]. Baseline assessment of blood pressure is required before commencing LEF, TAC, CSA or voclosporin. In addition, AZA, CSA and HCQ are prescribed based on weight-adjusted dosing; therefore, a baseline weight is required before initiating these treatments. Given these considerations, the GWG came to the consensus that best practice should involve recording a patient's height, weight and blood pressure prior to initiating any csDMARD.

Measurement of height and weight also allows calculation of body mass index (BMI). An elevated BMI is associated with higher levels of inflammatory markers [32], reduced response to csDMARDs [33] and may affect the interpretation of patient-reported outcome measures (PROMs). It also represents an independent risk factor for liver disease. Assessing BMI at baseline enables clinicians to recognize its potential impact on treatment response and disease monitoring.

An ECG at baseline may be indicated for patients commencing a csDMARD that is associated with an increase in blood pressure. A baseline ECG is important for patients who are starting TAC, as TAC can prolong the QT interval. The SmPC for TAC specifically recommends that caution should be exercised when starting TAC in patients with prolonged QT interval or risk factors for QT prolongation [34]. HCQ and chloroquine are associated with QT interval prolongation due to their effects on cardiac repolarization. In a study of over 800 patients with rheumatic diseases, QT prolongation occurred in 8.5% of those receiving HCQ, with chronic kidney disease, atrial fibrillation and heart failure identified as independent risk factors. ECG monitoring is not currently part of standard practice when initiating HCQ or chloroquine, with a white paper review by the American College of Rheumatology concluding that there is insufficient evidence to support universal ECG monitoring across all patient populations [35]. However, a baseline ECG may be appropriate for patients with additional risk factors for QT prolongation, and that co-prescription of other QT-prolonging medications should be avoided where possible. Voclosporin may also prolong QT, in a dose-dependent manner. The SmPC for voclosporin states that clinically significant QT prolongation may result from co-prescription of voclosporin with other medical products known to prolong QTc [36].

In addition to baseline clinical assessment, it is also important to conduct various laboratory tests. These tests serve two functions in csDMARD assessment: they act as a

screening tool for occult disease (renal, hepatic or haematological dysfunction) and they provide a reference point for future comparison. Screening for occult disease is particularly relevant given the higher prevalence of various comorbidities observed in patients with SARDs. Establishing baseline laboratory tests provides essential reference values for comparison with results after initiating csDMARD therapy. This is important given the adverse effects that some csDMARDs can have on full blood counts, renal and liver function.

It is highly recommended to assess full blood count, renal and liver profile. A full blood count helps identify pre-existing cytopenia, such as anaemia, leukopenia or thrombocytopenia, which may indicate underlying pathology and increase treatment risk. Liver profile tests include serum aminotransferases, bilirubin, alkaline phosphatase, albumin and clotting time, and can be categorized into those that either reflect liver cellular injury (e.g. aminotransferases) and those that reflect liver synthetic function (e.g. albumin and clotting). At baseline, it is advised that one test from each category is performed to evaluate liver health. Serum aminotransferases are sensitive markers of drug-induced hepatocellular damage. The most frequently tested enzymes are alanine aminotransferase [ALT, glutamic-pyruvic transaminase (SGPT)] and aspartate aminotransferase [AST, serum glutamic-oxaloacetic (SGOT)]. There is no strong evidence favouring the use of either ALT or AST as markers of liver cell injury before commencing csDMARD; the choice of test may be determined by assay availability in the local clinical setting.

Renal function is evaluated by measuring serum creatinine levels, subsequently allowing calculation of creatinine clearance and estimated glomerular filtration rate (eGFR). Whilst the majority of csDMARDs are not considered to be damaging to the kidneys, there is evidence that some csDMARDs can be nephrotoxic, particularly in patients with reduced renal function [37, 38]. Furthermore, for csDMARDs that are primarily excreted by the kidneys, such as MTX, the risk of adverse effects is increased in individuals with chronic renal impairment.

In certain instances, baseline assessment of HbA1C and lipid profile may also be indicated. The COMOrbidities in Rheumatoid Arthritis (COMORA) study demonstrated that across RA patients with no known diagnosis of diabetes mellitus or dyslipidaemia, 3.7% had hyperglycaemia and 11% had elevated LDL cholesterol levels, respectively [39]. Undiagnosed diabetes mellitus and/or dyslipidaemia is particularly relevant before commencing calcineurin inhibitors. There is evidence from systematic review and meta-analysis that both CSA and TAC are associated with an increased risk of developing new-onset diabetes mellitus [40]. Amongst calcineurin inhibitors, CSA confers the highest risk of dyslipidaemia and is associated with elevated total cholesterol and LDL cholesterol levels [41, 42]. Subsequently, it is recommended that HbA1C is measured prior to starting a calcineurin inhibitor (that is, CSA, TAC or voclosporin), and before starting CSA, baseline lipid profile tests are assessed. Given the association between diabetes mellitus and metabolic dysfunction-associated steatotic liver disease (MASLD), formerly referred to as non-alcoholic fatty liver disease (NAFLD), screening for diabetes before initiating MTX may also be beneficial, as the presence or absence of diabetes can help inform individualized monitoring strategies based on risk profiles.

Laboratory tests for inflammatory markers, such as ESR and CRP, primarily serve to evaluate the extent of underlying SARD disease activity, as opposed to representing a core aspect of csDMARD therapy monitoring; it may be appropriate for local services to combine blood tests for disease monitoring with csDMARD monitoring.

Recommendation 6: **In patients with increased risk for tuberculosis exposure, test for latent tuberculosis prior to initiating csDMARD therapy (GRADE 1B, SoA 97%).**

Screening for latent tuberculosis (LTBI) should not delay the initiation of csDMARDs. In addition, screening does not need to be repeated if it has been done previously and there are no new risk factors. If a test has previously been performed and is positive, it is assumed that the test will remain positive, even after treatment. Retesting is futile.

As outlined below, there is limited evidence to suggest a significant risk of TB reactivation with csDMARDs alone. Nonetheless, early identification of LTBI remains clinically valuable, particularly for patients likely to require more intensive immunosuppression in future. Early detection enables timely initiation of TB prophylaxis if needed, thereby reducing delays when escalation of therapy becomes necessary.

LTBI is characterized by an immune response to *Mycobacterium tuberculosis* antigens without clinical or microbiological evidence of active disease. Individuals are asymptomatic and non-infectious but harbour dormant *M. tuberculosis*, posing an increased risk of progression to active disease if their immune system is compromised.

Individuals at increased risk of tuberculosis include those with close contact with people who have active TB, those living in or originating from high-prevalence regions (such as sub-Saharan Africa, South and Southeast Asia, Eastern Europe and parts of Latin America), those residing or working in high-risk settings, and those with a history of injected drugs or alcohol misuse.

Reactivation of LTBI with biological and targeted synthetic DMARDs, as highlighted in numerous studies, has led national and international rheumatology guidelines to recommend LTBI screening before initiating these therapies. While there is limited evidence on reactivation with csDMARDs, available data indicate an increased risk with steroids, LEF and CSA, whereas no association has been found with SSZ or HCQ (although limited to single studies for both drugs). The evidence regarding MTX is conflicting. A nested case–control analysis conducted in Quebec (1992–2003) reported an increase rate among MTX users. Similar findings were reported in a Japanese adverse drug event reporting database [43]. However, other studies from Canada [44] and Taiwan [45] found no increased risk associated with MTX use.

NICE guidelines recommend screening individuals requiring immunosuppressive therapies, taking into account the extent of immunosuppression and risk factors for TB infection [46]. Screening involves evaluating prior TB exposure and treatment history, conducting a clinical examination, obtaining a chest X-ray, and performing either an interferon-gamma release assay (IGRA), a tuberculin skin test (TST), or both, as appropriate. Chest X-rays are a crucial part of TB screening, as neither a negative IGRA nor TST can reliably rule out active TB. Both IGRA and TST assess the T-cell response to TB antigens, but false-negative results occur in ~20% of patients with active pulmonary TB [47]. IGRAs are generally considered more accurate than TSTs for diagnosing LTBI and are less influenced by immunosuppressive treatments [48–51]. Given the limited concordance between TST and IGRA results [49, 50, 52], it

may be advisable to use both tests in cases of strong clinical suspicion for LTBI or in high TB risk settings [53]. Among IGRAs, the concordance between QuantiFERON-TB Gold In-Tube assay and T-SPOT.TB is high, so no specific test is preferentially recommended [54–56].

Patients screened for LTBI who test positive with an IGRA or TST should be referred to a TB specialist, and if active TB is ruled out, they should be offered treatment for LTBI.

Recommendation 7: **All adults starting csDMARD (except HCQ/mepacrine) should be screened for chronic infection with hepatitis B virus, hepatitis C virus or human immunodeficiency virus. In the paediatric age group, this is at the discretion of the clinicians, depending on individual case risk (GRADE 1B, SoA 97%).**

Screening for hepatitis B virus, hepatitis C virus or HIV should not delay the initiation of csDMARDs. In addition, screening does not need to be repeated if it has been done previously and there are no new risk factors.

This recommendation was informed by several key considerations: a 40% increase in viral blood-borne infections in the UK [57], the availability of highly effective antiviral therapies, and the substantial risk of severe complications if immunosuppression is initiated in undiagnosed individuals. Although direct evidence is limited, the GWG felt that the rising prevalence of infection, the national shift toward opt-out screening, and the reduced cost of testing together provided sufficient justification to support this clinical recommendation.

Screening for HBV and HCV

Hepatitis B (HBV) and hepatitis C (HCV) are blood-borne viruses that primarily target the liver. According to NICE recommendations, HBV and HCV testing should be offered to all adults and children at increased risk [58]. Chronic infection with HBV and HCV is often asymptomatic, underscoring the importance of screening to identify affected individuals. Up to 90% of those with HBV or HCV remain unaware of their condition, delaying treatment and increasing the risk of disease progression and further transmission. Groups with a higher risk compared with the general UK population include:

- Individuals born or raised in regions with an intermediate or high prevalence of chronic HBV or HCV (2% or greater). This encompasses all countries in Africa, Asia, the Caribbean, Central and South America, Eastern and Southern Europe, the Middle East and the Pacific Islands.
- Children born to mothers with the infection.
- Individuals who have ever injected drugs, including image and performance enhancing substances.
- Men who have sex with men (particularly HIV-positive men, who face a greater risk of HCV).
- Prisoners, young offenders.
- Children or young people in care homes.
- Additional high-risk groups:
  - HBV: include those who may have been exposed to sexually transmitted infections.
  - HCV: include individuals who received a blood transfusion before 1991 or blood products prior to 1986, before blood donor screening for HCV and heat treatment to inactivate viruses were implemented.

HBV screening should include hepatitis B surface antigen (HBsAg) and HB core antibody (anti-HBc), with serum HBV DNA and hepatitis B surface antibodies (anti-HBs) testing if HBsAg or anti-HBc is positive. These results guide monitoring and prophylaxis strategies. According to the 2025 American Gastroenterology Association guidelines, MTX and AZA pose a low risk of reactivation in both chronic HBV (HBsAg-positive) and resolved infection (HBsAg negative and anti-HBc-positive). The general recommendation, also supported by EULAR, is to monitor HBV DNA and liver function every 3–6 months for signs of reactivation, with referral to a hepatologist for antiviral therapy if HBV DNA becomes positive [53, 59]. In chronic HBV (HBsAg-positive) cases, hepatology referral for antiviral treatment should be considered when in doubt.

Screening for HCV involves testing for anti-HCV antibodies, followed by HCV RNA assessment (or HCV core antigen testing if RNA assays are unavailable). Patients with positive HCV RNA results should be referred to a hepatologist for evaluation and consideration of antiviral therapy [6, 53].

Hepatitis B infection

Acute HBV infection is usually self-limiting, with 95% of immunocompetent adults naturally clearing the virus within six months, leading to lifelong immunity. This process is marked by the loss of hepatitis B surface antigen (HBsAg) and the development of hepatitis B surface antibodies (anti-HBs). During acute infection, hepatitis B core antibodies (anti-HBc) appear, initially as IgM anti-HBc, which indicates recent infection. As the infection resolves, IgM is replaced by IgG anti-HBc, which persists for life as a marker of resolved infection. However, 5–10% of adults fail to clear HBV, resulting in chronic infection. The risk of chronicity is significantly higher in neonates (90%) and children under five (30–50%), due to an underdeveloped immune response. Patients with chronic HBV remain at risk of disease progression, including cirrhosis and hepatocellular carcinoma (HCC). Long-term antiviral therapy (e.g. tenofovir, entecavir) is used to suppress HBV replication to undetectable levels, reducing liver damage and preventing complications [60].

HBV reactivation is characterized by a loss of immunologic suppression of HBV activity. It can occur in patients who have previously cleared hepatitis B infection (HBsAg negative, anti-HBc positive) or in those with mild active chronic hepatitis B infection (HBsAg positive, anti-HBc positive). Reactivation is generally a consequence of chronic immunosuppression and depends on the degree of immunosuppression and the patient's HBV status, with HBsAg-positive individuals at higher risk [59]. In HBsAg-positive patients, serum HBV DNA levels reflect the balance between viral replication and immune control. In contrast, HBsAg negative, anti-HBc positive individuals typically have undetectable HBV DNA, though the virus remains in the liver in a dormant state, controlled by the immune system [61, 62]. Immunosuppressive therapy can enhance HBV replication in chronic infection and reactivate latent HBV in those previously considered recovered [63, 64]. The risk of reactivation of HBV with csDMARDs is relatively low in patients with resolved HBV infection [65], with rates similar to those observed with anti-TNF therapy. However, reactivation risk is substantially higher in patients with chronic HBV infection.

Hepatitis C infection

Acute HCV is typically mild, with spontaneous clearance occurring in ~30% of cases. If HCV RNA persists in the blood for more than six months, the infection is classified as chronic. Chronic HCV is generally a slowly progressive

disease, leading to cirrhosis in about 10–20% of individuals over 20–30 years due to ongoing hepatic inflammation. Once cirrhosis develops, the annual risk of HCC is ~1–5% [66]. Direct-acting antiviral (DAA) drugs have revolutionized the management of HCV. In contrast to HBV, the goal of treatment is to eradicate the virus, achieve a sustained virological response and halting disease progression. HCV is now considered highly curable with DAAs, with over 95% of patients achieving sustained virologic response [67].

Data on HCV reactivation associated with csDMARDs are limited, with most studies in this area conducted prior to the advent of newer, more effective antiviral treatments. The majority of research has focused on biological DMARDs, particularly anti-TNF therapies [68–70], and has found that while HCV reactivation can occur, it is relatively infrequent.

HIV infection

Although the UK has achieved a significant reduction in new HIV diagnoses, an estimated 6% of individuals living with HIV remain undiagnosed [71]. According to NICE guidelines, routine HIV testing should be offered to adults and children in areas with high HIV prevalence when they undergo blood tests for other reasons. Testing is also recommended for individuals from countries or groups with a high prevalence of HIV, those with a history of injecting drug use, men who have sex with men, individuals potentially exposed to sexually transmitted infections and those reporting sexual contact with someone from a high-prevalence region [72].

Prescribing csDMARDs to individuals with undiagnosed HIV infection can significantly increase their risk of opportunistic infections. This risk is likely to be higher in patients with advanced HIV with higher HIV viral loads and lower CD4 counts. Given the availability of effective HIV therapies, there is a compelling case for screening all patients prior to initiating immunosuppression. This recommendation aligns with guidance from other national and international societies [6, 53, 73].

Rescreening

Routine rescreening is not generally indicated but may be considered in patients with specific risk factors for infection.

Recommendation 8: **Age-specific vaccination recommendations from the UK Health Security Agency Green Book should be followed. An assessment of the patient's total immunosuppression should be made if live vaccines are being considered (GRADE 1B, SoA 100%).**

The UK Health Security Agency (UKHSA) Green Book, *Immunisation Against Infectious Disease*, provides national guidance on vaccination in the UK, incorporating recommendations from the Joint Committee on Vaccination and Immunisation (JCVI). Chapters 6 and 7 of the Green Book offer guidance on vaccinating patients at increased risk of vaccine-preventable diseases due to underlying chronic illnesses or immunosuppression [74]. Recommended vaccines for all patients include influenza, pneumococcus and COVID-19. The relevant vaccination recommendations from the JCVI are summarized in Table 1.

The influenza vaccine should be administered annually using quadrivalent influenza vaccines (QIV) as recommended by JCVI. In children, the live attenuated intranasal influenza vaccine (LAIV) is preferred due to superior effectiveness, particularly after a single dose and child-friendly administration. School-aged children up to year 11 (~16 years) receive vaccination through school programmes, while those aged 2–3 and 17–18 years are vaccinated through their GP [75]. JCVI advises against LAIV in severely immunocompromised children (see below). Children who cannot receive LAIV and at-risk children under 2 years should receive inactivated QIV vaccine via intramuscular injection.

The routine infant pneumococcal programme uses two doses of conjugate vaccine, PCV13 or PCV15 (at 12 weeks and one year), while children over 2 years and adults receive a single dose of polysaccharide vaccine, PPV23, covering 23 serotypes [76]. The vaccine should ideally be given before starting csDMARDs, as the VACIMRA trial showed stronger immune responses when PCV13 was administered one month before MTX rather than concurrently [81]. If this is not feasible, it should still be given regardless of treatment timing. Re-immunisation every five years is only recommended for those with asplenia, splenic dysfunction or chronic renal disease. For individuals with severe immunocompromise, an alternative schedule is recommended: PCV13 or PCV15 followed by PPV23 at least two months later for those over 2 years. While JCVI examples don't explicitly include rheumatic diseases, some patients with rheumatic conditions may have profound immune deficiencies requiring case-by-case evaluation and potential immunology consultation.

COVID-19 vaccination is currently recommended for all individuals aged 75+ (65+ prior to 2025) and those aged 6 months+ who are immunosuppressed due to disease or treatment [77, 78]. Real-world studies show only modest reduction in vaccine effectiveness in immunosuppressed individuals [82]. The JCVI recommends that vaccinated individuals who become immunosuppressed should receive an additional dose regardless of vaccination history. As guidance is likely to continue evolving, we advise regularly consulting the Green Book for the latest recommendations.

Varicella-zoster virus (VZV) causes chickenpox as its primary infection and shingles upon reactivation, as it remains latent in nerve ganglia and reactivates under impaired immunity. In November 2023, JCVI recommended adding chickenpox vaccination to routine childhood schedules using combined measles mumps, rubella and varicella (MMRV) vaccine [83]. The programme is scheduled to launch in England in January 2026. Current guidelines recommend vaccinating non-immune susceptible individuals before starting immunosuppressive treatment if sufficient time exists to complete the two-dose course, balancing the risks of delaying csDMARDs against varicella infection risk in immunosuppressed patients [84].

Shingrix is a non-live, adjuvanted recombinant zoster vaccine given as two doses (8 weeks to 6 months apart) to boost immunity against VZV reactivation. It is provided by the NHS for individuals aged 65+ and for those who are aged 18+ (previously 50+) and severely immunosuppressed, following JCVI advice to expand eligibility [85]. There are plans to lower the eligible age for immunocompetent individuals to 60 years, with phased implementation over a 10-year period. Immunosuppression criteria, as defined in the Green Book, include moderate-dose or long-term prednisolone, csDMARDs (MTX, AZA, MMF) or b/tsDMARDs [79]. Clinical trials and real-world studies show high effectiveness in preventing shingles even in older adults and those with immune-mediated diseases, though vaccine reactions can occur, SARD flares have not been reported [86, 87].

Table 1. JCVI vaccination recommendations and eligible populations at guideline publication

Vaccine	Target population	Administration	Special considerations
Influenza [75] (QIV, LAIV)	All individuals particularly children, elderly, immunosuppressed	Annually LAIV for children aged 2–17, QIV for others	Children under 2 or unable to receive LAIV get inactivated QIV
Pneumococcal [76] (PCV13/ PCV15, PPV23)	Infants All individuals 65+, immunosuppressed	PCV13/15 at 12 weeks & 12 months PPV23 single dose for children over 2 years and adults Booster every 5 years in high-risk	Severely immunosuppressed individuals should get PCV13/15 first, then PPV23 after 2 months
COVID-19 [77, 78]	All individuals 75+, Residents in care homes for older adults, immunosuppressed (from 6 months)	Booster doses for eligible populations based on JCVI updates	Immunosuppressed individuals may require an additional dose post-treatment
Shingrix [79] (Herpes Zoster)	All individuals 65+, immunosuppressed (from 18+)	Two doses 6–12 months apart for 65+; 8 weeks to 6 months apart for 18+ immunosuppressed	Expected NHS expansion to all individuals aged 60+
Measles, Mumps and Rubella (MMR) or Measles, Mumps, Rubella and Varicella (MMRV) rolled out from January 2026 [80]	Routine childhood schedule (12 and 18 months) Non-immune individuals before immunosuppression	Two doses at 12 and 18 months; catch-up for non-immune individuals before immunosuppression	Live vaccine, ideally given at least 4 weeks before immunosuppression

COVID-19: Coronavirus Disease 2019; JCVI: Joint Committee on Vaccination and Immunisation; LAIV: Live Attenuated Influenza Vaccine; MMR: Measles, Mumps and Rubella Vaccine; MMRV: Measles, Mumps, Rubella and Varicella Vaccine; NHS: National Health Service; PCV13: 13-valent Pneumococcal Conjugate Vaccine; PCV15: 15-valent Pneumococcal Conjugate Vaccine; PPV23: 23-valent Pneumococcal Polysaccharide Vaccine; QIV: Quadrivalent Influenza Vaccine.

Live-attenuated vaccines should generally be avoided in immunosuppressed patients due to the risk of infection with the attenuated pathogen. This is particularly relevant for travel vaccines (yellow fever, oral typhoid) and childhood vaccines (MMR, rotavirus, BCG). The preferable vaccination window is 4 weeks prior to treatment initiation [88]. International paediatric guidelines suggest VZV and MMR boosters may be safely given to patients on MTX and low-dose corticosteroids, based on limited safety data and expert consensus [89–92], and for VZV, the risk of wild-type virus exposure. The JCVI provides immunosuppression thresholds below which live vaccines may be administered: long-term, stable, low-dose corticosteroids, MTX (up to 25 mg/week in adults, 15 mg/m^2/week in children) or AZA (up to 3.0 mg/kg/day) [93]. Patients receiving combination therapy may be at higher risk, and the degree of immunosuppression should always be assessed on an individual basis. Non-live vaccines can be safely administered to immunosuppressed patients with SARD, ideally during disease quiescence and before planned immunosuppression to optimize efficacy. However, the priority is initiating necessary immunosuppressive treatment without delay, as managing the underlying SARD often takes precedence.

Vaccination responsibility typically falls to primary care practices commissioned through NHS Enhanced Services to vaccinate individuals. Unfortunately, uptake among SARD patients remains suboptimal, particularly in younger individuals [94, 95]. Since COVID-19, vaccine hesitancy has increased, with patients concerned about disease flares post-vaccination, though this risk may be overestimated as fewer than 5% of over 5000 surveyed patients reported flares requiring treatment changes following COVID-19 vaccination [96]. Rheumatology teams should focus on patient education and clear communication with primary care providers.

Recommendation 9: **Screen for varicella immunity in all children and in adults with no prior history of chickenpox, shingles or VZV vaccination who are commencing csDMARDs. In the paediatric age group, screening for immunity to measles is also recommended before starting csDMARD therapy (GRADE 1B, SoA 99%).**

It is important to establish VZV-immunity status based on a history of past chickenpox, varicella or shingles vaccination. Most, but not all adults in the UK are exposed to the virus in childhood. In children, immunity is dependent on the age at onset of the SARD, which may predate the age at which they are eligible for varicella vaccination. For those who are not immune and who subsequently commence immunosuppressive therapy, rheumatologists need to be aware of the risk of severe *de novo* infection and the indications for post-exposure prophylaxis with antiviral agents (e.g. aciclovir or valaciclovir) or varicella zoster immunoglobulin (VZIG) following a significant contact [97].

While the JCVI does not recommend routine measles screening for all patients receiving immunosuppression, consideration of measles immunity in paediatric patients starting csDMARD therapy serves important practical purposes. Knowledge of immunity status can prevent unnecessary school exclusions when children develop simple viral rashes, empowering families to make informed decisions about exposure risks.

Clinicians should be aware that measles serology has limitations, particularly in populations with high vaccination coverage or background exposure. In these settings, the proportion of false-negative test results may exceed the proportion of true negatives (true disease susceptibility), potentially leading to unnecessary interventions [98, 99]. Decisions regarding measles immunity testing should always be personalized to individual patients, taking into account their specific circumstances and risk factors. In adult patients, measles immunity testing may be warranted for individuals from countries without established vaccination programmes or for patients with an uncertain vaccination history.

For post-exposure prophylaxis decisions, measles serology alone should not be the sole determinant, and local epidemiology

should be considered given rising measles cases in the UK. Oral csDMARDs typically would not require prophylaxis based on immunosuppression level alone. When post-exposure measles prophylaxis is being considered for patients on more intensive immunosuppressive regimens (such as rituximab), clinicians should note that fatal cases have been reported in patients with previous detectable measles IgG [100, 101], highlighting the limitations of serological markers in severely immunocompromised individuals.

***Recommendation 10*: Following influenza or COVID-19 vaccination in adults, methotrexate should be withheld for up to two weeks, assuming disease activity and/or risk of flare allows. In the paediatric age group, this is up to the discretion of the clinician and an individualized approach is needed (GRADE 1A, SoA 99%).**

This recommendation is supported by evidence from multiple randomized controlled trials (RCTs) in adult patients, which evaluated the impact of temporarily withholding MTX around the time of vaccination on vaccine immunogenicity. These included three influenza vaccination studies, comprising a total of 693 participants, that investigated various MTX interruption strategies, such as pausing therapy prior to vaccination and discontinuing it for up to 4 weeks afterwards. A short-term 2-week interruption after vaccination was shown to be both effective and safe, with a lower rate of disease flares compared with a 4-week interruption [102, 103]. A comparable vaccine response was observed when a 1-week MTX interruption was compared with a 2-week interruption [104]. The data also indicated that stopping MTX before vaccination is not necessary to enhance immunogenicity [105].

Similar RCTs have investigated the impact of temporarily withholding MTX on vaccine immunogenicity following COVID-19 vaccination. These studies examined a 2-week interruption after the primary COVID-19 vaccine series and after third and fourth booster doses [106–108], involving a combined total of 639 participants with various immune-mediated inflammatory diseases. The findings corroborated results from the influenza studies. Four weeks after receiving a booster vaccination, participants who paused MTX for 2 weeks demonstrated significantly higher antibody responses compared with those who continued treatment. This enhanced immune response was sustained for up to 26 weeks post-vaccination and was consistent across various prognostic factors, including age, disease type and MTX dosage [108]. Results from observational studies, including one involving adolescent patients, were less conclusive [109, 110], although significant improvements in neutralization capacity were noted [111].

The decision to withhold MTX must carefully balance the potential benefits against the risk of SARD flares. In the COVID-19 vaccination studies, a higher number of flares were reported over 12 weeks in the MTX suspension arms [106–108]. Notably, these studies enrolled participants with stable, low disease activity, pre-selected by their clinicians as appropriate candidates for temporary MTX suspension. Extrapolating these findings to individuals with active or less stable disease may not be appropriate and warrants careful consideration.

The effects of MTX interruption observed with influenza and COVID-19 vaccinations may not extend to all vaccine platforms, particularly those that are less immunogenic, such as the polysaccharide pneumococcal vaccine. Determining whether a two-week MTX hold is appropriate for other vaccinations should be a clinical decision, factoring in the immunogenicity of the specific vaccine and the patient's disease activity and risk of flare. Additionally, it remains uncertain how the findings apply to other immunosuppressive therapies. While some medications, like rituximab, significantly blunt vaccine responses, others have minimal impact. This variability underscores the need for a tailored approach to vaccination and highlights an important area for future research.

This recommendation is in keeping with guidance from the other international rheumatology bodies [112].

Drug-specific recommendations

Methotrexate

Recommendation 11a	Before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing (GRADE 1C, SoA 100%).
Recommendation 11 b	All patients on methotrexate should have an agreed day of the week for dosing and be co-prescribed folic acid supplementation at a minimum dose of 5 mg once weekly, not on the day of methotrexate (GRADE 1B, SoA 100%).
Recommendation 11c	Non-invasive scoring using a Fibrosis index (FIB-4) followed by an elastography (e.g. Fibroscan®) if indicated is recommended for adults with risk factors for liver disease when starting methotrexate, although this should not delay methotrexate initiation (GRADE 1B, SoA 96%).

Azathioprine

Recommendation 12	Patients commencing azathioprine should have baseline thiopurine methyltransferase (TPMT) status assessed (GRADE 1B, SoA 99%).

Hydroxychloroquine

Recommendation 13a	All patients who have taken hydroxychloroquine for the equivalent of 5 years of continuous treatment or more should have annual retinopathy monitoring (GRADE 1B, SoA 100%).
Recommendation 13b	Patients who are at high risk of hydroxychloroquine retinopathy should have annual monitoring after 1 year of use. High risk factors include: tamoxifen use, in adults hydroxychloroquine doses >5 mg/kg actual body weight, renal impairment, e.g. eGFR <60 mL/min/1.73 m^2 and prior chloroquine use (GRADE 1B, SoA 99%).
Recommendation 13c	Information about duration of treatment with hydroxychloroquine must be shared when transitioning between services (GRADE 1C, SoA 100%).

Tacrolimus, ciclosporin

Recommendation 14	For patients on tacrolimus and ciclosporin, monitoring of electrolytes should include periodic monitoring of magnesium (GRADE 1B, SoA 98%).

Evidence supporting recommendations

Recommendation 11a: **Before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing (GRADE 1C, SoA 100%).**

MTX is administered once weekly in individuals with SARD. This frequency was adopted from the dermatological experience in the early 1980s and allows for effective suppression of the immune system to control disease activity while minimizing the risk of adverse effects associated with more frequent dosing. Although the active metabolite of MTX has a half-life of three days, studies indicate that twice-weekly administration does not provide significant efficacy advantages over the standard once-weekly regimen [113].

MTX has a narrow therapeutic index, meaning there is a small margin between its effective and toxic doses. High doses can result in life-threatening adverse events. Its unique once-weekly dosing regimen increases the risk of accidental overdose, particularly if mistakenly taken more frequently, such as daily. Between 2006 and 2020, 11 Yellow Card reports of serious toxicity due to daily dosing errors were recorded in the UK [114], with similar incidents reported across Europe. In response to the persistence of such errors, the European Medicines Agency (EMA) issued new guidance, including restricting prescribing to authorized professionals, enhancing packaging warnings, supplying tablets in blister packs instead of bottles, and providing patients with a reminder card to emphasize the once-weekly schedule and encourage recording their specific day of intake. Correct prescribing and administration of MTX is a key priority for the NHS and is included in the NHS Never Events list [115]. The British National Formulary (BNF) also highlights the risk of accidental overdose and recommends that MTX tablets be prescribed in a single strength, typically 2.5 mg, to minimize dosing errors [116].

A literature review on MTX safety covering a 1-year period (October 2023 to October 2024) found that nearly all severe toxicity cases resulted from dosing errors, typically daily instead of weekly administration. Clinical severity ranged from isolated dyspnoea to classic toxicity including mucositis, myelosuppression, liver and renal failure [117]. A root cause analysis study from India reported nine cases of MTX toxicity due to medication error; seven of these cases had errors during prescribing or dispensing. In all these cases, inadequate communication was a contributing factor [118].

Recommendation 11b: **All patients on methotrexate should have an agreed day of the week for dosing and be co-prescribed folic acid supplementation at a minimum dose of 5 mg once weekly, not on the day of methotrexate (GRADE 1B, SoA 100%).**

The recommendation for all patients to have an agreed day of the week for dosing is primarily to minimize the risk of accidental overdosing as discussed above. By assigning a specific weekly dosing day, patients are less likely to inadvertently take MTX more frequently than intended, a safety measure supported by national and international guidelines.

Co-prescription of folic acid supplementation at a minimum dose of 5 mg per week is strongly recommended for patients on MTX therapy. Evidence indicates that folic acid significantly reduces the risk of gastrointestinal side effects (e.g. nausea, vomiting and abdominal pain), hepatic dysfunction (as measured by elevated serum transaminase levels) as well as MTX discontinuation for any reason [119]. While there is insufficient evidence to specify the optimal day for folic acid administration, clinical trials have avoided administering folic acid on the same day as MTX.

Recommendation 11c: **Non-invasive scoring using a Fibrosis index (FIB-4) followed by an elastography (e.g. Fibroscan®) if indicated is recommended for adults with risk factors for liver disease when starting methotrexate, although this should not delay methotrexate initiation (GRADE 1B, SoA 96%).**

Evidence regarding the impact of MTX on liver fibrosis remains conflicting. While some studies have demonstrated a correlation between cumulative MTX dose and increased liver stiffness [120–122], others have found no such association [123–130]. Recent data have challenged the longstanding belief that MTX by itself leads to chronic liver disease. Many previously reported cases of MTX-related fibrosis and cirrhosis were likely overestimated, confounded by underlying metabolic syndrome or chronic liver disease [131].

MASLD (formerly NAFLD) is characterized by excessive hepatic fat accumulation in the absence of significant alcohol consumption or other causes of chronic liver disease. It is the most common cause of elevated hepatic transaminases and chronic liver disease in paediatrics and adults [132] and its prevalence among the general population ranges from 25% to 30% [133]. MASLD is frequent in rheumatological and dermatological populations treated with MTX [134]. Although a plausible pathophysiological mechanism exists by which MTX may exacerbate hepatic steatosis, and transaminase elevations have been observed in MASLD patients receiving MTX, whether MTX itself drives fibrosis progression remains uncertain.

Current data highlight the complex interplay between MTX and MASLD [131]. A meta-analysis of studies in adults with psoriasis found no significant association between MTX and liver fibrosis [128]. Instead, fibrosis appeared more strongly linked to confounding factors such as diabetes and obesity. Similar findings have been presented in other studies [122, 135–139]. Given the risk for MTX-related liver injury in high-risk individuals, targeted approaches to screening and monitoring are essential.

Pretreatment evaluation before commencing MTX should include assessment of risk factors for liver disease such as alcohol consumption, diabetes, dyslipidaemia and increased BMI [131]. In patients with identified risk factors, the FIB-4 should be calculated and where appropriate elastography may follow, but this should not delay the initiation of MTX therapy.

In primary care, NICE guidelines advise using a non-invasive scoring system first, such as the FIB-4 Score, Enhanced Liver Fibrosis test (ELF) and the NAFLD Fibrosis Score (NFS) in individuals where MASLD is suspected to guide the requirement for a liver elastography [140, 141]. The FIB-4 score estimates the risk of cirrhosis using readily available parameters: age, AST, ALT and platelet count [142]. A score of <1.30 is considered a low risk, 1.30–3.25 a moderate risk and >3.25 is regarded as high risk of liver fibrosis [140, 143]. Referral for FibroScan® is recommended for those with a moderate fibrosis risk score, and direct referral to hepatology for those with a high fibrosis risk score. While NICE advises considering a non-invasive scoring first, the blood tests required for these scores may not be readily available in all

settings. Consequently, FibroScan® is often used either as an alternative to or alongside these risk scores [144].

The FIB-4 demonstrates excellent diagnostic performance and is widely used to screen for fibrotic liver disease in targeted populations [131]. FIB-4 score could be impacted by active inflammatory disease (where this effects platelet and liver blood tests). No studies have directly evaluated the impact of using FIB-4 compared with not using it in patients being evaluated for csDMARD therapy. Numerous studies have, however, assessed the overall performance of FIB-4 in RA patients receiving csDMARDs, providing insights into its potential utility in this context [145–152]. The FIB-4 is not validated in children and performs poorly in the diagnosis of significant fibrosis in this population [153, 154].

Liver elastography is a validated non-invasive technique to evaluate liver steatosis and fibrosis [155]. Transient elastography (e.g. FibroScan®), the most widely used elastography method, employs ultrasound to deliver mechanical waves generated by vibrations into the liver. The measurement of the speed of propagation of the wave across the hepatic parenchyma provides an estimate of the liver elasticity, which in turn is a surrogate marker of liver fibrosis. The scan provides two parameters: the liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), which assess degree of liver fibrosis and steatosis, respectively [156]. It can distinguish normal liver or minimal fibrosis from cirrhotic liver disease. A LSM of 7.8 kPa or less suggests a low risk of advanced fibrosis. This tool provides valuable insights into liver stiffness and has shown utility in identifying MASLD when its results are combined with AST levels [157, 158].

The use of liver elastography is technically challenging in patients with obesity, where failure rates can reach ~20% [131]. An extra-large probe is available to enhance signal penetration through deeper tissues, reducing device failure rates in patients with obesity, although the use of this probe is not without its own limitations [156]. Additionally inter-operator variability is evident and relates to prior formal training and total number of scans performed [159, 160]. It is recommended that liver elastography is performed by those with formal training, who undertake regular scans in a dedicated clinic, to increase validity of results.

Although FibroScan® is recognized as a valuable tool [155], there is no current evidence evaluating its routine use as a baseline assessment for pre-existing liver fibrosis, predicting liver-related adverse effects, or optimizing csDMARD management strategies in individuals starting csDMARDs. As such, routine liver elastography is not recommended before commencing MTX.

In the paediatric population, NICE guidelines currently recommend screening for MASLD in children with risk factors including metabolic syndrome or type 2 diabetes, using liver ultrasound [161]. In this group, there is less evidence regarding the use of liver elastography. While the tool has shown good sensitivity and specificity for assessing liver fibrosis in children, cut-off points have not yet been well established [162, 163]. Transient electrography (FibroScan®) is the only technique with validated normative values [164, 165]. Performing the examination is technically more challenging, particularly in children under 6 years of age, and the results can vary depending on age, sex and the type of probe used. Moreover, existing studies have been conducted exclusively in tertiary care settings, limiting the applicability of accuracy data to a broader screening population [162].

Recommendation 12: **Patients commencing azathioprine should have baseline thiopurine methyltransferase (TPMT) status assessed (GRADE 1B, SoA 99%).**

AZA is a prodrug rapidly converted into its primary active metabolite, 6-mercaptopurine (6-MP). 6-MP is metabolized via two key pathways: the thiopurine methyltransferase (TPMT) pathway, which converts 6-MP into various inactive metabolites, and the xanthine oxidase (XO) pathway, which produces thiouric acid, excreted in the urine. Co-administration with a xanthine oxidase inhibitor, such as allopurinol or febuxostat, reduces the clearance of AZA, increasing the risk of toxicity. Therefore, prescribing AZA alongside a xanthine oxidase inhibitor requires careful consideration, including dose reduction of AZA, or the use of alternative treatments.

The accumulation of AZA metabolites is influenced by polymorphisms in the *TPMT* (thiopurine methyltransferase) gene, which determine TPMT enzyme activity. ~0.3% of the population have very low or absent TPMT activity due to inheriting two defective alleles (homozygous for *TPMT* variants). These individuals cannot clear even low doses of AZA, leading to the excessive accumulation of toxic thioguanine nucleotides, which can cause severe, prolonged and sometimes fatal pancytopenia. A meta-analysis of retrospective studies found that 86% of homozygous individuals developed significant myelosuppression [166]. In addition, around 10% of the population are heterozygous for defective *TPMT* alleles and are classified as intermediate metabolizers [167, 168]. Myelotoxicity can also be observed in these heterozygous individuals when exposed to conventional AZA doses [166].

TPMT enzyme testing enables safer and more effective AZA treatment. For intermediate metabolizers, a reduced AZA dose (30–80% of the target dose) can be used, while substantially reduced doses or alternative agents are recommended for poor metabolizers [169]. However, because myelosuppression can also occur in individuals with normal TPMT activity, TPMT screening cannot replace regular blood test monitoring during therapy.

The accumulation of AZA metabolites is also influenced by polymorphisms in the nucleoside triphosphate diphosphatase *NUDT15* gene, which affects the NUDT15 enzyme involved in inactivating thioguanine nucleotides. Variants in the *NUDT15* gene increase the risk of profound myelosuppression and are most prevalent in Asian and Hispanic populations. A significantly reduced dose is recommended for heterozygous individuals (intermediate metabolizers), while those with homozygous variants (poor metabolizers) are typically advised to avoid AZA therapy altogether [169].

NUDT15 testing is gaining recognition, particularly for patients of Asian or Hispanic descent. Although not yet standard practice across all UK healthcare settings, awareness is growing. In oncology and other specialized settings, genotyping for both TPMT and *NUDT15* before initiating thiopurine therapy is increasingly recommended [170].

***Recommendation 13a*: All patients who have taken hydroxychloroquine for the equivalent of 5 years of continuous treatment or more should have annual retinopathy monitoring (GRADE 1B, SoA 100%).**

***Recommendation 13b*: Patients who are at high risk of hydroxychloroquine retinopathy should have annual monitoring after 1 year of use. High risk factors include: tamoxifen use, in adults hydroxychloroquine doses >5 mg/kg actual**

body weight, renal impairment, e.g. eGFR <60 mL/min/1.73 m^2 and prior chloroquine use (GRADE 1B, SoA 99%).

Recommendations surrounding HCQ retinopathy monitoring follow guidance from the Royal College of Ophthalmology guidelines, 2020. Since the 2017 BSR DMARD guideline was published, there have been changes with regard to recommended HCQ dosage and monitoring. HCQ is prescribed to a target dose of 5 mg/kg actual body weight. Previous recommendations suggested a maximum HCQ dosage of 6.5 mg/kg ideal body weight, based upon the notion that HCQ distributed poorly in fatty tissues [171]. However, a large case control study by Melles and Marmor in 2014 found that retinal toxicity risk was better predicted by actual body weight rather than ideal body weight. They also saw a much lower risk of retinal toxicity with 5 mg/kg actual body weight or less (~2% within the first 10 years) compared with those using >5 mg/kg actual body weight (~10% within the first 10 years) [172]. Although no absolutely safe dose has been identified, the recommendation of 5 mg/kg actual body weight dosing has since been reiterated by American and British Ophthalmological guidance as well as European SLE guidance [173–175].

The previous BSR guideline advocated baseline formal ophthalmic examination [that is, optical coherence tomography (OCT)] within 1 year of commencing HCQ. Ophthalmic monitoring in this instance aimed to recognize a preclinical stage of retinal disease before bull's eye retinopathy developed. In 2014, Melles and Marmor reported a 7.5% prevalence of HCQ retinopathy from a cohort of 2361 patients who had taken HCQ continuously for at least 5 years [172]. Major risk factors for retinopathy identified included: >5 mg/kg body weight dose [odds ratios (OR) 5.67], kidney disease (eGFR <60 mL/min/1.73 m^2; OR 2.08) and concomitant tamoxifen use (OR 4.59). Subsequently, the American Academy of Ophthalmology 2016 and Royal College of Ophthalmologists 2018 guidance on HCQ retinopathy monitoring recommended ophthalmic examination within the first year of starting HCQ. This was to be followed by annual monitoring after 5 years of use or after 1 year for high-risk patients (doses >5 mg/kg actual body weight, eGFR <60 ml/min/1.73 m^2 or concurrent tamoxifen usage) [175, 176]. The purpose of this early examination was to rule out underlying retinal disease that might already compromise retinal function or complicate the recognition of retinopathy (for example, significant macular degeneration, severe diabetic retinopathy or hereditary disorders of the retina).

Two British studies from large tertiary centres audited their own HCQ monitoring services against the 2018 RCOphth guidance and found a lower prevalence of HCQ retinopathy than reported by Melles and Marmor [177, 178]. Marshall *et al.* described an overall HCQ retinopathy prevalence of 6.3% (1.6% definite and 4.7% possible retinopathy [177]), whilst Gobbett *et al.* described an overall HCQ retinopathy prevalence of 0.6% (0.3% definite and 0.3% possible retinopathy [178]). Furthermore, very few individuals referred for retinal assessments around the time of HCQ initiation exhibited abnormalities that precluded further HCQ retinal monitoring (none reported by Marshall *et al.* and 6.3% reported by Gobbett *et al.*) [177, 178]. This was acknowledged in the updated RCOphth 2020 HCQ retinopathy guidance which no longer recommended retinal monitoring around the time of HCQ initiation [174].

Melles *et al.* (2023) published a retrospective cohort study of 3325 patients initiated on HCQ between 2004 and 2015, with continued use >5 years [179]. This study saw a 2.5% cumulative incidence of HCQ retinopathy at 10 years and 8.6% at 15 years. However, they used spectral domain-OCT (SD-OCT) alone for monitoring and notably 69% of cases were mild in severity (focal disruption of the outer retina on either side of the fovea). In the UK, Alieldin *et al.* (2023) described a 1.06% prevalence of definite HCQ retinopathy and 0.7% with possible retinopathy in their Manchester-based cohort. They also noted that only two out of 344 patients referred for baseline monitoring had macular pathology that precluded effective monitoring [180]. No studies have been identified that directly compare baseline monitoring to no monitoring with regard to the detection and prevention of HCQ retinal toxicity.

In line with RCOphth HCQ retinopathy guidance, all patients should have monitoring with both SD-OCT and Fundus Autofluorescence (FAF) (with widefield angiography if available). Those with abnormalities on either SD-OCT or FAF should undergo visual field testing appropriate to the location of the abnormality seen on SD-OCT or FAF. If no abnormality is identified on visual field testing, multifocal electroretinography is advised for those with structural abnormalities consistent with HCQ retinopathy. The Regional Medicines Optimisation Committees (RMOCs), part of NHS England, advise that the primary prescriber of HCQ is responsible for arranging retinopathy monitoring assessments. However, the responsibility for conducting these assessments lies with the monitoring service provider and the ophthalmologist or lead service clinician [181]. According to the RCOphth, monitoring will likely be conducted in dedicated virtual clinics, where specialized retinal imaging is performed by trained staff [182].

In summary, based upon the available evidence and in keeping with current RCOphth guidance, baseline retinal monitoring is no longer recommended. Annual formal retinal monitoring should occur after 5 years of HCQ use and after 1 year for those deemed high risk (doses >5 mg/kg actual body weight, eGFR <60 ml/min/1.73 m^2 or concurrent tamoxifen usage). This guideline does not comment on the use and monitoring of chloroquine, though we note that this is deemed higher risk and for annual retinal monitoring after 1 year of use by the RCOphth 2020 guidance [182].

***Recommendation 13c*: Information about duration of treatment with hydroxychloroquine must be shared when transitioning between services (GRADE 1C, SoA 100%).**

We appreciate the importance of upholding excellent standards of care during the transition between services including from paediatric to adult rheumatology services. Consistent with EULAR/PReS recommendations for transitional care, we advise a detailed and robust transfer document must be completed [24] and where relevant, information of HCQ use must be included (dates of use, duration, doses prescribed, efficacy and complications). This is to ensure that retinal monitoring takes place at appropriate intervals and to avoid undue complications in a vulnerable population. There was limited evidence surrounding the risk of HCQ retinopathy in the paediatric population and, as such, our guidance is drawn from adult studies.

***Recommendation 14:* For patients on tacrolimus and ciclosporin, monitoring of electrolytes should include periodic monitoring of magnesium (GRADE 1B, SoA 98%).**

Calcineurin inhibitors can cause electrolyte derangements, particularly hyperkalaemia and hypomagnesemia. Whilst the evidence linking TAC and CSA with electrolyte derangements primarily derives from renal and allogeneic hematopoietic stem cell transplant patients [183–185], their use in SARDs still warrants regular electrolyte monitoring. Electrolytes should be measured at initiation and at regular intervals, with specific frequencies recommended in the monitoring schedule below. Certain patients may warrant more frequent monitoring; for instance, those co-prescribed medications such as proton pump inhibitors (known to cause hypomagnesemia) [186] and potassium-sparing diuretics [187].

Therapeutic drug monitoring (TDM)

CSA and TAC require regular TDM due to their narrow therapeutic windows and potential for serious adverse effects. This is not listed as a recommendation within this guideline as it is implicit in the prescribing of these medications. Trough levels should be measured immediately prior to the next scheduled dose, typically 12 h after the previous dose in twice-daily regimens. Target trough concentrations vary depending on indication, time since treatment initiation and comorbidities, but are generally in the range of 100–200 ng/ml for ciclosporin and 4–10 ng/ml for tacrolimus [188, 189].

Voclosporin has less intra- and inter-patient pharmacokinetic variability compared with traditional CNIs. Based on clinical trial data and regulatory guidance, routine TDM is not required for voclosporin and dosing is typically fixed, though caution is advised in the presence of renal or hepatic impairment or significant drug–drug interactions.

TDM for both HCQ and MMF is available in some specialist centres. While this guideline does not routinely recommend TDM for these agents, it may be a helpful adjunct in settings where it is accessible, particularly to support dose optimization, assess adherence and guide management in patients with an inadequate treatment response. This approach may be especially valuable in the paediatric population, where pharmacokinetics can be more variable. This is also considered in international SLE guidelines as a means to optimize treatment in centres where testing is available [173, 190].

Comorbidity recommendations

Recommendation 15	Lung disease: Routine screening for lung disease is not recommended before initiating csDMARD therapy. Screening for lung disease should be considered based on the specific diagnosis, presenting symptoms or findings from clinical examination (GRADE 1B, SoA 99%).
Recommendation 16	Liver disease: Patients with established liver fibrosis or cirrhosis should generally not be prescribed hepatotoxic csDMARDs (GRADE 1B, SoA 97%).
Recommendation 17	Renal disease: csDMARDs that are renally excreted must be used with caution in CKD ≥3 with consideration for dose reduction and increased frequency of monitoring. For the paediatric age group, it is recommended to seek advice from a paediatric pharmacist and/or a paediatric nephrologist (GRADE 1B, SoA 99%).
Recommendation 18	Cardiovascular disease and malignancy: Cardiovascular disease and prior malignancy are not considered contraindications to csDMARD therapy (GRADE 1B, SoA 99%).
Recommendation 19	Perioperative period: csDMARD should not be routinely stopped in the perioperative period. Individualized decisions should be made for high-risk procedures and/or patients at high risk (GRADE 1B, SoA 99%).
Recommendation 20	Intercurrent infection: During a severe infection (e.g. requiring intravenous therapy or hospitalization) csDMARDs should be temporarily discontinued until the patient has recovered from the infection (GRADE 1B, SoA 98%).

Evidence supporting recommendations

Multimorbidity is common in contemporary clinical practice, affecting ∼30% of the general population [191, 192]. In SARD, multimorbidity is increasingly prevalent; for example, the average patient with RA has 1.6 comorbid conditions, which increases with disease duration and disease activity [193]. Some comorbidities are more prevalent due to complications of the underlying disease (e.g. renal disease in SLE) or shared risk factors (e.g. smoking). It is beyond the scope of this guideline to review all comorbidities. Close collaboration between different medical specialities is essential for providing holistic care. Attention will be paid to the most prevalent comorbidities that have relevance to csDMARD prescribing.

***Recommendation 15*: Lung disease: Routine screening for lung disease is not recommended before initiating csDMARD therapy. Screening for lung disease should be considered based on the specific diagnosis, presenting symptoms or findings from clinical examination (GRADE 1B, SoA 99%).**

Respiratory conditions are disproportionately prevalent in patients with SARD. Data from the British Society for Rheumatology Biologics Register in RA confirmed the high prevalence of comorbidity particularly relevant to the UK, including asthma (10%) and COPD (5%) [194]. The elevated rates of COPD among individuals with SARD, particularly RA, are likely attributable to smoking, a shared and significant risk factor for both conditions. Some respiratory diseases, such as interstitial lung disease (ILD), may arise directly from the underlying SARD pathology. ILD associated with RA (RA-ILD) has an estimated prevalence of 10–30%. The risk of ILD is even higher with certain connective tissue diseases. For example, ∼65% of patients with systemic sclerosis, 80% of those with diffuse cutaneous systemic sclerosis, and 36–45% of patients with idiopathic inflammatory myopathy develop ILD. In antisynthetase syndrome, ILD prevalence may reach as high as 80% [195].

When initiating csDMARD therapy, it is important to consider underlying lung conditions as several csDMARDs have been linked to acute pneumonitis. In patients with reduced respiratory reserve, a sudden deterioration in respiratory function can have severe consequences, and evaluation for chronic lung disease prior to initiation of csDMARD therapy may be indicated.

All patients should have a thorough respiratory assessment, including detailed history of relevant symptoms and

respiratory examination. In patients with a clinical suspicion of parenchymal lung disease, formal lung function testing and appropriate imaging – such as chest radiograph and high-resolution computer tomography (HR-CT) scan – should be conducted, with referral to a respiratory specialist if indicated. Patients who currently smoke should be offered access to smoking cessation services. Screening for lung disease is guided by the underlying rheumatological diagnosis, presenting symptoms and findings from the clinical examination. The scope of screening should be tailored to the patient's clinical presentation and risk factors for lung disease, such as the presence of autoimmune conditions or a history of smoking, rather than being determined solely by the choice of csDMARD therapy.

Historically, there has been concern regarding MTX and its risk of pulmonary toxicity, with established lung disease once considered an absolute contraindication to its use. However, this stance was largely based on low-quality data from observational studies and case reports. More recent robust evidence suggests that the historic estimates of MTX-induced lung disease may have been overestimated, potentially due to channelling bias [196]. Two meta-analyses of RCT data from RA and psoriatic arthritis (PsA), published almost a decade ago, cast doubt upon the relationship between MTX use and respiratory morbidity [197, 198]. Since then, accumulating evidence has emerged to refute the association between MTX and the risk of *de novo* or worsening ILD, including results from a large randomized-controlled trial, the Cardiovascular Inflammation Reduction Trial (CIRT), which demonstrated that pulmonary adverse events, including pneumonitis were uncommon [122, 199].

Inception data from the Early RA Study (ERAS) and the Early RA Network (ERAN) demonstrated that MTX treatment was not associated with an elevated risk of RA-ILD and might even delay its onset [200]. Similarly, data from the French RA-ILD Network comparing RA patients with and without ILD revealed a lower frequency of MTX ever-use in RA-ILD patients compared with those without ILD, and in patients with RA-ILD, ILD detection occurred significantly later in MTX ever-users compared with never-users [201], suggesting a potential protective effect of MTX against the development or progression of ILD. A comprehensive systematic review and meta-analysis, encompassing 486 465 patients with RA with 3928 incident ILD outcomes, found no increased risk of incident RA-ILD for any specific csDMARD [202]. A potentially protective effect noted with MTX, with data from seven observational studies indicating that its use was associated with lower odds of developing incident ILD compared with other csDMARDs. For LEF and SSZ, no differences in the odds of developing ILD were observed between patients receiving these medications and those not receiving them.

Similar findings have been noted in a paediatric cohort. A small retrospective study involving 68 patients with JIA assessed the long-term effects of MTX on pulmonary function. The study found no correlation between lung function testing results and cumulative MTX dose or JIA subtype. Moreover, none of the patients developed clinically significant lung disease [203]. These findings have been mirrored by a recent study involving 14 patients with JIA: no relationship between MTX duration or cumulative dose and lung function test results was observed [204]. Although larger and more robust studies are needed in this population, these findings, along with evidence from adult patients with inflammatory arthritis, provide reassuring support for the respiratory safety of MTX in children.

The consensus from the GWG is that, based upon the existing evidence, the presence of a pre-existing lung condition alone should not be considered an absolute contraindication to the treatment with any csDMARD. However, careful attention must be given to assessing baseline respiratory health, and a thorough clinical assessment is essential, including a detailed history, physical examination and lung function testing, if indicated. Clinical assessment and lung function testing are more effective than chest radiographs in identifying patients with poor respiratory reserve in whom a significant decline in lung function could be life-threatening. In cases of poor respiratory reserve, this information will inform csDMARD selection and necessitate closer monitoring for acute pulmonary toxicity. Ultimately, treatment decisions should be made on an individual basis, weighing the available evidence and considering the risks and benefits for each patient.

Recommendation 16: **Liver Disease: Patients with established liver fibrosis or cirrhosis should generally not be prescribed hepatotoxic csDMARDs (GRADE 1B, SoA 97%).**

The increasing burden of liver disease is primarily driven by the three most common causes: alcoholic liver disease, MASLD and viral hepatitis. Fibrosis and cirrhosis often develop silently, with no noticeable signs or symptoms until advanced stages. In liver fibrosis, the organ's normal architecture is disrupted by excessive collagen deposition, which impairs its function. If left untreated, fibrosis can progress to cirrhosis, resulting in severe liver dysfunction, liver failure or complications such as portal hypertension.

There are no studies directly comparing the initiation or withholding of csDMARDs in individuals with ALT abnormalities. In patients with liver biochemical abnormalities without evidence of cirrhosis (that is, normal liver synthetic function), it is important to establish the underlying cause prior to commencing csDMARDs. If liver biochemistry does not normalize or an underlying cause is not identified, discussing csDMARD initiation with a gastroenterologist or hepatologist (including drug choice, lower starting dose and monitoring frequency) should be considered. Liver biochemical abnormalities are not an absolute contraindication to any csDMARD therapy, but preference should be given to a less hepatotoxic csDMARD (e.g. SSZ), and more cautious monitoring is advisable. If csDMARDs are used in patients with elevated liver enzymes, then particular attention to deteriorating trends in results is recommended.

Patients with established liver fibrosis or cirrhosis should generally not be prescribed hepatotoxic csDMARDs. In such individuals, the impaired metabolism of csDMARDs increases the risk of drug accumulation and toxicity [205–208]. Most csDMARDs undergo some degree of hepatic metabolism or bile conjugation and clearance. Manufacturer SmPCs consistently advise against using these drugs in patients with significant liver synthetic dysfunction. In contrast, MMF clearance appears to be largely preserved in patients with cirrhosis, although individual variations may occur depending on the specific type and severity of disease [209]. In certain case-by-case scenarios, clinicians and patients may decide that the potential benefits of treatment outweigh the risks, even in the context of cirrhosis. While current evidence does not support this practice, it is advisable to apply extreme caution, with careful consideration of

reductions in both dosage and frequency of administration. Further research is needed to directly compare the risks and benefits of initiating csDMARDs in patients with pre-existing liver abnormalities, as this would provide clearer guidance for managing these high-risk patients.

Recommendation 17: **Renal disease: csDMARDs that are renally excreted must be used with caution in CKD ≥3 with consideration for dose reduction and increased frequency of monitoring. For the paediatric age group, it is recommended to seek advice from a paediatric pharmacist and/or a paediatric nephrologist (GRADE 1B, SoA 99%).**

Chronic kidney disease (CKD) is an important comorbidity to consider when prescribing csDMARDs. In the UK, renal function is commonly reported using the estimated glomerular filtration rate (eGFR), calculated with the CKD-EPI formula, which incorporates serum creatinine, age and sex, with values standardized to a body surface area of 1.73 m^2. The calculation is now performed without race-based adjustments. NICE guidance stipulates that an eGFR of <60 ml/min/1.73 m^2 on at least two separate occasions, at least 90 days apart, is one of the measures that is diagnostic for CKD [210].

The 2022 Health Survey for England showed that amongst individuals aged 35 and over, 10% of men and 13% of women had stage 3–5 CKD [211]. The survey also demonstrated that the prevalence of CKD increases with age; 1% of adults aged 35–44 had stage 3–5 disease, compared with 36% of adults aged 75 and over. These findings are consistent with previous data demonstrating a relationship between older age and worsening renal function [212]. Nevertheless, given the reduced muscle mass associated with older age, the serum creatinine levels of elderly patients may lie within the normal range, despite underlying renal impairment. Therefore, it is prudent to assume at least mild renal impairment when prescribing csDMARDs in elderly patients.

There are numerous reasons why caution should be exercised when prescribing csDMARDs for patients with reduced renal function. Some csDMARDs may be directly nephrotoxic, exacerbating pre-existing renal impairment, whilst some are renally excreted (e.g. MTX, APL), risking accumulation and drug toxicity. Any established or newly identified renal dysfunction at baseline assessment should firstly be investigated to elucidate any underlying cause(s) and managed appropriately, as per NICE guidelines [213]. csDMARDs adjustments such as dose reduction (Table 2) or selecting alternative csDMARD strategies may be required to mitigate the risks associated with renal impairment. Where feasible, nephrotoxic csDMARDs should be avoided in patients with renal disease, given the risk of worsening pre-existing renal impairment. For csDMARDs where drug efficacy and toxicity are closely tied to plasma drug concentration, recommended dosing regimens can guide initial treatment, but subsequent doses should be amended based on therapeutic response and ideally plasma-drug concentrations.

Aside from changing dosing and the choice of csDMARD in renal impairment, more frequent routine monitoring is likely to be indicated, given the elevated risk of csDMARD toxicity. Notably, there is a paucity of evidence to guide tailored monitoring recommendations for specific drugs, therefore clinical discretion is advised. Further generic guidance about monitoring in patients with CKD stage ≥3 is discussed in the 'monitoring' section of this guideline.

Recommendation 18: **Cardiovascular disease and malignancy: Cardiovascular disease and prior malignancy are not considered contraindications to csDMARD therapy (GRADE 1B, SoA 99%).**

Cardiovascular disease is the leading contributor to the heightened prevalence of multimorbidity in individuals with RA and accounts for over 50% of premature deaths in this population [214, 215]. A large cross-sectional multinational study in individuals with RA reported a 6% prevalence of ischaemic cardiovascular disease, including stroke and myocardial infarction [39]. Ischaemic cardiovascular disease is not a specific contraindication to any of the csDMARDs included in this guideline. Evidence from two separate meta-analyses suggests that MTX use is associated with a reduced risk of cardiovascular events in patients with RA and PsA [216]. Additionally, prolonged use of other csDMARDs such as HCQ, LEF and SSZ has been linked to a reduced risk of cardiovascular morbidity in RA patients [217]. Numerous studies have also demonstrated a direct relationship between the severity of disease activity in rheumatic diseases and excess cardiovascular risk. Therefore, effective control of the rheumatic disease should be prioritized as a key component of cardiovascular risk management, as recommended in EULAR guidance [218]. Assessment of cardiovascular risk should remain integral to the overall management of patients with RA in particular, as detailed in the NICE quality statement for annual review [219].

MTX has even been evaluated for its potential role in preventing cardiovascular disease. The Cardiovascular Inflammation Reduction Trial (CIRT) specifically recruited individuals without SARD but with established cardiovascular disease and metabolic risk factors. Although the trial was halted due to a lack of efficacy in reducing cardiovascular events, no significant cardiovascular safety concerns related to MTX were identified [220].

Cardiovascular comorbidities have come under scrutiny in recent years in the wake of the use of JAK inhibitors. The post-authorization randomized open-label trial, ORAL surveillance, raised concerns about an increased risk of major adverse cardiovascular events (MACE) in patients taking JAK inhibitors, specifically tofacitinib in this trial. While beyond the scope of this guideline, it is worth noting these findings in the broader context of tailoring treatment to minimize overall risk [221].

Patients with SARD have an increased incidence of malignancy. For example, individuals with RA are at particularly higher risk for lung cancer and lymphoma compared with the general population [222]. While prolonged immunosuppression, such as that used following organ transplantation, substantially increases susceptibility to neoplastic disorders, particularly skin cancers [223, 224], the increased malignancy risk in SARD is more likely attributable to the underlying chronic inflammation and the disease itself rather than the use of disease-modifying therapies. There is evidence from studies conducted in transplant recipients as well as gastroenterology patients that there may be an association between long-term (5–10 years) use of MMF and/or AZA and the onset of malignancy, but this remains uncertain [225–228].

Based on the currently available evidence, prior malignancy is not considered a contraindication to treatment with any csDMARD. In cases where a csDMARD is implicated in a malignancy (e.g. MTX-induced lymphoproliferative disease), that particular csDMARD should not be used again. In patients with previous skin cancer, it may be appropriate to

Table 2. Recommended dose adjustment for csDMARDs in patients with chronic kidney disease at drug initiation

Drug	Summary of product characteristics (SmPC)			The Renal Drug Database		
	Chronic kidney disease stage (eGFR in ml/min)			eGFR range (ml/min)		
	III (30–59)	IV (15–29)	V (<15)	30–50	10–30	<10
APL	Normal dose	Reduce dose 30 mg OD (note change to initial dose titration – refer to SmPC)		Normal dose	Reduce dose 30 mg OD	
AZA[a]	Reduce dose to lower end of normal range[a]			For eGFR 20–50 dose as normal	For eGFR 10–20 use 75–100% of normal dose	50–100% of normal dose
CSA	Additional precaution advised in patients with impaired renal function at baseline. Dose reduction is required if eGFR declines on treatment.			Normal dose		
HCQ[b]	Not reported in SmPC			Normal dose		Maximum dose 200 mg daily
LEF[c]	Normal dose	Contraindicated[c]		Normal dose	Use with caution if eGFR <20	
Mepacrine	No SmPC Found			Normal dose		
MTX[d]	50% of normal dose	Contraindicated[d]		50% of normal dose (refer to RDD for full details)		Contraindicated
MCN	Use with caution. Dose reduction may be required.	Contraindicated		Normal dose		
MMF[e]	Normal dose	GFR <25 ml/min/1.73 m^2 maximum dose 1 g bd		Normal dose for eGFR 26–50	Maximum dose is 1 g bd for eGFR ≤25	
SSZ	For patients with baseline renal impairment, treatment should only be initiated if the benefits are considered to outweigh risk			Normal dose (use with caution)		Start at very low dose and monitor (use with caution)
TAC	No adjustment to initial dose required – monitor renal function carefully			Normal dose		
Voclosporin	Normal dose	Use with caution, starting dose 15.8 mg bd (67% of standard dose)		For eGFR 30–45. Dose as in normal renal function, if benefit outweighs risk.	For eGFR <30 ml/min avoid if possible. Initial dose 15.8 mg twice daily only starting if benefit outweigh risk	

This table includes information to assist prescribing in patients with chronic kidney disease at the time of csDMARD initiation. Please refer to the summary of product characteristics (SmPC) and Renal Drug Database for full prescribing information. Please consult the SmPC/Renal Drug Database if there is decline in renal function during treatment with csDMARD, as dose adjustments may be required.
Whilst SmPC and Renal Drug Database typically refer to GFR, in this guideline we refer to eGFR as we do not expect clinicians to directly measure creatinine clearance.
SmPC available at www.medicines.org.uk (accessed 21 January 2025).
The Renal Drug Database available at https://www.renaldrugdatabase.com/second/ (subscription required; accessed 7 July 2025).

[a] For AZA the SmPC states that haematological response should be carefully monitored, and doses should be further reduced if haematological toxicity occurs.
[b] For HCQ CKD eGFR <60 ml/min is a risk factor for HCQ retinopathy and requires earlier referral for retinopathy screening. For children with eGFR of <10 ml/min/1.73 m^2, discuss with paediatric renal specialist and consider reducing to 50% of normal dose.
[c] For LEF the SmPC states a contraindication in patients with moderate to severe renal insufficiency due to insufficient clinical experience in this patient group.
[d] For MTX the Renal Drug Database suggests a reduced dose for eGFR 10–30; however, the SmPC states that this is contraindicated and so prescribing should usually be avoided in this group.
[e] For children starting MMF with eGFR of <25 ml/min/1.73 m^2, discuss with paediatric renal specialist and consider reducing to 60% of normal dose.

involve a dermatologist in the ongoing management, including consideration for regular formal skin screening. Management and decision-making should be tailored to the needs of each patient. The incidence of *de novo* malignancy in patients taking csDMARDs for SARDs does not indicate a change to the current recommendations for cancer surveillance in the general population. Health professionals should ensure that patients are aware of existing national screening programmes for breast cancer, cervical cancer, bowel, prostate and lung cancer.

Recommendation 19: **Perioperative period: csDMARDs should not be routinely stopped in the perioperative period. Individualized decisions should be made for high-risk procedures and/or patients at high risk (GRADE 1B, SoA 99%).**

Surgical procedures are an important consideration for individuals with SARD, particularly those with joint involvement who may require orthopaedic interventions. Managing csDMARD therapy during the perioperative period is important as it directly impacts on surgical outcomes. Postoperative flares occur in ∼10–20% of patients with RA undergoing surgery, which can negatively affect recovery [229, 230], whilst active RA is associated with an elevated risk of infection, which is undesirable in the postoperative period.

Three RCTs in RA patients have demonstrated that continuing csDMARD therapy during the perioperative period does not significantly increase the risk of postoperative complications. In RA patients undergoing elective orthopaedic surgery, those randomized to continue MTX had a complication rate of only 2%, compared with 15% in those who interrupted therapy around the time of surgery [231]. This finding was further supported by another trial in RA patients undergoing surgical procedures, which found no significant difference in postoperative infections between patients who continued MTX and those who discontinued it [232]. One RCT examined the effects of interrupting LEF treatment around the time of surgery in RA patients undergoing joint replacement. This study found no significant difference in infection rates between those who continued treatment perioperatively and those who temporarily discontinued [233].

Several observational studies have also investigated perioperative csDMARD use in RA patients, comparing the rates of infection with patients not prescribed csDMARDs or not collecting pharmacy prescriptions of csDMARDs [234–236]. In these studies, continued MTX therapy was not associated with an increased risk of infection. Collectively, these studies support the continuation of MTX in the perioperative setting, particularly for patients with severe rheumatic disease, where the risk of a disease flare is considerable.

Evidence regarding the perioperative use of other csDMARDs, such as HCQ, AZA and SSZ, is limited but generally supports their continuation. Retrospective studies of patients undergoing joint surgeries found no significant association between the use of these csDMARDs and perioperative infection rates, suggesting that these agents are safe to continue in most cases [237]. Data on MMF and calcineurin inhibitors are lacking, although individuals receiving these medications in the post-transplant setting routinely continue them during the perioperative period. It is important to monitor tacrolimus plasma levels and renal function closely during this time, as perioperative factors can influence drug concentrations.

Based on this evidence, the consensus from the GWG is that csDMARDs should not be routinely stopped in the perioperative period. However, individualized decisions should be made for high-risk surgical procedures. This recommendation aligns with other national and international guidance [238, 239]. It is important to recognize that much of the available evidence regarding the perioperative management of csDMARDs is derived from historical studies with small sample sizes, retrospective designs and a lack of robust control groups, limiting the generalizability of their findings.

For surgical settings with a high risk of infection, decisions regarding csDMARD therapy should be tailored to the patient and surgical context. In such cases, temporary interruption of csDMARDs may be appropriate, with therapy stopped approximately two weeks before surgery and restarted once satisfactory wound healing is achieved. High-risk procedures include class 3 or 4 surgeries (e.g. contaminated or dirty procedures) and longer surgeries, typically exceeding 60 min in duration. Patient-specific factors such as advanced age and comorbidities that increase the risk of surgical site infections should be carefully considered on an individualized basis [240]. Additionally, temporary interruption of renally-excreted csDMARDs could be considered in patients with CKD at risk of decline in renal function in the perioperative period.

***Recommendation 20*: Intercurrent infection: During a severe infection (e.g. requiring intravenous therapy or hospitalization), csDMARDs should be temporarily discontinued until the patient has recovered from the infection (GRADE 1B, SoA 98%).**

Individuals with SARDs have an increased susceptibility to infections. This relationship is particularly well-documented in RA. An inception cohort of 609 RA patients reported a 70% higher rate of overall infections and an 85% increase in serious infections requiring hospitalization compared with age- and sex-matched controls [241].

This heightened infection risk arises from both the underlying disease and its treatment. In RA and SLE, high disease activity associates with an increased risk of infection [242]. A prospective analysis of 6242 RA patients on stable therapy found that each 0.6-unit increase in DAS28 score correlated with a 4% higher rate of outpatient infections and a 25% increased risk of infections requiring hospitalization [243]. Other well-established risk factors include older age, smoking, comorbidities and corticosteroid use [244, 245]. The heightened infection susceptibility linked to corticosteroids has been observed across SARDs and non-rheumatic conditions, with a clear dose-dependent effect [246–248].

The infection risk associated with csDMARDs, particularly MTX, remains uncertain, with conflicting evidence. A 2014 meta-analysis of seven trials assessing the efficacy and safety of MTX *vs* placebo in RA reported a higher infection risk with MTX use (49% *vs* 35%; RR = 1.3, 95% CI: 1.0–1.6) [249]. However, a 2018 meta-analysis of 12 RCTs examining infection risk with MTX across multiple SARDs, including RA, PsO, PsA, AS, IBD and SSc, found no significant association between MTX use and overall or serious infections [250]. Notably, a subgroup analysis restricted to RA patients identified an increased risk of overall infections (RR 1.25, 95% CI: 1.01–1.56), suggesting that infection risk with csDMARDs may be SARD-specific.

One of the largest RCTs evaluating csDMARD safety was the CIRT trial [122, 220], which investigated the efficacy of low-dose MTX on cardiovascular risk in individuals without SARDs. The study randomized 2391 patients to receive MTX for up to 5 years [dose range: 15–20 mg weekly, total exposure: 11 150 person-years (PYE)] and 2395 patients to receive placebo (total exposure: 11 220 PYE). In safety analyses, there was no significant difference in the risk of serious infections (2.2 *vs* 2.5 per 100 PYE, $P = 0.56$), while there was a modest increase in the risk of all infections (16.5 *vs* 14.4 per 100 PYE, $P = 0.02$). These findings indicate a small increase in non-serious infections but minimal impact on the risk of severe infections. It remains uncertain whether these results fully translate to populations with SARDs, where the use of csDMARDs could theoretically reduce overall infection risk by controlling disease activity.

Meta-analyses and observational studies have also evaluated the infection risk associated with other csDMARDs in RA. HCQ and SSZ are generally regarded as having the most favourable safety profiles, whereas increased infection risks have been reported with LEF [251, 252]. Most safety data on infection risk of MMF, AZA, CSA and TAC come from studies in patients with SLE, where these drugs have been linked to heighten infection risk [247, 253]. A nested case–control of 3339 patients with SLE found that MMF use was significantly associated with an increased risk of overall infection (adjusted OR 1.90, 95% CI 1.48–2.44), with a clear dose–response relationship [254], whilst a meta-analysis of 32 RCTs involving patients with lupus nephritis reported a significantly lower risk of serious infection with TAC when compared with glucocorticoids, cyclophosphamide, MMF and AZA [248]. HCQ confers a protective effect against infection; in a nationwide cohort study of 33 565 patients with SLE, HCQ users had a reduced risk of infection compared with non-users (HR 0.73, 95% CI: 0.68–0.77) [246].

Intercurrent infections are a well-recognized concern in individuals with SARDs, with both the underlying disease and immunosuppressive therapies contributing to increased susceptibility. These infections can be more severe, necessitating prompt and aggressive treatment. For patients with serious infections (for example, those requiring intravenous antibiotics or hospitalization) it is recommended to temporarily discontinue immunosuppressive drugs including MTX, LEF, SSZ, AZA, APL, MMF, CSA and TAC until the patient has recovered from the infection. In contrast, it is generally appropriate to continue these medications in patients with minor infections, such as uncomplicated urinary tract infections managed with a short course of oral antibiotics.

It is noteworthy that several csDMARDs interact with a range of antibiotics, especially for MTX, CSA and TAC. The risk of toxicity can persist for several weeks to months after csDMARD cessation in some cases (e.g. methotrexate-trimethoprim interaction). MCN and HCQ are considered safe to continue during both minor and severe infections [255–257].

csDMARDs should usually be restarted once the individual has recovered from the infection, considering the indication for the csDMARD and the risk benefit of continued treatment.

Monitoring schedule recommendations

Monitoring schedule induction phase (starting or adding a new csDMARD)

Recommendation 21	Prior to commencing a new csDMARD, patients should be assessed for risk factors for toxicity (GRADE 1C, SoA 100%).
Recommendation 22	In those without risk factors for toxicity FBC, electrolytes, renal function, ALT and/or AST, and serum albumin should be measured at week 2 and then monthly for the first 3–6 months of treatment (GRADE 1C, SoA 96%).
Recommendation 23	For those with risk factors for toxicity, more frequent monitoring is advised (GRADE 1C, SoA 99%).
Recommendation 24	When initiating ciclosporin, tacrolimus or voclosporin, more frequent monitoring is advised – fortnightly until stable dose for 6 weeks and then monthly for 3 months (GRADE 1C, SoA 99%).
Recommendation 25	For any increase in dosing, additional monitoring is recommended at week 2, and then revert to standard monitoring (GRADE 1C, SoA 98%).

Recommended DMARD blood monitoring schedule maintenance phase

Recommendation 26	For those without risk factors for toxicity, measure FBC, renal function, ALT and/or AST, and serum albumin every 3 months. The monitoring interval may be extended following individualized benefit–risk assessment (GRADE 1B, SoA 97%).
Recommendation 27	For those with risk factors for toxicity, these measurements should be taken more frequently, tailored to the individual's level of risk (GRADE 1B, SoA 97%).
Recommendation 28	Risk factors for DMARD toxicity should be reviewed at least annually, adjusting the frequency of monitoring according to the level of risk identified (GRADE 1C, SoA 98%).

Evidence supporting recommendations

These monitoring schedule recommendations refer to the laboratory monitoring of csDMARD use, rather than the broader requirements for clinical monitoring of SARDs. Monitoring disease activity is the responsibility of the supervising rheumatology team and individuals may require additional blood tests at more frequent intervals [258].

The evidence bases for selecting specific csDMARD monitoring schedules is weak, with few studies directly evaluating different approaches. Many trials have reported the incidence of adverse effects associated with individual therapies, providing useful insights to guide monitoring schedule decisions. These monitoring schedule recommendations are informed by csDMARD toxicity data from RCTs, observational studies, regulatory documents (e.g. SmPCs) and expert consensus. As previously recommended in the 2017 guideline, no routine blood monitoring is required for HCQ, MCN, mepacrine or APL.

A notable change in these updated recommendations compared with the 2017 guideline is the relaxation of the previously more frequent monitoring schedule. This adjustment reflects an evolving approach to patient care, balancing safety with practicality. Although no new clinical trials have directly compared csDMARD monitoring strategies, real-world experience during the COVID-19 pandemic provided valuable insights into optimizing monitoring frequency. The pandemic led to a reassessment of protocols, balancing blood monitoring for patient safety with protecting vulnerable individuals, reducing transmission risk in clinical settings, and freeing up capacity for inpatient and high-dependency care [259]. Although these widespread relaxed monitoring practices were undertaken out of necessity, this real-world scenario indicated that less frequent schedules might be possible in certain patients, without significantly increasing adverse outcomes.

The GWG agreed that a risk-adapted approach is essential, tailoring monitoring based on individual risk levels. While a standard monitoring schedule provides a foundation, certain patient characteristics and comorbidities can significantly influence toxicity risk, and when these factors are present, a more frequent monitoring schedule is warranted.

Monitoring schedule induction phase (starting or adding a new csDMARD)

Recommendation 21: **Prior to commencing a new csDMARD, patients should be assessed for risk factors for toxicity (GRADE 1C, SoA 100%).**

There has been considerable research into identifying predictors of drug toxicity, particularly for MTX. While findings remain inconclusive, several factors have emerged as potential risk indicators. The most consistently identified risk factor for MTX toxicity is chronic renal impairment (CKD stage 3 or worse) [117]. Other risk factors comprise increasing age, obesity, alcohol consumption, pre-existing liver disease, significant medical comorbidities, a history of toxicity from csDMARDs, and cytopenia or raised liver enzyme levels in the last 6 months [260–266]. While MTX has the most evidence-based data regarding toxicity risk factors, similar findings have been observed with SSZ and LEF [267, 268]. Studies on LEF have also identified epilepsy and antiepileptic treatments as significant predictors of target organ toxicity [267]. In patients prescribed thiopurines for at least 6 months, CKD-3, cytopenia or elevated liver enzymes during the first few months of treatment were noted to be predictors of liver, kidney or haematological toxicity [269].

There are limited data available on risk factors for toxicity in paediatric populations. A systematic literature review of 20 studies in JIA examined predictors of adverse events in children and young adults, focusing on liver toxicity, as well as gastrointestinal complaints and MTX intolerance. Potential predictors included ALT, thrombocyte levels and single nucleotide polymorphisms (SNPs) in the GGH and MTHFR genes, though these findings lacked validation [270]. The same group developed and internally validated a clinical prediction model for MTX intolerance in a large JIA cohort, incorporating clinical and laboratory factors. The model demonstrated moderate predictive ability. Further research in this area could enhance risk stratification and improve treatment safety and individualized care in this population.

In general, risk factor assessment should include:

- comorbidities (especially diabetes mellitus and chronic kidney disease);
- co-prescriptions of other csDMARDs;
- other medications;
- alcohol intake;
- BMI; and
- blood tests for FBC, renal function, ALT/AST and albumin.

It is important to recognize that the risk factors outlined here should serve as a guiding framework rather than a definitive or exhaustive list. Clinical judgement remains paramount, as individual patient factors, disease severity and treatment goals must be carefully weighed in therapeutic decision-making. A personalized approach, incorporating both clinical experience and emerging evidence, is essential to optimizing patient safety and treatment outcomes. This recommendation is intended to reinforce good practice rather than introduce a shift in routine care.

There is a growing recognition that structured risk calculators or risk stratification tools could improve clinical decision-making surrounding monitoring schedules. Retrospective cohort studies using the UK's Clinical Practice Research Datalink have developed and validated prognostic models to estimate the probability of clinically significant toxicity during long-term treatment with MTX, SSZ and LEF. By leveraging routinely collected clinical data, the models predicted the likelihood of csDMARD discontinuation due to abnormal blood test results from 6 months after first primary care prescription. The authors proposed that these risk scores could help tailor individual monitoring strategies; that is, patients at low risk of toxicity could undergo less frequent monitoring of blood tests, whereas those at high risk of toxicity may undergo more frequent testing [267, 271]. Although calculators that yield risk scores like this are not currently available for use in clinical practice, their development represents a step towards more personalized and efficient patient monitoring, and further research on this area is warranted.

Recommendation 22: **In those without risk factors for toxicity, FBC, electrolytes, renal function, ALT and/or AST, and serum albumin should be measured at week 2 and then monthly for the first 3–6 months of treatment (GRADE 1C, SoA 96%).**

The recommendation for more intensive monitoring during initiation of csDMARD treatment aligns with the 2017 guideline. However, the recommended monitoring frequency during the first 6 months of treatment has been reduced compared with previous guidance. This updated guidance now advises to conduct initial blood tests 2 weeks after starting csDMARD and thereafter monthly for the first 3–6 months of treatment, whereas earlier recommendations suggested testing every 2 weeks for the first 6 weeks, followed by monthly monitoring for 3 months once a stable dose was achieved (Fig. 1 and Table 3).

The GWG extensively debated this issue, weighing the burden of frequent laboratory monitoring against the increased incidence of abnormal test results during the first 6 months of csDMARD therapy. The GWG also agreed that conducting the first blood test two weeks after initiating csDMARD

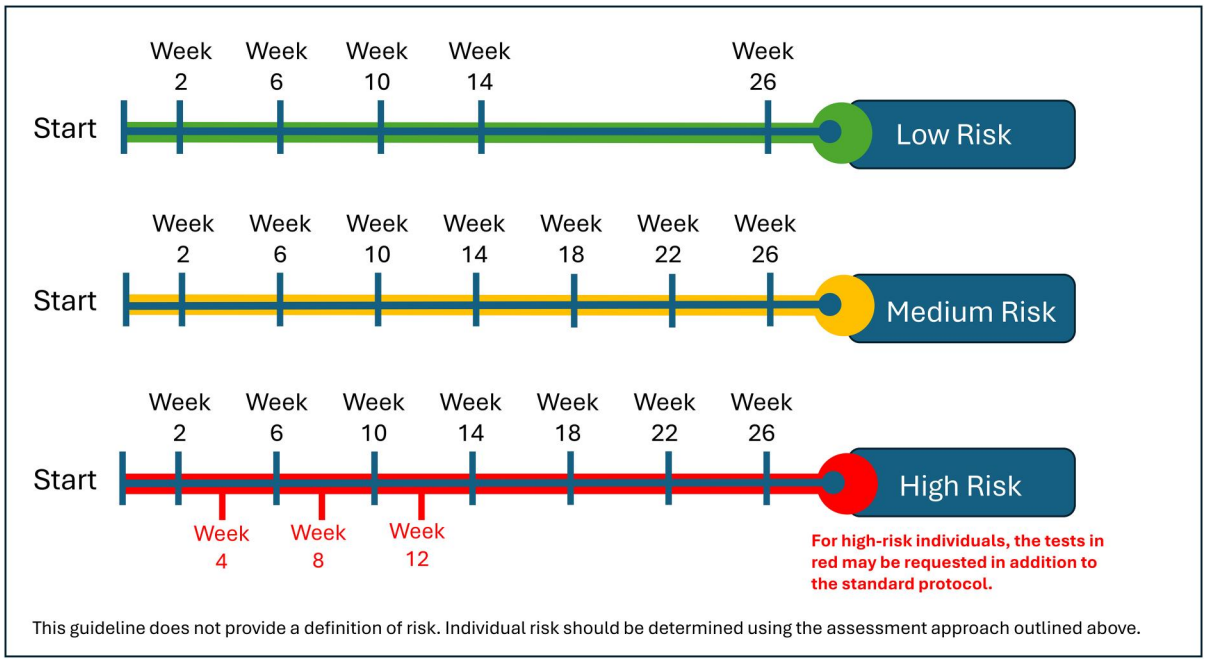

Figure 1. Monitoring schedule induction

Table 3. Monitoring frequency across induction and maintenance in the first year of treatment by risk category

Risk group	Example[a]	Monitoring schedule	No. of tests in 1st year
Low	Patient with normal BMI, no comorbidities, and normal baseline blood tests.	Week 2 Then every month for 3 months Then every 3 months Then every 6 months	6 *weeks: 2, 6, 10, 14* *then: 26* *then: 50*
Medium	Patient with elevated BMI, type 2 diabetes, drinks 10 units of alcohol each week, and normal baseline blood tests.	Week 2 Then every month for 6 months Then every 3 months	9 *weeks: 2, 6, 10, 14, 18, 22* *then: 26, 38, 50*
High	Patient with multiple comorbidities (on medication e.g. anticoagulation for atrial fibrillation or anti-seizure medication for epilepsy), borderline eGFR.	Week 2 Then every 2 weeks for 3 months Then every month	16 *weeks: 2, 4, 6, 8, 10,* *then: 14, 18, 22, 26, 30, 34, 38, 42, 46, 50*

[a] This column provides examples of patients with potential risk factors. The list is not exhaustive, and it is the responsibility of the initiating rheumatology specialist to determine the appropriate risk group.

therapy improves the detection of rare idiosyncratic drug reactions or toxicity, particularly from inadvertent dosing errors, which were most likely to occur at the start of treatment. However, due to logistical challenges and the lower risk in the paediatric population, it was acknowledged that this early test may not always be necessary in this group.

There are undoubtedly differences in the incidence of hepatotoxicity and cytopenia across the csDMARDs. The GWG consensus decision was that it was appropriate to align the monitoring schedule. Despite differences in the wording across individual SmPCs, standardizing recommendations helps reduce confusion and ensure more consistent and effective patient monitoring.

RCT data with serial laboratory monitoring indicate that the early phase of treatment carries a higher risk of laboratory abnormalities. Patients initiating csDMARD therapy have a greater likelihood of liver enzyme elevations compared with those starting biologics or JAK inhibitors. In early anti-TNF trials, AST and ALT elevations were reported in 32% and 44% of MTX users, respectively, compared with 16% and 24% of patients receiving etanercept [272]. The SELECT-EARLY trial of upadacitinib in MTX-naive patients reported AST and ALT elevations greater than three times the upper limit of normal (ULN) in 3.5% and 2.6% of MTX users, compared with 1.6% and 0.6% of those receiving upadacitinib 15 mg [273]. A meta-analysis of 32 studies involving 13 177 participants comparing MTX with other agents in adults with RA, PsA and IBD found an increased risk of elevated transaminases with MTX. The cumulative incidence of minor and major liver enzyme abnormalities was 7.9% and 3.3%, respectively, while the incidence of severe liver outcomes (liver failure, fibrosis, cirrhosis or death) remained 0% [274].

These findings are consistent with observational studies [275–277], which indicate that while laboratory abnormalities are common, they are often transient and rarely require permanent drug discontinuation. A single-centre study of MTX-naive RA patients reported ALT levels above the ULN in 39%, with 6% experiencing elevations >3× ULN. Notably, 30% of patients recorded their first ALT elevation within the first three months of treatment. Despite these abnormalities, only 3% discontinued MTX due to pathological ALT results [206].

The risk of cytopenia following csDMARD initiation has been assessed in the Scottish Early Rheumatoid Arthritis (SERA) inception cohort, a prospective study of patients with newly diagnosed RA. Low neutrophil counts were observed in 8% of those treated with MTX and SSZ, leading to temporary or permanent treatment discontinuation in ∼20% of cases. Overall neutropenic episodes were mild, transient and were not associated with an increased infection risk [278].

A retrospective review of 40 cases of MTX-related myelosuppression in individuals with RA found no early warning signs in routine blood monitoring to the onset of myelotoxicity, suggesting it occurs abruptly and often during intercurrent illness [265]. Myelosuppression may also emerge early as an idiosyncratic reaction to MTX and other csDMARDs. Clinicians and patients should recognize new mouth or throat ulcers as potential warning signs of pancytopenia, with mucositis possibly serving as an early indicator [279]. This highlights the importance of patient education and prompt medical attention for new symptoms.

Paediatric evidence on csDMARD safety and monitoring in SARDs remains limited [280–282]. Haematological abnormalities are rare. Intercurrent infections may cause transient dips in white cell count and/or neutrophils. Transient elevations of liver function enzymes, often with concurrent infections, usually settle without any action [283]. A small percentage of children/young people develop persistent or frequently raised liver function tests. A study from 2009 in children with JIA reported transient LFT elevations that were common but typically resolved within four weeks, with no clear association with NSAID use, age, disease duration or disease activity. Liver enzyme abnormalities exceeding 2× ULN were rare and occurred at similar rates in both MTX-treated and non-MTX groups [130].

***Recommendation 23*: For those with risk factors for toxicity, more frequent monitoring is advised (GRADE 1C, SoA 99%).**

This recommendation acknowledges that certain individuals will require additional vigilance. Risk factors for toxicity include older age, comorbidities (e.g. diabetes, renal impairment), high alcohol consumption, elevated BMI and concurrent use of other hepatotoxic or myelosuppressive drugs. More details on the evidence base regarding risk factors for toxicity have been described above. In high-risk individuals, increased monitoring intervals (e.g. fortnightly until stable dose for 6 weeks or fortnightly for the first 3 months of treatment, and then monthly for 3 months) can provide the safety net needed to detect abnormalities early (Fig. 1 and Table 3).

***Recommendation 24*: When initiating ciclosporin, tacrolimus or voclosporin, more frequent monitoring is advised – fortnightly until stable dose for 6 weeks and then monthly for 3 months (GRADE 1C, SoA 99%).**

In contrast with the previous guideline, a separate monitoring schedule has been adopted for calcineurin inhibitors. Their immunosuppressive profile and narrower therapeutic window necessitate more frequent blood testing in the induction phase to detect early toxicity signals. Given the relative paucity of robust predictors for toxicity with these agents, the guideline adopts a cautious approach, preserving more intensive schedules from previous guidance.

Most long-term safety data on CSA and TAC originate from other therapeutic areas, particularly transplant medicine [284, 285]. However, the risk profile in transplant recipients may not fully apply to SARD patients due to differences in baseline comorbidities, drug dosing and concurrent therapies. Real-world safety data on TAC in patients with lupus nephritis indicate that adverse drug reactions occur primarily within the first 28 weeks of treatment [286]. Long-term safety data on voclosporin remain limited; however, findings from the AURORA 1 trial in lupus nephritis suggest a better safety profile compared with other calcineurin inhibitors, particularly regarding metabolic disturbances and long-term nephrotoxicity [287].

***Recommendation 25*: For any increase in dosing, additional monitoring is recommended at week 2, and then revert to standard monitoring (GRADE 1C, SoA 98%).**

The recommendation for additional monitoring after a dose increase aligns with the recommendation for enhanced monitoring when initiating csDMARD therapy. For example, a patient on MTX 15 mg weekly and on 6 monthly monitoring, is dose increased. A single additional blood test two weeks after the dose change would be indicated, followed by returning to their established monitoring regimen.

This approach improves the detection of idiosyncratic drug reactions and toxicity from inadvertent dosing errors, which may be more likely following a dose escalation. However, due to logistical challenges and the lower risk of toxicity in the paediatric population, it is acknowledged that this additional test may not always be completed in this group.

Recommended csDMARD blood monitoring schedule maintenance phase

***Recommendation 26*: For those without risk factors for toxicity, measure FBC, renal function, ALT and/or AST, and serum albumin every 3 months. The monitoring interval may be extended following individualized benefit–risk assessment (GRADE 1B, SoA 97%).**

Once a patient has completed the induction phase and achieved stability on csDMARD therapy, the monitoring schedule becomes less intensive (Table 3). In patients without risk factors for toxicity, the GWG reached a consensus that monitoring should take place every 3–6 months. The decision between 3-monthly and 6-monthly intervals should be guided by clinical stability, the presence or emergence of comorbidities, and any medications that may affect csDMARD metabolism or clearance. For some patients, it may be appropriate to space monitoring further, but this should never exceed 12 months. This is in line with results of an interview study that recruited 18 patients and 13 clinicians from the UK [288]. Patients should also be advised to seek unscheduled testing if they develop symptoms suggestive of toxicity.

The evidence supporting less frequent monitoring during the maintenance phase of csDMARD therapy comes from

studies which report a low incidence of abnormal blood test results leading to treatment discontinuation in patients on established therapy, particularly beyond the first 12 months. An observational study of 15 670 MTX users and 2689 LEF users under shared-care prescribing with their GP found that discontinuation rates were highest in the first year. During this period, one in 24 MTX users and one in nine LEF users discontinued treatment due to abnormal blood test results, while severely abnormal results led to discontinuation in one in 169 (MTX) and one in 106 (LEF). After the first year, the risk declined, with annual discontinuation rates of one in 45 (MTX) and one in 32 (LEF) for abnormal results, and one in 352 (MTX) and one in 227 (LEF) for severe abnormalities [289]. A similar pattern of increased risk within the first year, with a reduction after 1 year of prescription in primary-care was observed for MMF [290].

The lower incidence of adverse events in prevalent csDMARD users is partly explained by the healthy user phenomenon, where patients who are at higher risk of toxicity from MTX will develop biochemistry abnormalities earlier on during treatment and subsequently be taken off therapy. Patients who remain on treatment by 12 months are in effect self-selected healthy users.

A three-year trial of MTX for cardiovascular event prevention in a population without SARD reported an even lower cumulative incidence of elevated liver enzymes (0.56%) and haematological abnormalities (0.95%). However, this may reflect the absence of concurrent csDMARD therapy and lower NSAID use in this population [122]. The study also included a run-in period prior to randomization, during which participants were initiated on MTX and excluded if they developed laboratory abnormalities or were unable to tolerate the drug, thereby likely reducing the incidence of adverse events reported in the trial.

***Recommendation 27*: For those with risk factors for toxicity, these measurements should be taken more frequently, tailored to the individual's level of risk (GRADE 1B, SoA 97%).**

Patients with risk factors for toxicity require more frequent laboratory monitoring, tailored to their individual risk profile. Identifying and assessing these risk factors is crucial to preventing serious adverse effects. Risk stratification studies have shown that individuals with high-risk profiles benefit from closer surveillance and adjusted monitoring intervals to ensure early detection of potential toxicity.

Certain drug regimens warrant intensified monitoring due to their higher toxicity risk, including MTX-LEF combination therapy and calcineurin inhibitors. The increased rate of liver enzyme abnormalities in patients on combination MTX and LEF have been demonstrated in both RCT and observational data. In RA, a RCT examining the addition of LEF in stable MTX users reported 10% of participants developed ALT elevations >2× upper limit of normal compared with 2.3% on MTX monotherapy [291]. In PsA, a single-centre RCT observed ALT elevations in 31% on combination therapy *vs* 7% on MTX monotherapy [292]. In the US CorEvitas (previously Corrona) database, elevations of >2× ULN occurred in 1–2% of patients on MTX or LEF monotherapy compared with 5% with the combination [293]. These studies demonstrate occurrence of liver enzyme abnormalities beyond the early months of treatment, supporting the recommendation for ongoing monthly monitoring for patients on MTX and LEF combination therapy.

Extending frequent monitoring beyond the initial period helps mitigate cumulative toxicity. In such cases, continuing monthly monitoring beyond the standard initial period may help detect cumulative toxicity before it leads to irreversible damage.

***Recommendation 28*: Risk factors for csDMARD toxicity should be reviewed at least annually, adjusting the frequency of monitoring according to the level of risk identified (GRADE 1C, SoA 98%).**

The GWG consensus highlighted the importance of assessing risk factors for csDMARD toxicity at least annually, to ensure appropriate monitoring and increasing earlier detection of adverse effects, as comorbidities, medication regimens and overall health status may change over time. Regular risk evaluation ensures that monitoring intensity is appropriately adjusted to balance patient safety with the burden of unnecessary testing.

This assessment can be conducted by either specialist rheumatology teams or primary care providers and should include a comprehensive evaluation of co-morbidities, medications, alcohol intake, BMI, kidney function and liver function to tailor monitoring frequency based on individual risk profiles. Shared care agreements should include the need for periodic risk assessment and make clear to primary care prescribers how this information should be used.

In adults with additional risk factors for liver disease, a non-invasive score using the FIB-4 or liver elastography could be used to screen for liver fibrosis. There is no evidence surrounding the frequency of screening for liver fibrosis in individuals receiving MTX who have additional risk factors for liver damage. NICE guidelines on screening in primary care recommend rescreening every 1–3 years in individuals at risk of chronic liver disease. A FIB-4 is recommended followed by liver elastography or referral to hepatology depending on the FIB-4 results [140]. A large population-based study from Sweden, not limited to individuals with SARD on csDMARDs, found that repeat testing within five years enhances the identification of individuals at higher risk of severe liver disease [294]. The consensus from the GWG is to consider rescreening annually in adult patients with risk factors for liver damage receiving treatment with MTX.

This guideline does not provide an exhaustive list of all potential drug toxicities. For instance, LEF has a recognized association with peripheral neuropathy, which is categorized as 'common' in the SmPC. As with any long-term therapy, clinicians should remain vigilant to the possibility that new symptoms may indicate drug-related adverse effects. Any such symptoms should be reviewed in the context of known side-effect profiles.

Summary of monitoring recommendations for DMARD therapy

The monitoring recommendations for individual csDMARDs are summarized in Table 4. As indicated in the 2017 guideline and in accordance with SmPC information, the following csDMARDs have no laboratory monitoring requirements according to existing product information: APL, HCQ, MCN and mepacrine. Routine SSZ monitoring can be discontinued once treatment has been stable for 12 months.

Table 4. Monitoring recommendations for each csDMARD: laboratory and other parameters

Drug	Laboratory monitoring	Other monitoring
APL	No routine laboratory monitoring	None
AZA	Standard monitoring schedule	None
CSA	Extend monthly monitoring longer term	BP and HbA1C at each monitoring visit during initiation and then every 3 months Lipids at baseline and after 1 month Magnesium at baseline and every 6 months
HCQ	No routine laboratory monitoring	Eye assessments (ideally including optical coherence tomography) as per Royal College of Ophthalmologists guidance
LEF	Standard monitoring schedule	BP and weight at each monitoring visit
Mepacrine	No routine laboratory monitoring	None
MTX	Standard monitoring schedule	None
MTX and LEF combined	Extend monthly monitoring longer term	None
Minocycline	No routine laboratory monitoring	None
MMF	Standard monitoring schedule	Must have ×2 negative pregnancy tests in women of childbearing age before starting
SSZ	Standard monitoring schedule for 12 months then no routine monitoring needed	None
TAC	Extend monthly monitoring longer term. Consider reducing to every 2–3 months if disease and treatment are stable	BP and HbA1C at each monitoring visit during initiation and then every 3 months Magnesium at baseline and every 6 months (or more frequently if co-prescribed PPI) ECG at baseline, 3 months and 9–12 months Lipids annually. Measurement of TAC trough levels should be considered at 1 week and 2–3 weeks after initiation and then periodically[a]
Voclosporin	Extended monthly monitoring longer term Consider reducing to every 2–3 months if disease and treatment are stable	BP and HbA1C at each monitoring visit during initiation and then every 3 months

[a] The frequency of drug level monitoring should be determined by risk factors for toxicity and frequency of clinical assessments. Based on data from patients with renal transplants, a trough level of 4–8 ng/ml may be effective without increased risk of toxicity [295].
APL: apremilast; AZA: azathioprine; CSA: ciclosporin; HCQ: hydroxychloroquine; LEF: leflunomide; MMF: mycophenolate; MTX: methotrexate; SSZ: sulfasalazine; TAC: tacrolimus.

Shared care agreements recommendations

Collaboration between primary care and specialist rheumatology providers

Recommendation 29	The management of patients on csDMARD therapy should be a collaborative effort between primary care and specialist rheumatology providers. A shared care protocol should be agreed upon (including in the paediatric age group when shared care exists) delineating the responsibilities of each party (GRADE 1C, SoA 100%).

Communication and documentation

Recommendation 30	Effective communication channels should be established between primary care and specialist rheumatology providers. Documentation of patient progress, including any adverse effects and laboratory monitoring results, should be routinely shared (GRADE 1C, SoA 99%).

Risk assessment

Recommendation 31	Prescribers should assess risk factors for DMARD toxicity at least annually, adjusting the frequency of monitoring according to the level of risk identified. Changes in risk factors should be communicated between primary care and specialist rheumatology providers (GRADE 1C, SoA 98%).

Evidence supporting recommendations

Many patients living with SARD are burdened by multiple comorbidities and require polypharmacy as part of their treatment plan. Therefore, medical professionals responsible for prescribing medicines should adopt a holistic approach, consider the patient's overall clinical context and ensure appropriate monitoring and review based on individual needs. Where csDMARD prescribing takes place in primary care, the following principles should be followed:

***Recommendation 29*: The management of patients on csDMARD therapy should be a collaborative effort between primary care and specialist rheumatology providers. A shared care protocol should be agreed upon (including in the paediatric age group when shared care exists) delineating the responsibilities of each party (GRADE 1C, SoA 100%).**

Different models exist for prescribing csDMARDs in SARDs [296]. These include sole management in secondary/tertiary care; sole management in primary care; and initiation in secondary/tertiary care before maintenance in primary care. Whilst each model has its respective strengths and weaknesses, in most cases, a shared-care model between primary and secondary/tertiary care is optimal. This recommendation is consistent with NICE guidelines, which state that csDMARD initiation (and initial monitoring) should be performed by a specialist in secondary care [297], and subsequent csDMARD prescribing and monitoring can be performed by GPs once a patient is stable on therapy. The advantages of initiating treatment in secondary/tertiary care include improved access to baseline investigations (e.g. laboratory tests and radiological imaging), more specialized clinician knowledge and tailored drug education for patients. Subsequently, once a patient is stable on csDMARD therapy,

transitioning to drug prescribing and monitoring in primary care can offer greater convenience to patients; alleviate pressures on secondary care services; and allow holistic management, taking into consideration important comorbidities such as hypertension, diabetes and hyperlipidaemia [298]. Local shared care arrangements should be determined by ICB commissioning pathways and negotiations between secondary care trusts and primary care providers.

The initiation of shared care in the paediatric population has been limited due to the restricted availability of paediatric phlebotomy services in primary care. Clinical teams should work collaboratively across primary and specialist care to minimize the impact of blood monitoring, especially acknowledging the distance that children may need to travel to access paediatric phlebotomy services. With increasing availability and improved service provision, access to shared care arrangements is expanding, facilitating better integration between primary and specialist care and improving treatment accessibility.

***Recommendation 30*: Effective communication channels should be established between primary care and specialist rheumatology providers. Documentation of patient progress, including any adverse effects and laboratory monitoring results, should be routinely shared (GRADE 1C, SoA 99%).**

Regular and effective communication between both primary and secondary care providers can help to ensure that prescribing responsibilities are clearly defined and monitoring schedules are adhered to. Where possible, a single prescribing record that is reliable, up-to-date and accessible to primary and secondary providers can enhance this communication channel. A common prescribing record is likely to be particularly beneficial when caring for patients with multiple chronic comorbidities and those at risk of drug interactions (e.g. MTX and trimethoprim).

Once a patient is stable on csDMARD therapy and agrees to a shared care plan, their secondary care team can submit a shared care request to the patient's primary care provider. If the primary care team accepts the request, along with the relevant decision form and monitoring schedule, they can assume responsibility for prescribing and monitoring csDMARD therapy. If any adverse events or abnormal findings arise during monitoring, the primary care team should promptly seek advice from the secondary care provider. Ideally, both primary and secondary care providers should have real-time access to key laboratory results to enable proactive discussions and timely management of abnormal results or clinical concerns.

***Recommendation 31*: Prescribers should assess risk factors for csDMARD toxicity at least annually, adjusting the frequency of monitoring according to the level of risk identified. Changes in risk factors should be communicated between primary care and specialist rheumatology providers (GRADE 1C, SoA 98%).**

As discussed in the monitoring schedule recommendations above, the frequency of monitoring should be determined by an individual's risk of csDMARD toxicity, which includes a comprehensive assessment of risk factors. All prescribers, including those in primary and secondary care, should assess changes to a patient's health status (e.g. hospital admission, changes in medication, or new symptoms indicative of toxicity) which may prompt a reassessment of monitoring requirements. Changes to monitoring should be shared between primary and secondary care via the shared care pathway.

MTX is the most commonly prescribed csDMARD and warrants discussion given its association with a significant number of medication-related safety incidents. In 2006, the now defunct National Patient Safety Agency (NPSA) issued a patient safety alert following the identification of 137 patient safety incidents that were associated with the use of oral MTX between 1993–2002. The common causes of harm related to MTX include prescriptions of the wrong frequency of dose, a lack of/poor monitoring, issues with transfer of care (e.g. hospital admission and discharge) and shortcomings in communication with patients [114, 299]. More recent data have shown that between 2006–2020 there were 11 Yellow Card reports of serious toxicity associated with inappropriate daily dosing of once-weekly MTX [114].

A further cause of considerable harm from one-weekly MTX can arise from inadvertent prescribing of 10 mg instead of 2.5 mg tablets [300]. Therefore, national NHS England and Specialist Pharmacy Service shared care protocol stipulates that that only 2.5 mg tablets should be prescribed for adult patients with SARDs [301]. Secondly, as per Medicines and Healthcare products Regulatory Agency recommendations (2020) for safe once-weekly MTX prescribing, it is important that medical professionals consider patients' overall polypharmacy burden and whether patients will be able to adhere to once-weekly dosing of MTX. MHRA recommendations also reiterate the importance of explicitly counselling patients about not taking MTX more frequently than prescribed. Finally, whilst current recommendations focus primarily on oral therapy, MTX also exists as a subcutaneous injection. Given that the instructions associated with each brand of device varies, patients should receive appropriate training and education tailored to the specific device prescribed, and brand changes should be avoided where possible.

Actions on abnormal results recommendations

Blood monitoring during csDMARD therapy aims to identify early signs of potential toxicity, but it is important to recognize that most laboratory abnormalities encountered do not require alteration of treatment. Many minor changes are transient, resolve spontaneously and are often unrelated to the csDMARD itself, arising instead from intercurrent illness, disease activity or other non-drug-related factors. A measured response to abnormal results is essential. Trends over time should be reviewed alongside absolute values, and isolated abnormalities should be interpreted cautiously. Decisions regarding treatment interruption, dose adjustment or additional investigations should be individualized, with discussion with the treating rheumatology team where needed. The following guidance outlines key principles for managing abnormal results and offers a framework for actions (Table 5) as well as considerations in renal disease (Table 2).

In contrast to the 2017 guidelines, MCV has been removed as a result that requires action. This change reflects a shift in emphasis informed by evidence and clinical experience [302]. Previously, elevated MCV was viewed as a potential marker of toxicity, particularly during MTX therapy, due to its association with folate antagonism or early bone marrow

Table 5. Monitoring outcomes: actions required and paediatric considerations

Result	Action	Children and adolescents
Platelet count <LLN	• If significant fall from previous test, interrupt csDMARD and contact rheumatology. • If minor change or just below LLN, assess for alternative causes and repeat after 2 weeks. • If persistent or recurs, discuss with the treating rheumatology team and consider reducing dose.	In addition to action in adults, if significant fall or platelet count $<100 \times 10^9$/L, to look into potential causes and contact paediatric rheumatology.
Neutrophil count <1.6 units	• If significant fall from previous test, interrupt csDMARD and contact rheumatology. • If minor change or just below LLN, assess for alternative causes and repeat after 2 weeks. • If persistent or recurs, discuss with the treating rheumatology team and consider reducing dose.	In addition to action in adults, if significant fall or neutrophil count $<1 \times 10^9$/L, interrupt csDMARD and contact paediatric rheumatology.
Lymphocyte <LLN	• Continue csDMARD. • Consider alternative causes. • Repeat blood test after 4 weeks. • If downward trend continues, contact the treating rheumatology team for advice. • Lymphopenia may not need change in csDMARD.	Same as for adults
Eosinophil count >ULN	• MTX: Stop MTX. Eosinophilia can occur with MTX-associated acute or chronic interstitial pneumonitis. Assess for lung disease and contact rheumatology. • Minocycline or SSZ: Stop csDMARD. Assess for severe allergic reaction including drug hypersensitivity syndrome and contact the treating rheumatology team.	• Mild increase may be seen in children with atopy. • If significant increase, please correlate clinically and contact paediatric rheumatology.
ALT/AST >2× ULN	• If significant rise from previous test, interrupt csDMARD and contact the treating rheumatology team. • If minor change, assess for alternative causes and repeat after 2 weeks. • If persistent or recurs, discuss with the treating rheumatology team . Dose reduction, increased monitoring frequency and/or further investigation may be required.	• If significant increase 3 × ULN, temporarily stop csDMARD for 2 weeks and arrange repeats. • If progressive increase, persistent or recurrent high values (2–3 × ULN), contact paediatric rheumatology.
Serum albumin <LLN	• Assess for alternative causes (e.g. active inflammation, nephrotic syndrome, malnutrition). • If albumin is progressively falling this can be a marker of liver disease which could be drug toxicity related. • If no other explanation, contact the treating rheumatology team rheumatology.	Same as for adults
Declining renal function	• Investigate for a cause of decline in renal function. • Contact the the treating rheumatology team for advice on csDMARD monitoring and dose.	Same as for adults
Changes in MCV	csDMARD can be continued.	Same as for adults

MCV not a predictor of stopping treatment and so has been removed.
LLN: lower limit normal; MTX: methotrexate; SSZ: sulfasalazine; ULN: upper limit normal.

suppression. However, MCV has not been shown to be a reliable standalone predictor of clinically significant haematological toxicity or a clear indicator for treatment discontinuation [303]. It is a non-specific finding, often presents without accompanying cytopenias, and lacks a consistent association with neutropenia or thrombocytopenia, parameters that are more clinically relevant for guiding treatment decisions.

Applicability and utility

This section outlines the relevance of this guideline to clinical practice and the factors that may influence their implementation across different settings. Some of the recommendations within this guideline are based primarily on expert consensus, with limited supporting evidence. This should be considered when assessing their applicability and utility in clinical practice.

Key Principles

- Trends in results are important to review in addition to absolute values.
- Always consider alternative causes for laboratory abnormalities.
- Persistent or recurrent abnormal values or progressively worsening values should prompt individualized decisions on interruption or dose reduction, frequency of monitoring and need for further investigations.
- For patients with vasculitis and CTD, in particular, decline in renal function and/or cytopenia may be due to disease flare.

Clinician responsibility

This guideline provides provide a framework to support clinical decision-making. However, they are not a substitute for professional judgement, which must account for the specific circumstances of each patient. Non-adherence to the recommendations should not automatically be regarded as negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Potential organizational barriers to the guideline

Several recommendations from this updated guideline have important implications for clinical workload and healthcare costs. Effective csDMARD monitoring requires robust systems to ensure not only do patients undergo regular blood tests, but also that results are reviewed and acted upon promptly and appropriately. This guideline adopts a more pragmatic approach to monitoring frequency, reflecting an evolving model of care that seeks to balance patient safety with service sustainability. This relaxation in monitoring intensity may help to reduce the burden on clinical services without compromising quality of care. However, some recommendations could increase the workload associated with initiating treatment. These include screening for hepatitis B, hepatitis C and HIV, screening for latent tuberculosis in at-risk individuals, and the use of FIB-4 scoring (which may only be available in primary care) and liver elastography.

There are uncertainties surrounding access to liver elastography in the UK, particularly in terms of availability and funding structures. While the broader health benefits of early detection and timely treatment of liver disease are well-recognized, there are financial and systemic implications of widespread implementation. Early identification of liver fibrosis would influence further use of MTX and could reduce the burden of advanced liver disease, lowering costs related to hospital admissions, liver transplants or other complications. The GWG acknowledges that potential savings must be weighed against the expense from widespread implementation of elastography, with increased referrals to hepatology specialists presenting challenges in workload and resource allocation, as well as the risks of overdiagnosis and unnecessary interventions.

The applicability and utility of this guideline will depend on how well services are able to integrate these changes into existing pathways. In settings with streamlined electronic systems and well-defined roles for laboratory result review, the reduction in routine monitoring may translate into significant efficiency gains. Conversely, the upfront workload associated with expanded screening may be more challenging in resource-limited environments.

Implementation planning should account for the balance between long-term benefits and short-term resource demands, and commissioners will need to consider how best to support services in delivering high-quality care under these updated recommendations.

Audit tool

We have created an audit tool for csDMARD initiation and monitoring (see Supplementary Data S3).

Research recommendations

The GWG members proposed research recommendations then voted to select the top recommendations. These are as follows:

1) Development of standardized national patient education tool.
2) What is the safety and efficacy of live vaccines in patients treated with csDMARD?
3) What impact do csDMARDs (MTX and others) have on vaccine response, including routine childhood immunisations?
4) What is the effect of pausing csDMARDs other than MTX on vaccine induced immunity?
5) What is the clinical utility of serial FibroScan® monitoring during MTX treatment?
6) What is the effectiveness of HCQ retinopathy monitoring?
7) Should csDMARDs be continued or paused during intercurrent infection?
8) What are the risk factors for drug toxicity during csDMARD initiation and are these the same risk factors for late onset toxicity?
9) Develop risk stratification algorithms/tools for monitoring frequency, which can be incorporated into healthcare records and automated monitoring systems.
10) What is the acceptability of extended monitoring intervals for patients, primary care and rheumatology teams?
11) What is the economic and environmental impact of stratified blood monitoring?
12) What is the clinical utility of a 2-week blood test following csDMARD initiation?
13) What are the primary care perspectives on shared care including implementing risk adjusted monitoring schedules?
14) What are the optimal communication pathways for primary care, rheumatology teams and patients to share information?

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

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