Version 2: Updated 15th April 2020

Azathioprine, leflunomide, mercaptopurine, and methotrexate drug monitoring in primary care during COVID-19

The following advice is for the management of patients taking DMARDs for rheumatology related conditions.

General guidance on management of rheumatology patients during COVID-19 is available from the British Society for Rheumatology.

This page gives advice on drug monitoring in primary care during COVID-19 for the following drugs when used as DMARDs in stable patients (*stable patients are defined as those who have been on current treatment for >12 months and at a stable dose for >6 weeks*):

Azathioprine, Leflunomide, Mercaptopurine, and Methotrexate

For this group of drugs, usual monitoring recommendations are:

- Patients on any one these medicines usually require FBC, CrCl or calculated GFR, ALT and/or AST, and albumin monitored every 3 months
- Additionally, blood pressure and weight to be checked at each monitoring visit for leflunomide
- More frequent monitoring is appropriate in patients at higher risk of toxicity

During the COVID-19 pandemic, recommendations to reduce attendances are:

- Where DMARD use has been successful and stable (*see definition of stable above*) consider extending the monitoring interval to up to every 6 months
- However, extending blood monitoring is **not suitable** if the patient has:
    - poor renal function with CKD ≥ 3
    - severe liver disturbance or abnormal liver results due to DMARDs within previous 3 months
    - severe abnormal WBC results due to DMARDs within previous 3 months

For patients with symptoms of COVID-19, recommendations are:

- Consider stopping medication (see *"Should patients cease their medication as a precaution?"* advice from BSR) and seek specialist advice on when to re-start
- Undertake additional blood tests after self-isolation and within two weeks of re-starting medication
- If results okay—revert to monitoring every 6 months; if abnormal—seek specialist advice
- Refer patients to advice from Versus Arthritis

This page was developed in conjunction with Kalveer Flora, Chair, Rheumatology Pharmacists UK (RPUK); Lead Pharmacist, Specialised Rheumatology CRG for NHS England. We are hugely grateful for her input

Sulfasalazine drug monitoring in primary care during COVID-19

The following advice is for the management of patients taking DMARDs for rheumatology related conditions.

General guidance on management of rheumatology patients during COVID-19 is available from the British Society for Rheumatology.

This page gives advice on drug monitoring in primary care during COVID-19 for sulfasalazine when used as a DMARD in stable patients (*stable patients defined as those who have been on current treatment for >12 months and at a stable dose for >6 weeks)*

For sulphasalazine, the usual monitoring recommendations are:

- After 12 months, no routine monitoring required unless patient is at high risk of toxicity in which case monitoring may be more frequent

During the COVID-19 pandemic, recommendations are:

- No change to the existing monitoring regimen is recommended

For patients with symptoms of COVID-19, recommendations are:

- NICE and the BSR recommend to continue sulfasalazine in patients known or suspected to have COVID-19
- Refer patients to advice from Versus Arthritis

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Hydroxychloroquine drug monitoring in primary care during COVID-19

The following advice is for the management of patients taking DMARDs for rheumatology related conditions.

General guidance on management of rheumatology patients during COVID-19 is available from the British Society for Rheumatology.

This page gives advice on drug monitoring in primary care during COVID-19 for hydroxychloroquine in stable patients (*stable patients defined as those who have been on current treatment for >12 months and at a stable dose for >6 weeks)*

For hydroxychloroquine, usual monitoring recommendations are:

- annual eye assessment (ideally including optical coherence tomography) if continued for ≥5 years (see RCO advice)
- No routine laboratory monitoring is required for hydroxychloroquine

During the COVID-19 pandemic, recommendations are:

- Consider suspending annual eye assessment with ophthalmologist advice

For patients with symptoms of COVID-19, recommendations are:

- NICE and the BSR recommend to continue hydroxychloroquine in patients known or suspected to have COVID-19
- Refer patients to advice from Versus Arthritis

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Ciclosporin drug monitoring in primary care during COVID-19

The following advice is for the management of patients taking DMARDs for rheumatology related conditions.

General guidance on management of rheumatology patients during COVID-19 is available from the British Society for Rheumatology.

This page gives advice on drug monitoring in primary care during COVID-19 for ciclosporin when used as a DMARD in stable patients (*stable patients are defined as those who have been on current treatment for >12 months and at a stable dose for >6 weeks*)

For ciclosporin, the usual monitoring recommendation is:

- 4 weekly monitoring of FBC, calculated GFR, CrCl, ALT and/or AST, albumin, BP and glucose
- Depending on local policy, people who have been stable for 12 months *may* be considered for reduced monitoring frequency on an individual basis
- More frequent monitoring may be appropriate in patients at higher risk of toxicity

During the Covid-19 pandemic, the recommendation to reduce attendances is:

- For those on 4 weekly monitoring, consider extending the monitoring interval to between 6 to 8 weeks with specialist advice
- For those who receive monitoring less frequently, seek specialist advice for extensions to monitoring during the COVID-19 pandemic
- For those who receive monitoring more frequently due to being at higher risk of toxicity, seek specialist advice for extensions to monitoring during the COVID-19 pandemic

For patients with symptoms of COVID-19, recommendations are:

- Consider stopping medication (see *"Should patients cease their medication as a precaution?"* advice from BSR) and seek specialist advice on when to re-start
- Undertake additional blood tests after self-isolation and within two weeks of re-starting medication
- If results okay—revert to monitoring at extended interval; if abnormal—seek specialist advice

- Refer patients to advice from Versus Arthritis

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Penicillamine drug monitoring in primary care during COVID-19

The following advice is for the management of patients taking DMARDs for rheumatology related conditions.

General guidance on management of rheumatology patients during COVID-19 is available from the British Society for Rheumatology.

This page gives advice on drug monitoring in primary care during COVID-19 for penicillamine when used as a DMARD in stable patients (*stable patients are defined as those who have been on current treatment for >12 months and at a stable dose for >6 weeks*)

For penicillamine, the usual monitoring recommendation is:

- 4 weekly monitoring of FBC, CrCl or calculated GFR, ALT and/or AST, albumin, urinalysis (blood and protein)
- Depending on local policy, people who have been stable for 12 months *may* be considered for reduced monitoring frequency (every 3 months) on an individual basis
- More frequent monitoring may be appropriate in patients at higher risk of toxicity

During the COVID-19 pandemic, the recommendation to reduce attendances is:

- For patients not already being monitored on a 3 monthly basis, consider extending the monitoring interval to up to 3 monthly
- For those who receive monitoring more frequently due to being at higher risk of toxicity, seek specialist advice for extensions to monitoring during the COVID-19 pandemic

For patients with symptoms of COVID-19, recommendations are:

- Consider stopping medication (see *"Should patients cease their medication as a precaution?"* advice from BSR) and seek specialist advice on when to re-start
- Undertake additional blood tests after self-isolation and within two weeks of re-starting medication
- If results okay—revert to monitoring at extended interval; if abnormal—seek specialist advice

- Refer patients to advice from Versus Arthritis

This page was developed in conjunction with Kalveer Flora, Chair, Rheumatology Pharmacists UK (RPUK); Lead Pharmacist, Specialised Rheumatology CRG for NHS England. We are hugely grateful for her input

Management of patients currently on warfarin during COVID-19

This page gives advice on management of patients taking warfarin in primary care during the Covid-19 pandemic

Normal practice is to monitor INR up to a maximum of every 12 weeks

During the Covid-19 pandemic, recommendations to help minimise attendances include the following

1) For patients with prior DVT or PE and where risk of recurrence is now low, consider stopping warfarin

2) For other patients, consider switching to a DOAC; however, DO NOT switch if the patient:

- has prosthetic mechanical valve; consult cardiologist
- has moderate to severe mitral stenosis
- has antiphospholipid antibody syndrome (APLS)
- is pregnant, breastfeeding or planning pregnancy
- requires a higher INR than the standard INR range of 2.0–3.0
- has severe renal impairment (creatinine clearance < 15ml/min)
- takes interacting medicines such as certain HIV antiretrovirals or hepatitis antivirals (check HIV drug interactions)

3) If the patient is in a category below, seek specialist anti-coagulation advice prior to switching to a DOAC:

- has active malignancy and/or chemotherapy
- takes phenytoin, carbamazepine, phenobarbitone or rifampicin
- has venous thrombosis at unusual sites
- is on triple therapy i.e. dual antiplatelet plus warfarin

4) Where switching to a DOAC is possible, follow Royal Pharmaceutical Society advice; in addition:

- If a switch to a DOAC is being considered across a patient cohort, take a phased approach over the 12 week cycle to protect the supply chain for all patients
- Consider prioritising patients (i.e. switching first) with poor control of their INR as this cohort will require the most frequent INR checks.

5) Where warfarin remains necessary, a number of options exist to help minimise attendances for INR monitoring

- **Advice on extending INR testing intervals**

As many stable patients as possible should continue to have their INR monitored at no less frequently than every 12 weeks, as this is the international guidance. Self-monitoring and community INR monitoring are options to reduce attendances; however:

- Where patients normally have their INR monitored more frequently than 12 weekly, consider moving to 12 weekly where safe to do so
- Where necessitated to do so by COVID-19 self-isolation following symptoms, consider extending INR monitoring interval from every 12 to every 14 weeks; but see also options below.

- **Self monitoring**

Increasing self-monitoring may help reduce both attendances and INR monitoring workload across the system.

Consider:

- Patients or family members need to be carefully selected for use of CoaguChek, taking into account their manual dexterity, cognitive function, vision and ability to use the technology.
- Patients or family members living with them will need to be taught to self-test their INR using a CoaguChek machine (providing this can be obtained) and to phone in the results.
- There are challenges associated with implementation: e.g. purchasing equipment, providing test strips, training patients, and undertaking quality assurance checks.

Further advice on self-monitoring can be found from NICE in their diagnostic guidance DG14.

- **Community monitoring via teams visiting patients**

Continuation of the safe monitoring of INR for patients in the community when isolated for long periods during COVID-19 is essential.

Home visiting phlebotomy services linked to INR monitoring services (e.g. GP surgeries or Community trusts) will be key to continued safe monitoring of patients on warfarin during COVID-19.

Further guidance can be found in NHS England and NHS Improvement's advice on COVID-19 Prioritisation within Community Health Services (*refer to point 45 of Adult and Older People Services section)*

- **Other options**

For other patients in whom DOACs are not an option, consider a Low Molecular Weight Heparin (LMWH) if the patient can be taught to self-inject or a family member living with them can administer the injection.

As a last resort, for individual patients where INR testing cannot be carried out and therefore warfarin cannot be dosed safely, warfarin therapy could be temporarily stopped. Any decision to stop must take into account the balance of benefit and risk for the individual patient, and should include discussion with both the patient and advice sought from the anticoagulation clinic. Regular review should be undertaken with a view to restarting warfarin as soon as is safely possible.

Note that patients with mechanical valves in situ must continue on warfarin at all times, and cardiologist advice should be sought where regular INR testing cannot be undertaken.

The advice on warfarin was developed in conjunction with Helen Williams, Consultant Pharmacist for Cardiovascular Disease and Clinical Director for Atrial Fibrillation, Southwark CCG and Health Innovation Network, South London.

Lithium drug monitoring during COVID-19 for stable adult patients

General guidance on the management of medicines to treat mental health conditions during COVID-19 is available from the Royal College of Psychiatrists

Normal monitoring recommendations for lithium are:

- thyroid function, renal function and weight check normally every 6 months; or every 3 months in at-risk patients (defined below)
- once stable, serum lithium levels every 3 months for the first year then normally every 6 months thereafter; or continue every 3 months in at-risk patients (defined below)

During the COVID-19 pandemic, recommendations are:

- If patients are not in the at-risk category (defined below) then monitoring intervals can be extended by up to 3 months; however, patients must keep in good physical health and maintain good fluid intake and should resume normal monitoring intervals as soon as possible and safe to do so
- If patients are in the at-risk category (defined below) then their normal monitoring interval should be continued and extension is in most circumstances inappropriate

At-risk patients are defined as:

- Elderly (> 65 years)
- Have received less than 12 months treatment
- Renal impairment (eGFR < 60ml/min)
- Impaired thyroid function at last test
- Raised calcium levels at last test
- Poor symptom control or suspected poor adherence
- Last serum lithium > 0.8mmol/L

- Recent (i.e. since last blood test) introduction or removal of interacting medications (See BNF for exhaustive list. Key interacting medications include, NSAIDs, ACEi, ARB and thiazide diuretics)

For patients with COVID-19 symptoms, recommendations are:

- If patient does not have symptoms of lithium toxicity, continue lithium but take lithium serum level and U&Es
- If patient has symptoms of lithium toxicity WITHOLD lithium, take URGENT lithium serum level and U&Es
- Symptoms of lithium toxicity include: diarrhoea, vomiting, tremor, mental state changes, or falls
- Advise patients to maintain their fluid intake and not to take over-the-counter NSAIDs (e.g. ibuprofen), but to take paracetamol instead.

This page was developed in conjunction with Professor David Taylor, Director of Pharmacy at the Maudsley Hospital; and Peter Pratt, Specialist Mental Health Pharmacy Advisor at NHSEI. We are hugely grateful for their input.

Clozapine drug monitoring during COVID-19 for stable adult patients

General guidance for medicines management of mental health patients during COVID-19 is available from the Royal College of Psychiatrists

Usual care and monitoring can be summarised as:

- An important part of clozapine safety is maintenance of good physical health and awareness of clozapine-related adverse drug events (such as constipation or fever); patients must report potentially serious ADEs urgently to a clinician
- Establish leucocyte and neutrophil levels via one of the central clozapine monitoring systems before making any new supply
- A patient's individual risk of clozapine-induced neutropenia and agranulocytosis determines the frequency of testing; testing intervals are every week, every 2 weeks, or every 4 weeks
- Flexibility exists in testing intervals and quantities that can be dispensed to patients for individual clozapine brands as shown in the tables below

*Table 1: Shows maximum clozapine cover period for **Clozaril®** and **Denzapine®***

Monitoring Frequency	*Sample Due Day*	*Maximum Cover Period*
Weekly	Every 7 Days	10 Days (additional 3 days supply)
Fortnightly	Every 14 Days	21 Days (additional 7 days supply)

Four Weekly	Every 28 Days	42 Days (additional 14 days supply)

*Table 2: Shows maximum clozapine cover period for **Zaponex®***

Monitoring Frequency	*Sample Due Day*	*Maximum Cover Period*
Weekly	Every 7 Days	14 Days (additional 7 days supply)
Fortnightly	Every 14 Days	21 Days (additional 7 days supply)
Four Weekly	Every 28 Days	42 Days (additional 14 days supply)

During the COVID-19 pandemic, recommendations are:

- Normal monitoring of WCC for clozapine-treated patients may be unavoidably disrupted during the pandemic
- Where possible, follow the licensed dispensing and testing interval extensions tabulated above
- Where further extensions are required, these may fall outside the licence. Patients should be risk stratified and monitored as below:
  1. Patients in the first 18 weeks of clozapine use are at the highest risk of neutropenia and agranulocytosis and should continue weekly monitoring within limits tabulated above
  2. Patients in weeks 19 to 52 without a history of low white cell count related to clozapine should be reviewed on an individual basis. Some extension beyond manufactures' limits may be appropriate. Seek advice from the relevant clozapine manufacturer as well as local medical and ethical bodies (which should already exist).
  3. Patients with more than 1 year of use and without a history of low white cell count related to clozapine: consider temporary extension of blood tests from every 4 weeks to up to every 12 weeks.
- Where any extension to clozapine blood testing is made, the relevant manufacturer **must** be made aware; they will note that clozapine is dispensed off licence and may require off licence forms to be completed
- Further advice on the management of clozapine during COVID-19 is available from each manufacturer of clozapine: Clozaril®, Zaponex®, and Denzapine®
- South London and Maudsley Hospital have also produced guidance for use during the COVID-19 pandemic.
  - Clozapine and COVID-19: initiation, continuation and special precautions
  - Clozapine – emergency protocol for patients on monthly monitoring

For patients with COVID-19 symptoms, recommendations are:

- Continue clozapine but take a blood sample immediately to determine WCC; absolute neutrophil count (ANC); and clozapine plasma concentration
- If the patient is suspected of having a serious clozapine-related ADE then stop clozapine and investigate appropriately
- Symptoms of COVID-19 can mimic clozapine related ADEs: notably, myocarditis and neutropenic sepsis; specific considerations include:
    - Myocarditis: clozapine related myocarditis is more likely to occur within the first 6 weeks of treatment. Therefore after the initial period, the likelihood of any myocarditis being clozapine related reduces.
    - White cell count: COVID-19 can cause a reduction in WCC but does not appear to affect neutrophil levels, whilst clozapine does. Therefore if neutrophil levels are stable, continue clozapine. See further advice: Clozapine and blood dyscrasias in patients with coronavirus (COVID-19)

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