High cost drugs pathways for rheumatoid arthritis in adults

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Version 6.0

This supersedes previous version v4.1

Review due 2 years from publication

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DOCUMENT CONTROL

REVISION DATE	ACTIONED BY	SUMMARY OF CHANGES	VERSION
Oct 2016	Meghna Jani, Vanessa Reid & Sarah Jacobs	Version 3 updated with up to date references and guidelines, with the same format as AS/PsA pathway, NICE guidance and biosimilars	3.1
Nov 2016	Meghna Jani	Abbreviated text prior to pathways, addition of TA415, modified content in pathways as per GMMMG working group discussions, updated formatting issues	3.2
Dec 2016	Sarah Jacobs	Checked accuracy of references, comparison to other biologics pathways, formatting	3.3
March 2017	Ben Parker	Additional checking and amendments	3.4
March 2017	Meghna Jani	Final amendments and update references. Added pre-biologic screening section	3.5
June 2017	Meghna Jani, Ben Parker, Vanessa Reid	Changes made post consultation comments	3.6
July 2017	Sarah Jacobs	Final changes post consultation - added free of charge statement, updated special situations sections.	4.0
December 2017	Meghna Jani	Added baricitinib, tofacitinib and sarilumab as per NICE TA466, TA480 & TA485	4.1
May 2020	RDTC, on behalf of working group	Updated to reflect most recent available evidence and full reflect NICE guidance.	5.0
October 2021	Update by current author list	Updates to reflect most recent available evidence and full reflect NICE guidance including the use of HCD for moderate RA	5.1
March – May 2022	Update by current authors & Andrew Martin	Amendments made as a result of consultation comments and feedback on those from authors	5.2 – 5.9
June-October 2022	Update by current authors & Anna Pracz	Further review including alignment with existing HCD pathways. Penultimate review (awaiting BSR guidance publication)	5.10- 5.12
November 2022	Update by current authors	Final review by authors including new BSR guidance for use of HCD in pregnancy	5.13-5.14
December 2022	Anna Pracz	Submission to CRG and inclusion of their comments.	5.15-5.16

Approvals

This document must be approved by the following before distribution:

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GM Rheumatology working group	05.12.2022	5.15
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Distribution

Final version available on GMMMG website **http://gmmmg.nhs.uk/**

Contents

High cost drugs pathways for severe and moderate rheumatoid arthritis in adults

1. Background

The pathway is intended as guidelines for the use of high cost drugs in treatment of rheumatoid arthritis (RA). It has been written using up to date published research and evidence based medicine. This pathway originated as a clinical project implemented by Manchester Academic Health Science Centre (MAHSC), a joint project between rheumatology departments at Salford Royal Hospital, Manchester University Foundation Trust and the University of Manchester, and has since extended to the Greater Manchester hospital trusts.

Currently the pathways include following classes of high cost disease-modifying anti-rheumatic drugs (DMARDs):

- biologic DMARDs (biologic agents, biologicals)
  - tumour necrosis factor (TNF) - alpha inhibitors (anti-TNFs): adalimumab, certolizumab, etanercept, golimumab, infliximab
  - fusion proteins: abatacept (CD80/86:CD28 inhibitor) and rituximab (CD20 inhibitor)
  - interleukin-6 inhibitors: sarilumab and tocilizumab
- targeted synthetic DMARDs (small molecules)
  - Janus kinase inhibitors (JAKi): baricitinib, filgotinib, tofacitinib and upadacitinib.

2. NICE guidance

Biological therapies and Janus kinase inhibitors are indicated when a patient's rheumatoid arthritis is moderate or severe and has an inadequate response to conventional disease-modifying anti-rheumatic drugs (cDMARDs), or these options are contraindicated or not tolerated. [1]

Links to the relevant NICE guidelines and technology appraisals are listed below. The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the same indication. (1)

Any new high cost drugs that receive positive recommendation from NICE between this document iteration are approved for routine withing criteria specified in NICE technology appraisal and will be included in upcoming pathway updates.

NICE All NICE products on arthritis – any guidance, advice and quality standards

NICE NG100 Rheumatoid arthritis in adults: management

Management of moderate rheumatoid arthritis

In addition to treatment of severe rheumatoid arthritis, NICE has more recently approved filgotinib (February 2021), adalimumab, etanercept and infliximab (July 2021), and upadacitinib (November 2021) for use in moderate disease (DAS 3.2 to 5.1) following failure of two or more cDMARDs; for treatment algorithm see flowcharts in sections 13-14.

2.1 Biologic DMARDs

- NICE TA375 (2016): Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
- NICE TA195 (2010): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
- NICE TA415 (2016): Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
- NICE TA225 (2011): Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

[1] In TA130 (October 2007), NICE defined inadequate response to conventional DMARDs, as trial of two drugs including methotrexate (unless contraindicated). A trial of a conventional DMARD was defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

- NICE TA247 (2012): Tocilizumab for the treatment of rheumatoid arthritis
- NICE TA485 (2017): Sarilumab for moderate to severe rheumatoid arthritis
- NICE TA715 (2021): Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed

2.2 Targeted synthetic DMARDs

Janus kinase (JAK) inhibitors are a relatively new class of drug introduced in 2017. They are orally available disease-modifying anti-rheumatic drugs with similar efficacy to biologics. (2; 3)

- NICE TA466 (2017): Baricitinib for moderate to severe rheumatoid arthritis
- NICE TA480 (2017): Tofacitinib for moderate to severe rheumatoid arthritis
- NICE TA665 (2020): Upadacitinib for treating severe rheumatoid arthritis
- NICE TA744 (2021): Upadacitinib for treating moderate rheumatoid arthritis
- NICE TA676 (2021): Filgotinib for treating moderate to severe rheumatoid arthritis

3. Initiating treatment with a high cost drug

All NICE-approved high cost drugs for treatment of rheumatoid arthritis are routinely commissioned if prescribed in accordance with this pathway and used in line with criteria in the relevant NICE technology appraisal. This includes any new high cost drugs that are approved by NICE between pathway revisions.

The choice of treatment should be guided by clinical judgement, national and local guidance, and the overall value proposition offered by the individual medicines. There are numerous factors which may influence the choice of drug at each point in the pathway, including disease presentation, extra-articular manifestations, co-morbidities, dexterity, previous treatment history and adherence, route of administration, frequency, devices available. These factors should be considered in a discussion between the patient and their clinician, including the advantages and disadvantages. The rationale for choice should be documented.

Patients with other concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway.

If more than one treatment is suitable, the best value product should be chosen (taking into account price per dose, dosage and treatment frequency and administration costs and biosimilar availability). At the time of this version publication this was biosimilar adalimumab. See GMMMG (2016): Prescribing of high cost biosimilar biological medicines. Clinicians should also contact pharmacy for advice on the relative cost of these drugs. If the least expensive product is not prescribed, the reasons why must be documented made available to commissioners if requested. Records can be made on Blueteq forms where applicable.

In line with the MHRA guidance (2008): Biosimilar products, biologics including biosimilars must be prescribed by brand name (i.e. the brand of biosimilar or originator product) to support ongoing pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new high cost drug medicine (including biosimilars and newer classes of drugs, e.g. JAK inhibitors) and additional monitoring is indicated through the MHRA's Black Triangle Scheme.

Patients should be enrolled on to the relevant registry which serves data collection on the safety and effectiveness of medicines in clinical practice. See section 11 for more on registries.

Treatment should be reviewed to assess efficacy as per NICE guidance, and thereafter at least every 12 months. For treatment pathways, see flowcharts in sections 13-14.For specific treatment selection criteria see table 2 in section 12 lists available treatments.

4. Biosimilars

Use of biosimilars, including switching from originator to a biosimilar, has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The British Society for Rheumatology (BSR) have published a biosimilar position statement which states:

- When considering switching patients on a biologic originator product to a biosimilar, patients must be provided with sufficient information to make an informed decision, with the support of their rheumatology multidisciplinary team.
- No patients should be switched from one biosimilar to another biosimilar of the same originator product purely based on cost, as there are potential concerns over patient safety and immunogenicity.
- When the specific biologic prescribed is unavailable, the dispensing pharmacist must contact the prescribing clinician to seek advice as to appropriate short-term alternatives. The patient must be always informed about any discussions concerning their medicine.

Furthermore, the GMMMG advised in its statement on biosimilar, regarding changing from originator to a biosimilar (1):

- There is evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

N.B. Inflectra® and Remsima® are different brands of infliximab and are marketed by different companies, but it should be noted that they are the same biosimilar (CPT-13, produced by the same manufacturer, Celltrion).

5. Alternative dosing of high cost drugs (including dose escalation and de-escalation)

Treatment optimisation, including dose escalation, and de-escalation, is licensed for several drugs.

For treatment initiation refer to individual drug's SPC via https://www.medicines.org.uk/.

For some drugs, reduced doses are indicated in the elderly, renal impairment, hepatic impairment and according to blood test results – see section 21 for specific monitoring considerations and summary of product characteristics for adjusted dosing.

Patients with other concomitant inflammatory disorders may benefit from dose escalation, where recommended by manufacturer or supported by other clinical evidence; see other relevant GMMMG High Cost Drugs pathways for more information.

Table 1. Standard and alternative HCD regimens (4)

Drug	Standard maintenance dose	Alternative regimes
Abatacept (IV)	500mg, 750mg, 1000mg as per body weight every 4 weeks	Not specified in the marketing authorisation
Abatacept (SC)	125mg once weekly	Not specified in the marketing authorisation
Adalimumab (SC)	40mg every 2 weeks	40mg every week, or 80mg every 2 weeks, based on adequate response, drug level and/or antibody where appropriate[2]
Certolizumab pegol (SC)	200mg every 2 weeks	400mg every 4 weeks
Etanercept (SC)	50mg once weekly	25mg twice weekly
Infliximab (IV)	3mg/kg every 8 weeks	3mg/kg up to every 4 weeks OR up to 7.5mg/kg (in 1.5mg increments) up to every 8 weeks, drug level and/or antibody where appropriate
Golimumab (SC)	50mg monthly	100mg monthly, in patients >100kg who do not achieve an adequate response after 3-4 months at 50 mg

[2] In monotherapy. (4)

Drug	Standard maintenance dose (4)	Alternative regimes (4)
Rituximab (IV)	Two 1g doses given 2 weeks apart. Further 1g doses may be repeated at minimum 6 monthly intervals	Two 500mg doses given 2 weeks apart OR a single 1g dose. Further doses to be repeated after 6 months
Sarilumab (SC)	200mg every 2 weeks	Not specified in the marketing authorisation
Tocilizumab (IV)	8mg/kg every 4 weeks	Not specified in the marketing authorisation
Tocilizumab (SC)	162mg every week	Not specified in the marketing authorisation
Baricitinib (PO)	4mg once daily	2 mg once daily may be considered once sustained disease control achieved
Filgotinib (PO)	200mg once daily	Not specified in the marketing authorisation
Tofacitinib (PO)	5mg twice daily or 11mg MR once daily	Patients taking 5 mg twice daily may switch to 11 mg once daily modified release
Upadacitnib (PO)	15mg once daily	Not included in the marketing authorisation

IV – intravenous; PO - oral; SC – subcutaneous

In sustained remission, tapering of biologic agents should be considered. (5)

6. Treatment failure with a high cost drug

The available guidance recommends considering changing to an alternative high cost drug if treatment fails due to inefficacy or adverse events. (6) For the purposes of this pathway, this can include failure due to inefficacy:

- Primary failure: rheumatoid arthritis disease activity does not improve adequately to a high cost drug within the timescales defined in the marketing authorisation and NICE technology appraisal (see section 2)
- Secondary failure: rheumatoid arthritis disease activity initially improves adequately within the timescales defined in marketing authorisation and NICE technology appraisal (see section 2), but the patient subsequently loses this response. Although all high cost drugs are highly efficacious in the short term, longer-term attrition is observed. In effect, changes to therapy may be required for longer term disease control for a life-long condition.

There may be other reasons for treatment discontinuation, including:

- Adverse effects resulting in reduced tolerability
- Newly identified drug safety issue during successful treatment resulting in a newly identified relative or absolute contraindication
- Patient becoming pregnant (see section 18.2)

7. Sequential use of high cost drugs

Prior to switching to a subsequent treatment, consideration may be given to dose escalation where there is evidence to support safety and efficacy (see section 5), and when an inadequate primary response may be due to insufficient drug dosing. For example, in obese patients or when disease relapses during the treatment cycle.

Degree of response or lack of response to one high cost drug is not predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class. (7)

High cost drugs for rheumatoid arthritis currently have several different molecular targets (e.g., TNFα, IL-6), or have varying affinity or avidity where the target is the same. Using an agent with a different mechanism of action to the failed therapy may result in regaining disease control.

Choice of subsequent agent should be made following review by a specialist with consideration given to the mechanism of action of previously used drugs, the severity and current level of disease control, the presence of co-existing conditions, as well as the patient's past medical history and with regards to contraindications and precautions to available treatment options. This should be a shared decision with the patient. See section 3 for more details on factors to consider when initiating treatment with a new high cost drug.

In complex cases, it is recommended to seek advice from other professional colleagues, e.g. as a part of multi-disciplinary team discussion. Where available, specialist pharmacist should be involved in decision making.

With each new treatment, patients must meet the criteria laid out in the relevant NICE technology appraisal or otherwise stipulated in this pathway. There is no need for an individual funding request in such circumstances.

Recommendations differ on the need for a washout period when switching from one high cost drug to another. There are very little published data on this topic. The following should be considered when switching: clinical circumstances, drug levels (where appropriate), half-life of the drug (table 3 in section 17), safety (e.g. bridging with steroids) and practical considerations. Considering the above, the next drug could be started when the next dose of the previous drug was due or at least after one-half life of current drug has passed, as clinically appropriate.

Switching to the biosimilar of a successful treatment (e.g. as a part of switching programme) is not considered a sequential high cost drug use.

Repeated pre-high cost drug checks should be considered when switching to a new agent as per clinical judgement, and depending on the duration of previous therapy, the clinical picture of individual patient and relevant risk factors.

8. Data collection requirements

Patient-level information including full clinical details, e.g. disease scores at treatment initiation and assessment for continuation, previous drug history, reasons for change of treatment must be made available to commissioners. This is expected to be via Blueteq or equivalent, where commissioned.

Where available and subject to contractual arrangements Blueteq or equivalent forms which comply with this pathway should be filled in for each new high cost drug at initiation and continuation to secure funding.

Where agreed, data available from Blueteq (or equivalent) system or clinical audit may be used to monitor compliance with NICE and GMMMG pathway and for other purposes (e.g. service development or pathway extension for newly identified cohorts of patients).

9. Individual funding requests (IFR)

Individual funding request will be considered under the GM EUR Operational Policy.pdf (gmeurnhs.co.uk).

Exhausting the treatment options in this pathway does not automatically establish exceptionality.

10. Free of charge schemes

All free of charge schemes must be approved in accordance with trust guidance and the GMMMG Free of Charge guidance. (8) Approval should be agreed at the trust's medicines management committee.

There must be clear exit criteria that do not place financial burden on commissioners and do not raise patients' expectations of continuation of treatment.

11. Research

Where available, enrolment in a suitable registry or observational clinical trial is encouraged so that specific information about these treatments in rheumatoid arthritis can be captured.

Clinicians are strongly encouraged to participate in long-term safety studies or registries such as the British Society of Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA). For more information on the BSRBR-RA visit www.bsrbr.org/. For eligibility see https://bsrbr.org/hospitals/eligibility/. In addition, opportunities for local observational research studies may also be considered.

Some sites host early and later phase clinical trials of novel high cost drugs. Active trials can be found on the NIHR website.

12. Available drugs and factors affecting drug choice

Where multiple treatment options are clinically suitable the best value drug, all factors considered, should be chosen. See section 3 for considerations regarding new drugs initiation.

Note that all bDMARDs and JAK inhibitors may increase infection risk. In some cases, e.g., interstitial lung disease, careful assessment and systemic monitoring is required, and respiratory opinion is advised. Consider oral or intravenous options if needle phobia or inability to self-administer subcutaneous injections; intravenous preparations may help address adherence issues, or severely impaired manual dexterity.

Biological DMARDs and JAK inhibitors should be given in combination with MTX, unless MTX is contraindicated or withdrawn due to adverse events. In specific clinical circumstances, most bDMARDs can be used as monotherapy* (non-methotrexate cDMARD or no cDMARD).

Abbreviations GMMMG RA pathway

ADAb – anti-drug antibodies
ADR – adverse drug reaction
CRP – C-reactive protein
CCP – cyclic citrullinated peptide
bDMARD – biological DMARD (adalimumab, etc)
cDMARD – conventional DMARD (methotrexate, etc)
ESR - erythrocyte sedimentation rate
HCD – high cost drug
ILD – interstitial lung disease
JAK inhibitors – Janus kinase inhibitors (baricitinib, etc)
MTX – methotrexate
RF – rheumatoid factor
SLE – systemic lupus erythematosus
TB – tuberculosis
UC – ulcerative colitis
VTE/PE – venous thromboembolism /pulmonary embolism

Table 2. Available HCDs – information to support choice

Drug	Mode of action	Route	Moderate RA	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.
Abatacept	Fusion protein	IV & SC	No	Consider first line if: ILD (9) (10) Consider if high risk of infection or previously hospitalised with infection whilst another biologic/JAK inhibitor (10) (11) Monotherapy possible, if required by clinical circumstances - off label and outside of NICE, but evidence-based (12)
Adalimumab	TNF-inhibitor	SC	Yes	Licensed & NICE-approved in psoriasis (TA146), Crohn's (TA187), UC (TA329), hidradenitis suppurativa (TA392), uveitis (TA460) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Certolizumab pegol	TNF-inhibitor	SC	No	Consider first line in women who are pregnant or breastfeeding, or who are likely to become pregnant during treatment (4) (13) Licensed in US (but not UK) for Crohn's. Some evidence for efficacy in uveitis[3], but no licence. Monotherapy possible if required by clinical circumstances (on label and within NICE)
Etanercept	TNF-inhibitor	SC	Yes	NICE-approved in psoriasis (TA103), but not in GMMMG psoriasis pathway due to lower efficacy. Consider if anti-TNF is otherwise appropriate, but patient at risk of TB or has potential serious infection risk or previous hospitalisation for infection while on anti-TNFs (10) (11) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Infliximab	TNF-inhibitor	IV	Yes	Must be used with methotrexate (monotherapy not an option). NICE-approved in psoriasis (TA134), Crohn's (TA187), UC (TA329). Some evidence for efficacy in uveitis (but no licence) (14).

[3] Based on clinical experts' opinion.

Drug	Mode of action	Route	Moderate RA	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.
Golimumab	TNF-inhibitor	SC	No	NICE-approved in UC (TA329). Consider for use in patients weighing >100kg (higher dose licensed in this population). Must be used with methotrexate (monotherapy not an option)
Rituximab	CD-20 inhibitor	IV	No	Consider first line if: - recent history of lymphoma/lymphoproliferative disease (10) or latent TB with contraindications for chemoprophylaxis (15) - ILD (9) (10), SLE / connective tissue disease (10) (see also NHSE policy: rituximab in SLE) - Felty's syndrome (16), rheumatoid vasculitis (10), history of demyelinating disease (15) Monotherapy possible (preferably with leflunomide), if required by clinical circumstances (off label and outside of NICE but evidence-based and recommended by BSR (17) (18))
Sarilumab	IL-6 inhibitor	SC	No	Consider if AA amyloidosis (19) Giant cell arteritis (licensed in US, but not UK). Monotherapy possible if required by clinical circumstances (on label and within NICE)
Tocilizumab	IL-6 inhibitor	IV & SC	No	Consider if AA amyloidosis (19) (20) NICE-approved in giant cell arteritis (TA518) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Baricitinib	JAK inhibitor	PO	No	NICE-approved in atopic dermatitis (TA681) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Filgotinib	JAK inhibitor	PO	Yes	NICE-approved in UC (TA792) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Tofacitinib	JAK inhibitor	PO	No	NICE-approved in psoriatic arthritis (TA543) and UC (TA547) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Upadacitinib	JAK inhibitor	PO	Yes	NICE-approved in psoriatic arthritis (TA768) Licensed in UC Monotherapy possible if required by clinical circumstances (on label and within NICE)

*Monotherapy as used in NICE technology appraisals, i.e. without MTX and with/without non-MTX cDMARD (e.g. leflunomide)

13. GM HCD Pathway for moderate rheumatoid arthritis (DAS 3.2 to 5.1)

Moderate active disease (DAS 3.2 to 5.1) despite intensive therapy with combination of cDMARDs

→ **Decision not to treat with a biologic/JAK inhibitor**
Continue with- cDMARD. Clearly document rationale for non-escalation. Review every 3-6 months as per NICE guidance.

If DAS>5.1:
- **Enter severe RA pathway**

At all stages when treating with HCD
- Consider entry to a trial or registry (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency
- See section 21 for drug specific screening questions for pre-admission

First line (HCD-naive): choose based on clinical factors and best value.
For more details see section 12 and purple box to the right.

Review at 3-6 months, as per NICE guidance (NG100) or as clinically appropriate
The aim of treatment is to achieve remission or low disease activity. Assess as per NICE guidance. Advice varies with drug and treatment stage, but generally:
- EULAR criteria met for moderate response (reduction in DAS28 of >0.6)
- Aim for remission in patients with increased risk of radiological progression.

Adequate response (i.e. at least moderate EULAR response)
Reduction in DAS28>0.6

Inadequate response
Reduction in DAS28 ≤0.6 **or**
Ongoing severe active disease
Consider stopping or review at 6 months

→ **Primary failure**
Criteria for response not met within timescales defined by NICE

Continue treatment
Review every 3-6 months as per NICE guidance.
For patients in sustained remission on HCD+ cDMARD (once steroids tapered & stopped) consider dose tapering (where appropriate), in discussion with the patient. This may be achieved by reducing the dose or increasing the dose interval (see section 5). (4; 33; 29; 28; 5)
Return promptly to previous regimen if treatment target no longer met (6)

Secondary failure
Loss of response after 3-6 months
Emerging adverse drug reactions or novel contraindications

→ **Optimise dose prior to switching**, if possible.
Review patient factors as described above.
If on anti-TNF and measurement of trough drug levels and anti-drug antibodies available, consider performing testing, ideally within 24 hours of next dose (30; 31; 32).

→ **Choose an alternative high cost drug**
Consider patient and disease factors, previously used drugs and their mode of action, drug levels, immunogenicity. See purple box and table 2 in section 12 for choice.

Therapeutic drug monitoring (adalimumab/infliximab)
- Target adalimumab drug trough level ≥ 5 mcg/mL (suggest aim: 5-10 mcg/mL)
- Target infliximab drug trough level = 7-10 mcg/mL

Drug levels low/ undetectable and ADAb-ve
- Check adherence
- Increase drug dose or frequency
- Add in cDMARD

Drug levels low/ undetectable and ADAb +ve
Potential loss of response
- Add in cDMARD
- Switch to another anti-TNF*
- Swap to non-anti TNF or JAK inhibitor

Drug level within or above range/ADAb +/- ve and clinical loss of response
Likely non-TNF driven disease
Switch to:
- non-anti-TNF
- JAK inhibitor

*Consider etanercept if not already used as considered less immunogenic (32) or appropriate alternative (if ADAb levels allow)

Anti-TNF drug level & antibodies undetectable -assess adherence, increase drug dose and frequency if appropriate – see section 5. Consider BMI: Is dose weight-adjusted? If adjustments do not result in adequate response, consider switching to alternative bDMARD or JAK inhibitor. See section 12 for choice.

Options to use in moderate disease include ONLY:
adalimumab, etanercept, infliximab, filgotinib, or upadacitinib.

Seropositive & seronegative

Anti-TNF +/- MTX
- Adalimumab or etanercept

Anti-TNF + MTX
- Infliximab

JAKi +/- MTX
- Filgotinib or upadacitinib

14. GM HCD Pathway for severe rheumatoid arthritis (DAS28 > 5.1)

Active disease despite intensive therapy with combination of cDMARDs DAS>5.1

At all stages when treating with HCD
- Consider entry to a trial or registry (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency
- See section 21 for drug specific screening questions for pre-admission

First line (HCD-naive): choose based on clinical factors and best value.
For more details see section 12 and purple box to the right.

Review at 3-6 months, as per NICE guidance (NG100) or as clinically appropriate
The aim of treatment is to achieve remission or low disease activity. Advice varies with drug and treatment stage, but generally:
- Reduction in DAS28 of ≥1.2 **or** EULAR criteria met
- Aim for remission in patients with increased risk of radiological progression.

Adequate response
Reduction in DAS28 of ≥1.2 **or** EULAR criteria met **and** minimal active disease

Moderate response
Reduction in DAS28 0.6-1.1 **or** reduction in DAS28 of ≥1.2 but ongoing active disease

Inadequate response
Reduction in DAS28 < 0.6 **or** Ongoing severe active disease.

Primary failure
Criteria for response not met within timescales defined by NICE

Review every 3-6 months as per NICE guidance
If non-adequate response, decision to continue with treatment will depend on clinical judgement and shared decision making with patients.
For patients in sustained remission on biologic + cDMARD (once steroids tapered & stopped) consider dose tapering (where appropriate), in discussion with the patient. This may be achieved by reducing the dose or increasing the dose interval (see section 5). (4; 33; 29; 28; 5)
Return promptly to previous regimen if treatment target no longer met (6)

Choose an alternative high cost drug
Consider patient and disease factors, previously used drugs and their mode of action, drug levels, immunogenicity. See table 2 in section 12 for choice.

Secondary failure
Loss of response after 3-6 months
Emerging adverse drug reactions or novel contraindications

Optimise dose prior to switching, if possible.
Review patient factors as described above.
If on anti-TNF and measurement of trough drug levels and anti-drug antibodies available, consider performing testing, ideally within 24 hours of next dose (30; 31; 32).

For therapeutic drug monitoring (adalimumab/infliximab)
➢ **see previous page (section 14)**

Consider presence of CCP & RF antibodies, when assessed.

For more details on drug choice see table 2 in section 12

If seropositive, consider with MTX:
- Anti-TNF
- Rituximab
- Abatacept
- Tocilizumab/sarilumab
- JAK inhibitor

If seronegative, consider with MTX:
- Anti-TNF
- Tocilizumab/sarilumab
- JAK inhibitor
- Rituximab/abatacept (if no suitable alternatives)

Biological DMARDs and JAK inhibitors should be given in combination with MTX, unless MTX is contraindicated or withdrawn due to adverse events. In specific clinical circumstances, most bDMARDs can be used as monotherapy (non-methotrexate cDMARD or no cDMARD). See table 2 for details.

If MTX contraindicated or not tolerated after an appropriate trial, and only in specific clinical circumstances, consider monotherapy with:
- Anti-TNF (but not infliximab or golimumab)
- Tocilizumab/sarilumab (if symptoms of IL-6-mediated disease)
- Rituximab with a non-MTX cDMARD (preferably leflunomide) or no-cDMARD
- Abatacept monotherapy

15. Contraindications, special warnings and precautions

15.1. Cautions and contraindications

Cautions, contraindications, and special warnings to use of systemic agents for rheumatoid arthritis are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients.

For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis.

15.2. Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway. Visit www.gov.uk/drug-safety-update for up-to-date information on safety issues.

- Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies, 2021, Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular risk (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments.
- Tofacitinib (Xeljanz▼): new measures to minimise risk of venous thromboembolism and of serious and fatal infections; 2020. Maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism unless there is no suitable alternative treatment. Due to risk of serious and fatal infections, healthcare professionals are advised only to use tofacitinib in patients older than age 65 years if there is no alternative treatment.
- Baricitinib (Olumiant▼): risk of venous thromboembolism (2020) Discontinue baricitinib treatment permanently if clinical features of deep vein thrombosis or pulmonary embolism occur. Prescribers are reminded to use caution if using baricitinib in patients with risk factors for deep vein thrombosis or pulmonary embolism in addition to rheumatoid arthritis.
- Tocilizumab (RoActemra): rare risk of serious liver injury including cases requiring transplantation (2019), Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be measured before starting treatment with tocilizumab and monitored every 4–8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Serious liver injury has been reported on treatment with tocilizumab from 2 weeks to more than 5 years after initiation.
- Live attenuated vaccines: avoid use in those who are clinically immunosuppressed; April 2016
- Tumour necrosis factor alpha inhibitors; December 2014. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.
- Rituximab: progressive multifocal leukoencephalopathy in a patient (2014) A case of progressive multifocal leukoencephalopathy (PML) with a fatal outcome was reported in a patient with rheumatoid arthritis who had not previously received treatment with methotrexate or a TNF antagonist.

In November 2022, the European Medicines Agency published results of review of the safety of JAK inhibitors. The recommendations include restricting use of these drugs in some patient groups to reduce the risk of serious side effects with JAK inhibitors. The MHRA has said it will look at safety measures around use of JAK inhibitors. (21) Until then clinical judgement is necessary to determine best drug choice for individual patient.

15.3. Malignancy

The use of rheumatology high cost drugs in patients with a history of malignancy should involve a detailed discussion with the patient around the risks and benefits of treatment and consideration should be given to involving their oncologist. If a cancer occurs during treatment with a high cost drug, oncologist advice on treatment might be sought.

16. Pre-high cost drug screening

A checklist template is provided at the end of the document (section 21) and can be adapted locally if necessary.

16.1. Tuberculosis (TB)

Interferon gamma (gIFN) testing is recommended prior to commencing biologic/JAK treatment if available. Parts of Greater Manchester are identified as areas of high-risk for tuberculosis. In patients with high index of suspicion or risk of tuberculosis consider referring to previously published algorithms for additional screening (22) and referral for a respiratory opinion if deemed necessary: See NICE guideline NG33, Tuberculosis (Sept 2019), for further information.

With anti-TNF therapy, risk of tuberculosis reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). (10) There also appears to be a signal of concern from clinical trials with newer monoclonal antibodies such as certolizumab and golimumab, however data from observational studies are currently lacking. (10)

16.2. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic and JAK inhibitors, This is particularly relevant to rituximab (see: MHRA Drug Safety Update (Dec 2013) Rituximab: screen for hepatitis B virus before treatment).Screening should include: (10)

- Hepatitis B: screen for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc, HBcAb), followed by HBV DNA test if HBsAg or anti-HBc are positive.
- Hepatitis C: screen for anti-hepatitis C antibodies. If test is positive, hepatitis C RNA or core antigen assays should be performed.

If either hepatitis B or hepatitis C infection is suspected, discuss with a hepatologist. Treatment with a biological DMARD may be appropriate but should follow a risk/benefit decision made with a hepatologist, infectious disease or another relevant specialist.

16.3. Human immunodeficiency virus (HIV)

Screening for HIV is recommended for all patients starting a biologic and JAK inhibitors. NICE Quality Standard QS157 (Sept 2017) recommends young people and adults are offered HIV testing when admitted to hospital in areas of extremely high HIV prevalence, or when having a blood test when admitted to hospital in areas of high HIV prevalence. Greater Manchester is an area of high and extremely high HIV prevalence. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis recommends risk factors for HIV infection should be documented prior to commencing a biologic and, if present, an HIV test should be performed. If considering the use of a biologic or a JAK therapy in HIV positive patients, this should be discussed with an HIV specialist.

17. Surgery and perioperative risk

Potential benefit of reduced risk of post-operative infections by stopping treatment should be balanced against risk of flare in disease activity. For most high cost drugs consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug.
For higher risk procedures consider stopping 3–5 half-lives (if this is longer than one dosing interval) before surgery. (10)

In all cases rheumatology consultant should be involved. High cost drugs should be recommenced after surgery when there is evidence of wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection. For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis or review trust perioperative guidelines where applicable.

Table 3. Peri-operative supportive information (4) (10) (23)

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One mean half-life	Five half-lives
Abatacept IV	Monthly	Week 5	14 days	70 days
Abatacept SC	Every week	Week 2	14 days	70days
Baricitinib	Once daily	Day 4*	13 hours	3 days
Adalimumab	Every 2 weeks	Week 3	14 days	70 days
Certolizumab pegol	Every 2 weeks Every 4 weeks	Week 3 Week 5	14 days	70 days
Etanercept	Weekly or twice weekly	Week 2	3 days	15 days
Filgotinib	Once daily	Day 5**	19 hours	4 days
Golimumab	Every 4 weeks	Week 5	14 days	70 days
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9 days	45 days
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4-7	18 days	90 days
Sarilumab SC	Every 2 weeks	Week 3***	21 days	105 days
Tocilizumab IV	Every 4 weeks 4mg/kg 8mg/kg	Week 5	 11 days 13 days	 55 days 65 days
Tocilizumab SC	Every week	Week 3	13 days	65 days
Tofacitinib	Twice daily	Day 4*	3 hours	15 hours
Tofacitinib MR	Once daily	Day 4*	6 hours	30 hours
Upadacitinib	Once daily	Day 4*	14 hours	3 days

*Tofacitinib is rapidly eliminated but treatment effects do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life (4). Although not stated in summary of product characteristics this may be applicable to all JAK inhibitors due to mechanism of action. Prescribers may wish to consider longer time to surgery, i.e. Week 2.
**No published guidance available, recommendation based on half-life (4) or dosing interval (10).
***No published guidance available; recommendation based on dosing interval (10). Prescribers may also wish to consider time to surgery of Week 4 based on half-life (4).

18. Fertility, pregnancy and lactation

Prescribers should be mindful that evidence base evolves and to use the most up to date national guidance if in doubt. At the time of writing, the BSR pregnancy and breastfeeding guideline renewed in October 2022 was based on most up to date evidence and should be referred to in first instance. Where data is not available (e.g. for newer drugs), manufacturers' recommendations may be taken into consideration.

18.1. Fertility and conception

Medicines included in this pathway may affect fertility and conception. Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks after treatment has stopped (see table 4 in section 18.2). **Paternal exposure to high cost drugs included in this pathway is compatible with pregnancy.** (13)

When giving family planning advice, the clinician should consider the half-life of the drug in use, advice on length of contraception after the last dose, and existing evidence for use in pregnancy and breastfeeding.

18.2. Pregnancy

Among biologics, anti-TNFs, can be considered during pregnancy. The BSR (13) advise that:

- Women stable on anti-TNF therapy with known placental transfer (adalimumab, infliximab, golimumab) do not need to be switched to an anti-TNF with established minimal placental transfer (certolizumab) before or during pregnancy.
- Certolizumab due to no to minimal rate of transplacental transfer, can be considered for use thorough pregnancy.
- Patients who stop anti-TNF therapy during pregnancy may, if needed, be re-loaded as soon as

possible after delivery to manage maternal disease, given infection or other complications of postpartum are excluded, and regardless of breastfeeding status.

- Lower grade, limited evidence is available for non-anti-TNFs and other biologics and is insufficient to recommend for use in pregnancy, unless there are no alternatives to control sever disease.
- JAK inhibitors are contraindicated and should be stopped at least two weeks pre conception and should not be used during breastfeeding.

No studies of sarilumab, upadacitinib and baricitinib were identified in the guidance review; filgotinib was not included in evidence searches.

The decision to continue treatment in pregnancy needs to be individualised, considering all relevant factors (e.g., alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare caused by cessation of therapy, and the impact of a flare on the mother and the unborn child). This should be discussed by a multi-disciplinary team.

The following table contains advice from BSR and also lists manufacturers' recommendations on time to continue contraception after treatment cessation and compatibility with pregnancy trimesters.

For stopping biologics in pregnancy to enable infant vaccinations per UK schedule see section 18.4.

Table 4. Peri-conception and pregnancy compatibility

Drug	**Time to continue contraception after treatment cessation [SPCs]** (4)	**Compatibility with trimesters [BSR 2022]** (13)		
		Peri- conception	**First**	**Second/ Third**
Abatacept	14 weeks	Consider stopping at conception**	Severe disease if no alternatives	Severe disease if no alternatives
Adalimumab	5 months	Yes	Yes	Yes
Certolizumab	5 months	Yes	Yes	Yes
Etanercept	3 weeks	Yes	Yes	Yes
Golimumab	6 months	Yes	Yes	Yes
Infliximab	6 months	Yes	Yes	Yes
Rituximab	12 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Sarilumab	3 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Tocilizumab	3 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Baricitinib*	1 week	Stop ≥2 weeks pre-conception	No	No
Filgotinib*	1 week	Stop ≥2 weeks pre-conception	No	No
Tofacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No
Upadacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No

* However, as effects of JAK inhibitors may persist after drug elimination, a waiting period of one menstrual cycle before conception is advised.

** May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.

Further information to support decision-making is available from:

- BSR guidance on prescribing of drugs in pregnancy and lactation
- Summaries of product characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at https://uktis.org or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (https://uktis.org/surveillance/reporting-an-exposure-in-pregnancy/). UKTIS are commissioned by the UK Health Security Agency (formerly Public Health England) to perform national surveillance of known and emerging human teratogens across the UK.

Advice and risk assessment for individual patients may also be available by contacting a local medicines information service via hospital pharmacy departments.

18.3. Breastfeeding

Biologics in general, and in particular anti-TNFs, are considered compatible with breastfeeding. The BSR (13) advise that:

- Anti-TNFs are compatible with breastfeeding.
- Non-anti-TNF biologics are compatible with breastfeeding (based on limited evidence).
- JAK inhibitors should be avoided in breastfeeding.

Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot always be excluded. A decision on whether to breastfeed and continue or discontinue therapy should be made considering the benefit of breastfeeding to the child and the benefit of woman.

Further information to support decision-making may be available from:

- BSR guidance on prescribing of drugs in pregnancy and lactation
- Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk
- Summaries of product characteristics (www.medicines.org.uk)
- Local medicines information service via hospital pharmacy departments.

18.4. Vaccination of infants exposed to drugs due to maternal treatment

Immunisation schedules in infants after in utero exposure to biologics will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccine. (13) The BSR recommend that:

- Women considered to have low risk of disease flare on withdrawal of anti-TNF in pregnancy could stop infliximab at 20 weeks, adalimumab and golimumab at 28 weeks and etanercept at 32 weeks so that a full-term infant may receive the normal UK vaccination schedule, including rotavirus vaccine at 8 weeks.
- Adalimumab, etanercept, infliximab or golimumab may be continued throughout pregnancy, to maintain disease control. In such case, immunisation with live vaccines should be avoided until infants are 6 months of age.
- Exposure to certolizumab in utero does not require any changes to vaccination schedule.

Table 5. Pregnancy exposure and impact on infant live vaccines schedule (13)

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Abatacept	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Adalimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Certolizumab	No adjustment to vaccination including live vaccines needed.
Etanercept	If stopped by 32 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Golimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Infliximab	If stopped by 20 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Rituximab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Sarilumab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Tocilizumab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
JAK inhibitors	Not applicable. Contraindicated in pregnancy.

The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (24)

- BCG for tuberculosis – variation across the country depending on incidence of TB. Some areas of GM are considered to have high incidence. Isolated cases of neonates who died from disseminated BCG vaccination or TB infection after exposure to an anti-TNF medicine in utero were reported to

MHRA. they were probably not known to be immunosuppressed at the time of vaccination. (25) The BCG vaccine may easily be deferred to be given later in life. (13)

- Rotavirus - all infants. Rotavirus is the most common cause of gastroenteritis in infants in the UK. (26) The rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception. (26) Although there is limited evidence of safety and efficacy in infants with immunosuppression, vaccination of infant exposed in utero may be considered following careful consideration of the risks and benefits and following specialist consultation.

For advice on other live vaccinations following exposure to biologics in breastmilk, healthcare professionals should contact the relevant specialist for advice.

If there is any doubt as to whether an infant due to receive a live attenuated vaccine may be immunosuppressed due to the mother's therapy, including exposure through breast-feeding, specialist advice should be sought. (27)

Current vaccination strategies with non-live vaccines for infants who have been exposed to biologic medicines *in utero* do not differ from those for unexposed infants.

19. Vaccinations

19.1. Routine vaccinations

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of biologic therapy, with reference to Department of Health Guidance. During biologic therapy, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once only. For vaccination of infants see section 18.4.

19.2. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and cautioned in patients on JAK inhibitors. It is safe to administer a live vaccine 4 weeks prior to commencing biologic or tofacitinib therapy, when necessary. There is no contraindication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

When a live vaccine is required by a patient on a high cost drug, stopping treatment (following careful assessment of the risks and benefits) may enable a necessary vaccination to be administered. The decision to vaccinate should be guided by the drug half-life (see table 3 in section 17). For further relevant summaries of products characteristics, www.medicines.org.uk

- the Green Book, https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book (27)
- Specialist advice

The table below shows all live vaccines available in the UK.

Table 6. Live vaccines available in the UK

Live vaccine	Brand name(s)
Tuberculosis - BCG	Bacillus Calmette-Guerin Vaccine
Influenza (nasal)	Brand can change yearly in the UK
Measles, mumps and rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster vaccine	Varilrix®, Varivax®, Zostavax®
Yellow fever vaccine	Stamaril®

19.3. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on high-cost therapies, though they may elicit a lower response than in immunocompetent individuals.
Non-live vaccines should be given 2-4 weeks before starting immunosuppressant therapy, as response after starting treatment can be poor.
For information on specific vaccines please refer to the appropriate Summary of Product Characteristics (www.medicines.org.uk) or the Green Book: Immunisation against infectious disease. (27)

For information on COVID-19 vaccines please refer to the Green Book: Immunisation against infectious disease Chapter 14a.

Shingrix® a non-live vaccine for varicella zoster virus (VZV) is now available in the UK. From 2021, individuals who are eligible for shingles vaccine (adults aged 70-79 years), but who are contra-indicated to the receipt of the live vaccine should be offered Shingrix® instead. Adults should receive two doses of Shingrix® a minimum of 2 months apart. For more information please refer to the Green Book: Immunisation against infectious disease Chapter 28a (27)

20. Checklist for patient screening on selection for high cost drugs

Screening investigations requested in clinic				
		Y/N	**Initial**	**Results/Details**
FBC/U&E/LFT/ESR/CRP				
ANA *(If positive also order ENA/dsDNA/C3/C4)*				
HIV, HBV *(surface antigen, core antibody)**, **HCV** *(antibody test) If positive result please refer to hepatology/GUM/ID as relevant* * Reactivation has been reported in HBsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status				
Varicella zoster IgG (If negative inform GP and patient)				
TB screening *(g-IFN testing)* *If positive refer to respiratory*				
Chest X-ray *(within the last 6 months)* *(± pulmonary function tests/HRCT thorax)* **CXR checked by/date**				
Additional investigations for rheumatoid arthritis	**Ensure RF/anti-CCP status** Don't repeat if previously positive result.			
Additional investigations for rituximab	**Serum immunoglobulins** (document low level & seek advice if appropriate: monitor if low especially in older patients) (+/- B cells)			
Additional monitoring: Tocilizumab/Sarilumab/JAKi	**Fasting lipids** (if abnormal treat according to local guidelines)			
Screening questions asked in clinic				
		Y/N	**Initial**	**Details**
Previous TB/TB contact (*details*)				
Travel abroad since last review *(i.e., TB/viral hepatitis high risk countries)* *Which country/Dates*				
History of heart failure (NYHA class III or IV) *(details)*				
History of recurrent infection *(details)*				
History of interstitial lung disease *(details such as extent of ILD)*				
History of cancer/malignancy *(Type/Date when occurred/Date of all clear)*				
Date of last mammogram (50yr +) *(encourage patient to visit GP if >3 years)*				
Date of last smear (25yr +) *(encourage patient to visit GP if >3 years)*				
History of allergy/infusion reaction to any agent *(to what/type of reaction)*				
History of cardiovascular risk factors				
History of thrombotic event (e.g. DVT/PE)				
Any live vaccinations in the last 4 weeks				
History of demyelinating disease *(details)*				
History of diverticular disease *(details)*				
Concurrent immune disease (e.g., uveitis, IBD, psoriasis)				
Education				
Pregnancy/breastfeeding advice given				
Vaccination advice given				
Patient counselled and educated				
Patient consent to be approached for research				

21. Specific monitoring considerations

See screening questionnaire (section 20) for full details of baseline monitoring that should be performed in all patients considered for high cost drugs.
Ongoing monitoring in line with BSR guidance is recommended for all patients, e.g., FBC, creatinine/calculated GFR, ALT/AST and albumin every 3-6 months. (10)
Additional monitoring is recommended for some biologics and for the JAK inhibitors, as described below.

21.1 Tocilizumab and sarilumab

<table>
<tr><td colspan="3">FBC (monitoring of absolute neutrophil count [ANC] and platelets) (4; 10)</td></tr>
<tr><td>Recommended monitoring</td><td colspan="2">• Check FBC 4-8 weekly for the 1st 6 months then every 12 weeks thereafter. Timing of these tests should ideally be:
○ IV tocilizumab: before the next scheduled infusion
○ SC tocilizumab 3 days before every fourth injection
○ SC sarilumab 3 days before every fourth injection</td></tr>
<tr><td rowspan="8">Recommended actions</td><td colspan="2"><u>ANC</u> (laboratory value: cells x 10^9/L)</td></tr>
<tr><td colspan="2">Initiation is not recommended in patients with ANC <2 x 10^9/L</td></tr>
<tr><td>>1</td><td>Maintain dose</td></tr>
<tr><td>0.5 to 1</td><td>Interrupt dosing. When ANC >1, resume as below.</td></tr>
<tr><td><0.5</td><td>Discontinue treatment</td></tr>
<tr><td colspan="2"><u>Platelets</u> (laboratory value: cells x 10^3/microlitre)</td></tr>
<tr><td>50 to 100</td><td>Interrupt dosing. When platelets >100, resume as below</td></tr>
<tr><td><50</td><td>Discontinue treatment</td></tr>
<tr><td colspan="2"><u>Resuming after interruption</u>
• Tocilizumab IV: resume at 4 mg/kg. Increase to 8 mg/kg as clinically appropriate.
• Tocilizumab SC: resume with every other week dosing. Increase to weekly when appropriate
• Sarilumab: resume at 150 mg every 2 weeks and increase to 200 mg every 2 weeks as clinically appropriate</td></tr>
<tr><td colspan="3">LFTs (monitoring of transaminases: ALT & AST) (4; 10)</td></tr>
<tr><td>Recommended monitoring</td><td colspan="2">• Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported. When clinically indicated, other LFTs including bilirubin should be considered.
• Check LFTs 4-8 weekly for the 1st 6 months then every 12 weeks thereafter. Timing of these tests should ideally be
○ IV tocilizumab: the week before the next scheduled infusion
○ SC tocilizumab 3 days before every fourth injection
○ SC sarilumab 3 days before every fourth injection</td></tr>
<tr><td rowspan="3">Recommended actions</td><td>>1 to 3 x upper limit of normal (ULN)</td><td>Dose-modify concomitant DMARDs, if appropriate.
For persistent increases in this range reduce dose of <u>tocilizumab</u> as below, or interrupt until ALT/AST have normalised. No dose reduction is recommended for <u>sarilumab</u>
• IV tocilizumab: reduce dose to 4 mg/kg. Restart at 4 mg/kg or 8 mg/kg, as clinically appropriate
• SC tocilizumab: reduce dose to every other week. Restart with weekly or every other week injection, as clinically appropriate.</td></tr>
<tr><td>>3 to 5 x ULN</td><td>Interrupt treatment until <3 x ULN, then:
• Tocilizumab: Follow recommendations above for restarting treatment after elevations >1 to 3 x ULN
• Sarilumab: Resume at 150 mg every 2 weeks and increase to 200 mg every 2 weeks as clinically appropriate</td></tr>
<tr><td>>5 x ULN</td><td>Discontinue treatment</td></tr>
<tr><td colspan="3">Lipids (4; 10)</td></tr>
<tr><td>Recommended monitoring and actions</td><td colspan="2">Tocilizumab & sarilumab
• Fasting lipid profile should be assessed at baseline and repeated at 3 months
• Studies have suggested that any initial rise in lipid levels tends to stabilise within 3 months, and BSR currently recommend that the repeat lipid profile should be performed at 3 months. (10)
• Any further monitoring should be in line with local practice and guided by presence of other risk factors.
• Increase in lipid profile should be treated as per local policy</td></tr>
</table>

21.2 Rituximab

Serum immunoglobulins (4; 10)	
Recommended monitoring	• Check immunoglobulins at baseline (IgA, IgG, and IgM). Low level of immunoglobulins, especially IgG, is associated with a higher risk of neutropenia and infection in patients receiving rituximab • Check serum immunoglobulins prior to each cycle of rituximab.
Recommended actions	• Risk of infection increases as serum IgG falls below normal. Consider reduced rituximab dose (e.g., 2 x 500 mg infusions) in this situation • There is no evidence to establish an absolute threshold for total immunoglobulin, IgG or IgM where rituximab should be withheld.

21.3 Tofacitinib

Dose adjustments are required in hepatic and renal impairment, See SPCs for further information.
MHRA alert: Tofacitinib Drugs Safety Update, October 2021 Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (4)		
Recommended monitoring	• Check FBC at baseline, 4-8 weeks after initiating treatment, and 3-monthly thereafter	
Recommended actions	**ALC** (laboratory value: cells x 10^9/L)	
	Initiation is not recommended in patients with ALC <0.75	
	ALC >0.75	Maintain dose
	ALC 0.5-0.75	• If ≥2 sequential values in this range, ○ tofacitinib 5 mg BD or 11 mg OD: interrupt dosing • When ALC >0.75, treatment should be resumed as clinically appropriate.
	ALC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	ANC (laboratory value: cells x 10^9/L)	
	Initiation is not recommended in patients with ANC <1	
	ANC >1	Maintain treatment
	ANC 0.5-1.0	• If ≥2 sequential values in this range, ○ tofacitinib 5 mg BD or 11 mg OD: interrupt dosing • When ANC >1, treatment should be resumed as clinically appropriate.
	ANC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	Haemoglobin (laboratory value: g/dL)	
	Initiation is not recommended in patients with haemoglobin <9 g/dL	
	Decrease ≤2, and absolute value ≥9	Maintain dose
	Decrease >2 **or** absolute value <8	Confirm with repeat testing. Interrupt dosing until haemoglobin values have normalised.
Hepatic transaminases (ALT & AST)		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected	
Lipid parameters		
Recommended monitoring	• Lipid parameters should be assessed at baseline and repeated after 8 weeks. Maximum effects on lipid parameters are normally seen within 6 weeks. Treat as per local practice guidelines	
Renal impairment		
Recommended actions	• Creatine clearance <30ml/min dose should be reduced to 5mg once daily	
Age considerations		
Tofacitinib	• Do not use in patients over 65 years.	

21.4 Baricitinib, filgotinib, upadacitinib

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (4)		
Recommended monitoring	• Check FBC at baseline and then no later than 12 weeks after initiation of treatment	
Recommended actions	**ALC** (laboratory value: 10^9 cells/L)	
	ALC > 0.5	Continue treatment
	ALC <0.5	Interrupt treatment. Restart once ALC >0.5.
	ANC (laboratory value: 10^9 cells/L)	
	ANC >1.0	Continue treatment
	ANC <1.0	Interrupt treatment. Restart once ANC >1.0.
	Haemoglobin (laboratory value: g/dL)	
	Hb >8	Continue treatment
	HB <8	Interrupt treatment. Restart once Hb >8
Hepatic transaminases		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management Note: In the filgotinib SmPC there is no requirement for monitoring of hepatic transaminases.	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected	
Lipid parameters		
Recommended monitoring	• Lipid parameters should be assessed at baseline and repeated after 12 weeks.	
Recommended actions	• Treat any lipid abnormalities in line with local practice.	
Renal impairment		
Recommended actions **Baricitinib**	• The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Baricitinib is not recommended for use in patients with creatinine clearance < 30 mL/min	
Recommended actions **Filgotinib**	• A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) and is therefore not recommended for use in these patients.	
Recommended actions **Upadacitinib**	• No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment. Upadacitinib 15 mg once daily should be used with caution in patients with severe renal impairment.	
Age considerations		
Baricitinib	• A dose of 2 mg once daily is appropriate for patients such as those aged ≥ 75 years	
Filgotinib	• A starting dose of 100 mg once daily is recommended for patients with rheumatoid arthritis aged 75 years and older as clinical experience is limited.	
Upadacitinib	• No dosage adjustment necessary	

22. References

1. Prescribing of high cost biosimilar biological medicines. GMMMG. 2016. Accessed via https://gmmmg.nhs.uk/guidance/high-cost-drugs/.
2. TA480: Tofacitinib for moderate to severe rheumatoid arthritis. Excellence, National Institute for Health and Care. 2017.
3. TA466: Baricitinib for moderate to severe rheumatoid arthritis. National Institute for Health and Care Excellence. 2017.
4. Summaries of product characteristics, accessed via electronic Medicines Compendium at https://www.medicines.org.uk/emc/.
5. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Schett, G, et al. 2016, Ann Rheum Dis, Vol. 75, pp. 1428-37.
6. NG100: Rheumatoid arthritis in adults: management. National Institute for Health and Care Excellence. 2018.
7. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Smolen, JS, et al. 2020, Ann Rheum Dis, Vol. 0, pp. 1-15.
8. Free of charge (FOC) medicines schemes. Regional Medicines Optimisation Committee. Accessed via https://gmmmg.nhs.uk/guidance/high-cost-drugs/, 2018.
9. The safety of biologic therapies in RA-associated interstitial lung disease. Jani, M, et al. 2014, Nat Rev Rheumatol, Vol. 10, pp. 284-94.
10. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Holroyd, C R, Seth, R and Mukhari, M. 2, 2019, Rheumatology, Vol. 58, pp. e3-e42.
11. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Singh, JA, et al. 1, 2016, Vol. 68, pp. 1-25.
12. Abatacept monotherapy compared with abatacept plus disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients: data from the ORA registry. March, Truchetet ME et al. s.l. : Arthritis Res Ther., 2016, Vol. 18:72.
13. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Russel et al. s.l. : Rheumatology, 2022, Rheumatology, Vol. 00, pp. 1693-7. https://doi.org/10.1093/rheumatology/keac551.
14. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious Uveitis: fundamentals Of Care for UveitiS (FOCUS) initiative. . Dick AD, Rosenbaum JT, Al-Dhibi HA et al. s.l. : Ophthalmology, 2018;, Vols. 125:757–773.
15. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Smolen, JS, et al. 2017, Ann Rheum Dis, Vol. 76, pp. 960-77.
16. Biological Agents in the Management of Felty's Syndrome: A Systematic Review. Narvaez, J, et al. 5, 2012, Semin Arthritis Rheum, Vol. 41, pp. 658-68.
17. BSR and BHPR guidelines on the use of rituximab in rheumatoid arthritis. Bukhari, et al. 12, s.l. : Josh Dixey on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group, 2011, Vol. 50, pp. 2311-2313.
18. Rituximab for rheumatoid arthritis. Cohen, MD and Keystone, E. 2015, Rheumatol Ther, Vol. 2, pp. 99-111.
19. AA amyloidosis – Benefits and prospects of IL-6 inhibitors, Modern Rheumatology. Okuda, Y, et al. 1, 2014, Modern Rheumatology, Vol. 24, pp. 137-43.
20. Good medium-term efficacy of tocilizumab in DMARD and anti-TNF-a therapy resistant reactive amyloidosis. Hakala, M, et al. 3, 2013, Ann Rheum Dis, Vol. 72, pp. 464-5.
21. UK medicine regulator considering safety measures for JAK inhibitors following new guidance. Robinson, J. s.l. : Pharmaceutical Journal, Nov 2022 . https://pharmaceutical-journal.com/article/news/uk-medicine-regulator-considering-safety-measures-for-jak-inhibitors-following-new-guidance.
22. You can't always get what you want, but if you try sometimes (with two tests - TST and IGRA - for tuberculosis) you get what you need. Winthrop KL. et al. 11, 2012, Ann Rheum Dis, Vol. 71, pp. 1757-60.
23. Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Goodman, S.M., et al American College of Rheumatology/American Association of Hip and Knee Surgeons. s.l. : Arthritis Care Res , 2022. https://doi.org/10.1002/acr.24893.
24. The complete routine immunisation schedule from February 2022. UK Health Security Agency. 2022.
25. Drug Safety Update. Live attenuated vaccines: avoid use in those who are clinically immunosuppressed. MHRA. 2016.
26. UK immunisation schedule: the green book, chapter 11. UK Health Security Agency. 2020 update. last accessed Nov 2022.
27. Immunisation against infectious disease: the green book. UK Health Security Agency. 2022 (last update).
28. Step-down strategy of spacing TNF-blocker injections for establish rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS). Fautrel, B, et al. 2014, Ann Rheum Dis, Vol. 75, pp. 59-67.
29. Maintenance, reduction or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Smolen, JS, et al. 2013, Lancet, Vol. 381, pp. 918-29.
30. High frequency of antidrug antibodies and association of random drug levels with efficacy in certolizumab pegol-treated patients with rheumatoid arthritis: results from the BRAGGSS cohort. Jani, M, et al. 2015, Ann Rheum Dis, Vol. 76, pp. 208-13.
31. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Jani, M, et al. 8, 2015, Arthritis & Rheumatology, Vol. 67, pp. 2011-19.
32. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory disease: a real issue, a clinica perspective. Vincent FB et al. 2013, Ann Rheum Dis, Vol. 72, pp. 165-78.
33. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. van Herwaarden N. et al. 2015, BMJ, Vol. 350, p. h1389.
34. Abatacept monotherapy compared with abatacept plus disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients: data from the ORA registry. Truchetet ME et al. s.l. : Arthritis Res Ther., 2016. 18:72.