Executive Summary

The current version of the GMMMG's High Cost Drugs Pathways for Rheumatoid Arthritis in adults was published in December 2017 with a review suggested for July 2019. However, the review was delayed until September 2021 due to Covid-19.

Key Points
The main changes include:

- Incorporating treatment for moderate RA. Rather than write a separate pathway it was decided to incorporate this into the existing pathway.
- Incorporating the following NICE TAs:
  - NICE TA715 adalimumab, etanercept, infliximab and abatacept for adults with moderate rheumatoid arthritis who have tried conventional DMARDs but they have not worked.
  - NICE TA676: Filgotinib for moderate to severe RA
  - NICE TA744: Upadacitinib for moderate RA
- Addition of moderate RA treatment flowcharts
- Update of special monitoring considerations particularly JAK inhibitors and addition of MHRA alert for tofacitinib
- Addition of using abatacept and rituximab as monotherapy (i.e. on its own or with a DMARD that is not MTX) which is off label & outside NICE guidance. The number of patients for whom this is used is likely to be small, the alternative to which would be an alternative biologic so is likely to be cost-neutral
- Adding the use of 40mg once weekly adalimumab which is already licensed in monotherapy (defined by manufacturer as adalimumab without methotrexate) but are now recommending weekly use with MTX and or DMARDs. This is likely to be cost-saving compared with the option of using a more expensive biologic
- Updating the tables in the pregnancy section
- Updating the tables in the pre-op surgery section
- Adding table alternative dosing of high-cost drugs

The pathways have been drafted to reflect the group's preference that local multidisciplinary team (MDT) decision replace need for individual funding request (IFR) in patients receiving more than five sequential high cost drugs.

Views on the above, and in particular on the MDT's role, are encouraged from the representatives of all healthcare sectors in Greater Manchester and the public. The pharmaceutical industry is invited to comment on factual inaccuracies only.

High-cost drugs pathway for Rheumatoid Arthritis in adults

October 2021

Version 5.1 FINAL DRAFT
This supersedes previous version v4.1

Review due TBC 2023

Current authors Greater Manchester Rheumatoid Arthritis working group:
Meghna Jani[1], Vanessa Reid[2], Rebecca Heaton[3] Ben Parker[4], Louise Mercer[5], Audrey Low[6], Dipak Roy[7], Maya Buch[8], Anindita Paul[9]

Past authors Greater Manchester Rheumatoid Arthritis working group:
Hector Chinoy[10], Ian Bruce[11], Dawn Bell[12]

[1]Consultant Rheumatologist, Salford Royal Hospital, SRFT, UK
[2] Lead Rheumatology Pharmacist, Manchester Royal Infirmary, MFT, UK
[3] Lead Rheumatology Pharmacist, Stepping Hill Hospital, Stockport NHS FT, UK
[4]Consultant Rheumatologist & Honorary Senior Lecturer, Manchester Royal Infirmary, MFT, UK
[5] Consultant Rheumatologist, Stepping Hill Hospital, Stockport NHS FT
[6] Consultant Rheumatologist, Salford Royal Hospital, SRFT, UK
[7] Consultant Rheumatologist, Tameside Hospital, Tameside and Glossop Integrated Care NHS FT, UK
[8]Professor of Rheumatology, Manchester Royal Infirmary, MFT, UK
[9]Consultant Rheumatologist & Senior Lecturer, SRFT, UK
[10]Consultant Rheumatologist, Royal Bolton Hospital, Bolton, UK
[11]Professor of Rheumatology, Manchester Royal Infirmary, MFT, UK
[12]Lead Rheumatology Pharmacist, Wythenshawe Hospital, MFT, UK

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. To include the use of high-cost drugs for moderate RA	5.1

Main changes to version 5.1

- Re-formatted in line with other updated HCD pathways
- Requirement for MDT approval after X biologic treatments added
- Flowcharts update to include all NICE-approved treatments
- Updated to reflected most recent available evidence
- Updated to reflect treatment for moderate RA

Approvals

This document must be approved by the following before distribution:

TITLE	DATE OF ISSUE	VERSION
GM Rheumatoid Arthritis working group		
GMMMG High Cost Drugs Subgroup		
GMMMG		

Distribution

Final version available on GMMMG website

Contents

High-cost drugs pathway for severe and moderate rheumatoid arthritis in adults

1. Introduction

The pathway is to be used as a guideline for the use of high-cost drugs in rheumatoid arthritis (RA). It has been written using up to date published research and evidenced based medicine. This pathway originated as a clinical project implemented by MAHSC, a joint project between rheumatology departments at Salford Royal Hospital, Manchester University Foundation Trust and the University of Manchester, and has now extended to the Greater Manchester hospital trusts.

All biologics may be used in accordance with NICE TAs, but the most cost-effective treatment option should be selected, when suitable. For drugs where a biosimilar exists the best value biological medicine should be used in preference to the originator version, in line with NHSE commissioning framework. (1) Specific treatment selection criteria are detailed in sections 6-10. A prescribing of high-cost biosimilar biological medicines position statement has been approved by GMMMG; see section 11.

2. Aims

The aims of the pathway are:

1. Describe instances where the use of a particular biologic drug may be preferred over another, based on current safety and efficacy data.
2. Present the evidence for monotherapy (treatment without methotrexate) with rituximab and abatacept in order to enable consistent evidence-based clinical practice and reduce the number of Individual Funding Requests (IFRs) across the region.
3. Advise on use of a subsequent biologic where one treatment line is stopped within one month of initiation due to a severe adverse event (e.g., injection site reaction).
4. Present the evidence and recommendations for dose optimisation where clinically appropriate
5. To encourage clinicians to enrol patients into clinical trials/studies where appropriate.
6. To support the use of cost-effective options by promoting the most appropriate tariff-excluded drug at each stage, e.g., best value biosimilars.

3. NICE guidance

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. (2)

Any new high-cost drugs or biologics that are approved between GMMMG RA pathway iterations will be considered for inclusion in this pathway. The use of any new high-cost drugs or biologics should be in accordance with the associated NICE TA and can be considered as an alternative, not additional to, the number of drugs allowed as monitored approval within the pathway.

NICE rheumatoid arthritis pathways overview

3.1 Monoclonal antibodies and fusion proteins

- NICE TA375 (Jan 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 (Aug 2010): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
- NICE TA415 (Oct 2016): Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
- NICE TA225 (June 2011): Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs
- NICE TA247 (Feb 2012): Tocilizumab for the treatment of rheumatoid arthritis

- NICE TA485 (Nov 2017): Sarilumab for moderate to severe rheumatoid arthritis
- NICE TA715 (July 2021): Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed

3.2 Janus kinase (JAK) inhibitors

Janus kinase (JAK) inhibitors are a relatively new class of drug introduced in 2017. They are orally available disease-modifying anti-rheumatic drugs (DMARDs) with similar efficacy to biologics. (3; 4)

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

3.3 Management of moderate rheumatoid arthritis

NICE have now approved filgotinib (Feb 2021) and adalimumab, etanercept and infliximab (July 2021) and upadacitinib (Nov 2021) for use in moderate disease (DAS 3.2 to 5.1) following failure of two or more conventional DMARDs (see flowchart in section 9-10).

4. Sequential use of high-cost drugs

- The core high-cost drugs for rheumatoid arthritis currently have seven different molecular targets (e.g., TNFα, IL-6), or have varying affinity or avidity where the target is the same.
- Lack of response to one high-cost drug in the management of rheumatoid arthritis is not predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class. (5)
- Although all high-cost drugs are highly efficacious in the short term, annual attrition is expected. Changes to therapy are likely to be required for longer term disease control for what is a life-long condition.
- Consideration can be given to escalating the dose of the high-cost drug therapy in adults where there is evidence to support safety and efficacy, there is no financial cost to the NHS, and when an inadequate primary response may be due to insufficient drug dosing. For example, in obese patients or when rheumatoid arthritis relapses during the treatment cycle. See section 5.2 for statement on the available evidence.
- Evidence for the sequencing of high-cost drugs for RA is limited. This pathway offers advice on situations where agents may be most beneficial, based on the most recent available national and international guidance.
- Where available, enrolment in a suitable registry or clinical trial is encouraged so that specific information about these treatments in rheumatoid arthritis can be captured.

5. Drug considerations and positioning

Systemic biological therapies and Janus kinase inhibitors are reserved for when a patient's rheumatoid arthritis has an inadequate response to conventional DMARDs, or these options are contraindicated or not tolerated.

There are numerous factors which influence the choice of drug at each point in the pathway. The choice should be made on an individual basis after discussion between the patient and their clinician about the advantages and disadvantages of the treatments available. Where more than one agent is clinically appropriate the most cost-effective drug should be chosen, in line with NICE guidance. Clinicians should contact pharmacy for advice on the relative cost-effectiveness of these drugs. See sections 6-10 for a flowchart summarising the treatment pathway.

5.1 First line biologics

Where multiple treatment options are clinically suitable the least expensive drug, when all factors are considered, should be chosen.

Consider patient factors such as extra-articular manifestations, device, dexterity, dose frequency, route of administration, likely adherence, co-morbidities, weight, and drug history.

Treatment should be reviewed to assess efficacy at 3-6 months as per NICE guidance or where clinically appropriate, and thereafter every 6 months. See flowcharts in sections 6-10 for a summary of the treatment pathway.

5.2 Alternative dosing of high-cost drugs

Dose escalation/descalation or optimisation is licensed for several drugs:

Drug	**Standard dose**	**Alternative dose** (6)
Adalimumab	40 mg every 2 weeks	40 mg every week, or 80 mg every 2 weeks, based on adequate response, drug level and/or antibody where appropriate
Abatacept IV	500mg, 750mg, 1000mg as per body weight every 4 weeks	N/A
Abatacept SC	125mg once weekly	N/A
Certolizumab pegol	200 mg every 2 weeks	400 mg every 4 weeks
Etanercept	50mg once weekly	25 mg twice weekly
Infliximab IV	3 mg/kg every 8 weeks	3 mg/kg up to every 4 weeks OR up to 7.5 mg/kg (in 1.5 mg increments) up to every 8 weeks, drug level and/or antibody where appropriate
Infliximab SC	120mg every 2 weeks	N/A
Golimumab	50 mg monthly	100 mg monthly, in patients >100 kg who do not achieve an adequate response after 3-4 months at 50 mg.
Tocilizumab SC	162 mg every week	Following dose interruption due to laboratory abnormalities, dosing may resume at 162 mg every other week in some cases.
Tocilizumab IV	8mg/kg every 4 weeks	Following dose interruption due to laboratory abnormalities, dosing may resume at 4mg/kg every 4 weeks in some cases.
Sarilumab SC	200mg every 2 weeks	Following dose interruption due to laboratory abnormalities, dosing may resume at 150mg every 2 weeks in some cases
Baricitinib	4 mg once daily	2 mg once daily, may be considered once sustained disease control achieved and for patients over the age of 75yrs old.
Tofacitinib	5 mg twice daily or 11 mg MR once daily	Patients taking 5 mg twice daily may switch to 11 mg once daily modified release
Filgotinib	200mg once daily	100mg once daily is recommended for patients aged over 75yrs old and moderate to severe renal impairment (eGFR 15-60mL/min). Not recommended eGFR <15ml/min
Upadacitnib	30mg once daily	Upadacitinib 15 mg once daily should be used with caution in patients with severe renal impairment. Upadacitinib 30 mg once daily is not recommended for patients with severe renal impairment.
Rituximab	1gram 2 doses 2 weeks apart at least every 6 months	Doses of 500mg 1 doses 2 weeks apart or 1 dose of 1gram can be used at least every 6 months

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

5.3 Treatment failure

The available guidance recommends considering changing to an alternative high-cost drug in adults if treatment fails due to inefficacy or adverse events. For the purposes of this pathway, this will be taken to include:

1. Primary failure: the rheumatoid arthritis does not respond adequately to a first high-cost drug within the timescales defined in the respective NICE technology appraisals (see section 3) **or**
2. Secondary failure: the rheumatoid arthritis initially responds adequately within the timescales defined by NICE, but the patient subsequently loses this response, **or**
3. The first high-cost drug cannot be tolerated or becomes contraindicated.

Where patients discontinue a drug for one of the following reasons, this will not be regarded as one of the sequential options in the patient's pathway:

- adverse effects or contraindications become evident during the first six months
- newly identified safety issue during successful treatment leads to a newly identified contraindication
- patient becomes pregnant (see section 13b)
- patient is switched to a biosimilar during successful treatment, as part of a switching programme

5.4 Choosing an alternative biologic

The choice of alternative high-cost drug should be made on the same principles as the first choice (see section 5.1).

6. GM HCD Pathway for severe rheumatoid arthritis: first choice high-cost drug in combination with methotrexate DAS28 > 5.1

Box 1: Available drugs, and factors affecting drug choice

Where multiple treatment options are clinically suitable the least expensive drug, all factors considered, should be chosen. All bDMARDs and JAK inhibitors may increase infection risk. In some cases (e.g., interstitial lung disease) careful assessment and systematic monitoring (see published algorithm (26)) is required, and respiratory opinion is advised. Consider IV or oral option if needle phobia, adherence issues, or severely impaired manual dexterity.

Adalimumab:	SC. Licensed & NICE-approved in psoriasis (TA146), Crohn's (TA187), UC (TA329), hidradenitis suppurativa (TA392), uveitis (TA460).
Certolizumab pegol:	SC. Consider first line in women who are pregnant or breast-feeding, or who are likely to become pregnant during treatment (6; 9)). Licensed in US (but not UK) for Crohn's.
Etanercept:	SC. 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. (8; 32)
Infliximab:	IV & SC. NICE-approved in psoriasis (TA134), Crohn's (TA187), UC (TA329). Some evidence for efficacy in uveitis (BSR guidance, no license).
Golimumab:	SC. NICE-approved in UC (TA329). Consider for use in patients weighing >100kg (higher dose licensed in this population).

Consider first line if SLE / connective tissue disease (8) (see also NHSE policy: rituximab in SLE), chronic heart failure stage 3 (except rituximab) (6), Felty's syndrome (30; 29; 31), rheumatoid vasculitis (8), history of de-myelinating disease (5), ILD (38)

Rituximab:	IV. Consider first line (with or without MTX) if recent history of lymphoma/lymphoproliferative disease (8) or latent TB with contraindications for chemoprophylaxis (33) or seropositive for CCP or RF.
Abatacept:	IV & SC. (with or without MTX). Consider if injection site reactions to anti-TNFs. Consider if patient previously hospitalised with infection while on anti-TNFs, (8; 32) or seropositive for CCP or RF. (15; 16; 17; 18)
Sarilumab:	SC As for tocilizumab (see below), except giant cell arteritis US licence.
Tocilizumab:	IV & SC. Consider if symptoms of IL-6-mediated disease (e.g. high ESR/CRP, anaemia of chronic disease, high ferritin) (34), AA amyloidosis (35; 36). Use with caution in diverticular disease (6). Giant cell arteritis (TA518)

[o]
Associated with increased risk of herpes zoster infection and VTE/PE. Note MHRA alert Tofacitinib

Baricitinib:	NICE-approved in atopic dermatitis (TA681)
Filgotinib:	TA676
Tofacitinib:	NICE-approved in ulcerative colitis (TA547).
Upadacitinib	TA665

Box 2: Abbreviations

- cDMARD – conventional DMARD (methotrexate, sulfasalazine, etc)
- bDMARD – biological DMARD (adalimumab, infliximab, etc)
- JAK inhibitors – Janus kinase inhibitors (tofacitinib, baricitinib, etc)
- ADAb – anti-drug antibodies
- MTX - methotrexate

Active disease despite intensive therapy with combination of cDMARDs

- See section 19 for high-cost drug screening questions for pre-admission
- At any stage: consider entry to a trial or registry (where criteria are met)
- At all stages: review applicable patient factors, e.g., device, dexterity, dose frequency, route of administration, adherence, co-morbidities, weight, drug history
- At all stages: Stopped due adverse effects/side effects within 1st 6 months – not accounted as line of therapy

↓

At all stages

- bDMARDs should be given in combination with MTX, unless MTX contraindicated or withdrawn due to adverse events. See section 8 for advice on bDMARDs as monotherapy.
- If patient also has psoriasis or inflammatory bowel disease, use a biologic that is approved for use by the appropriate GMMMG High-Cost Drugs Pathway.

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First line (biologic-naive): choose based on clinical factors (see box 1)

↓

Review at 3-6 months, as per NICE guidance or as clinically appropriate

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Adequate response
Assessed as per NICE guidance. Advice varies with drug and treatment stage, but generally either:

- Reduction in DAS28 of ≥1.2 (more info here) **or**
- EULAR criteria met (more info here)

See also: DAS28 scores for EULAR response

↓

Continue treatment
Review every 3-6 months.
For patients in sustained remission on biologic + cDMARD (once steroids tapered & stopped) consider dose tapering, in discussion with the patient.
This may be achieved by reducing the dose or increasing the dose interval. (6; 37; 21; 20; 22)
Return promptly to previous regimen if treatment target no longer met (19)

→

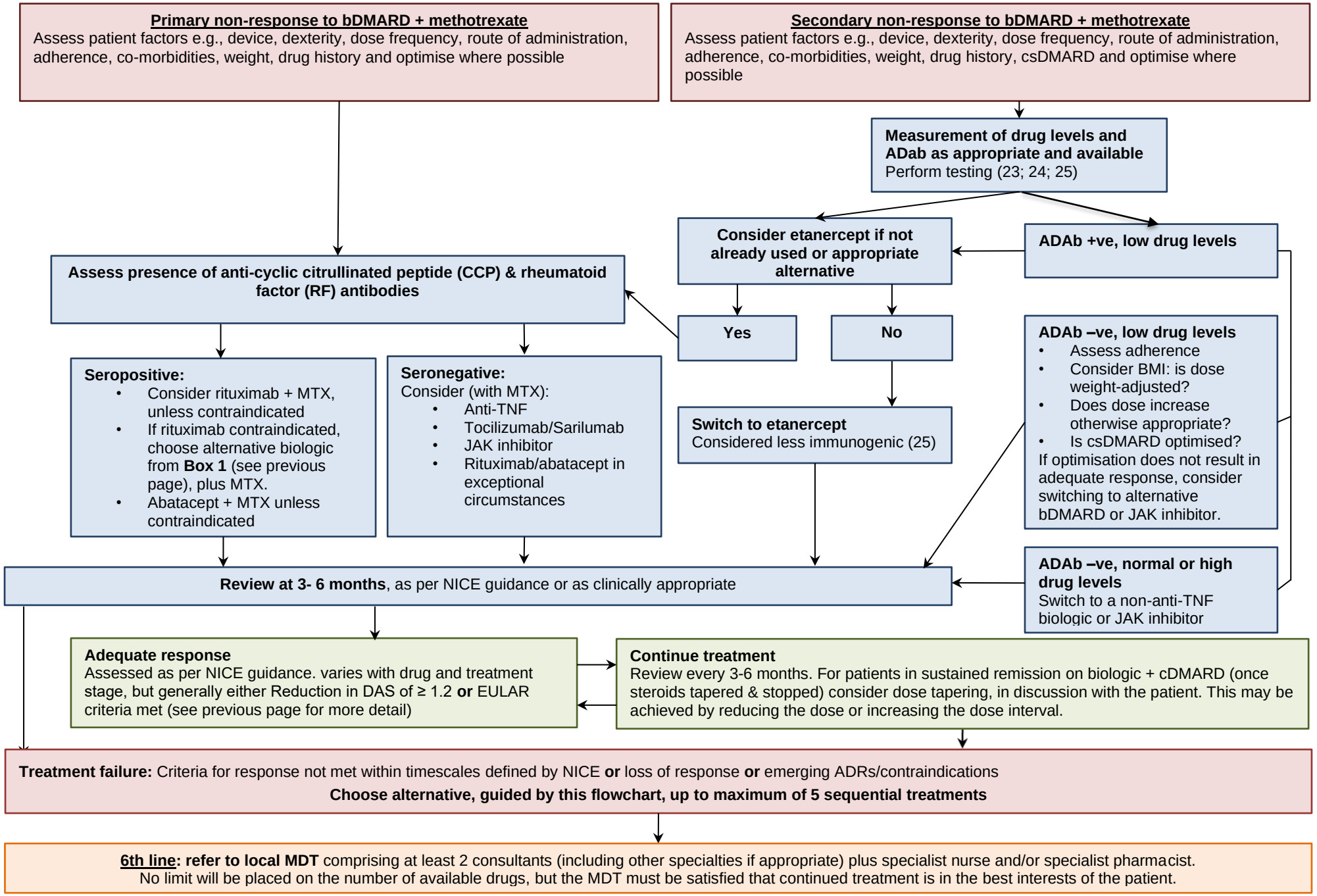
Secondary failure

- Loss of response after 3-6 months
- Emerging ADRs

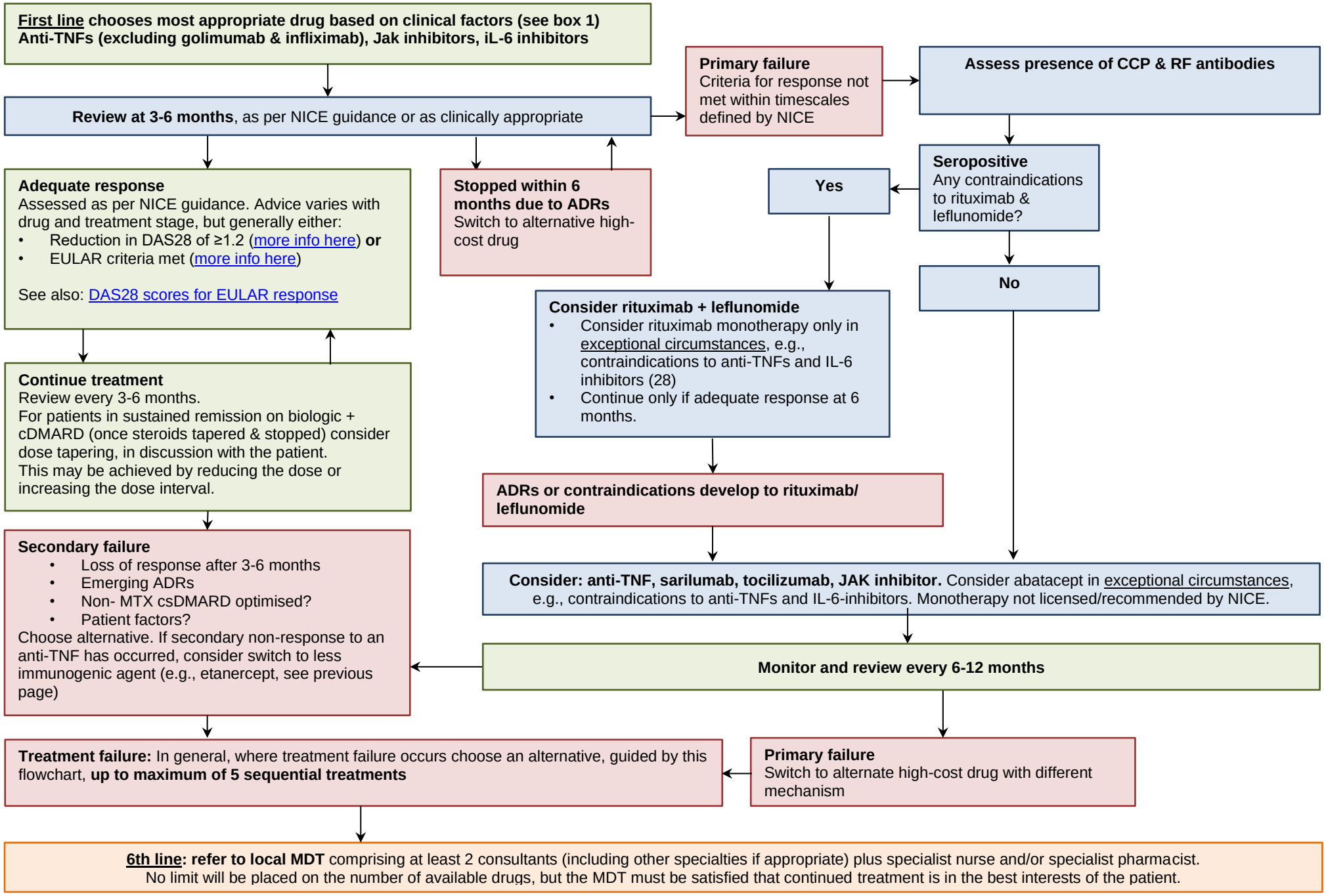
Go to next page: secondary non-responders

Primary failure
Criteria for response not met within timescales defined by NICE
Go to next page: primary non-responders

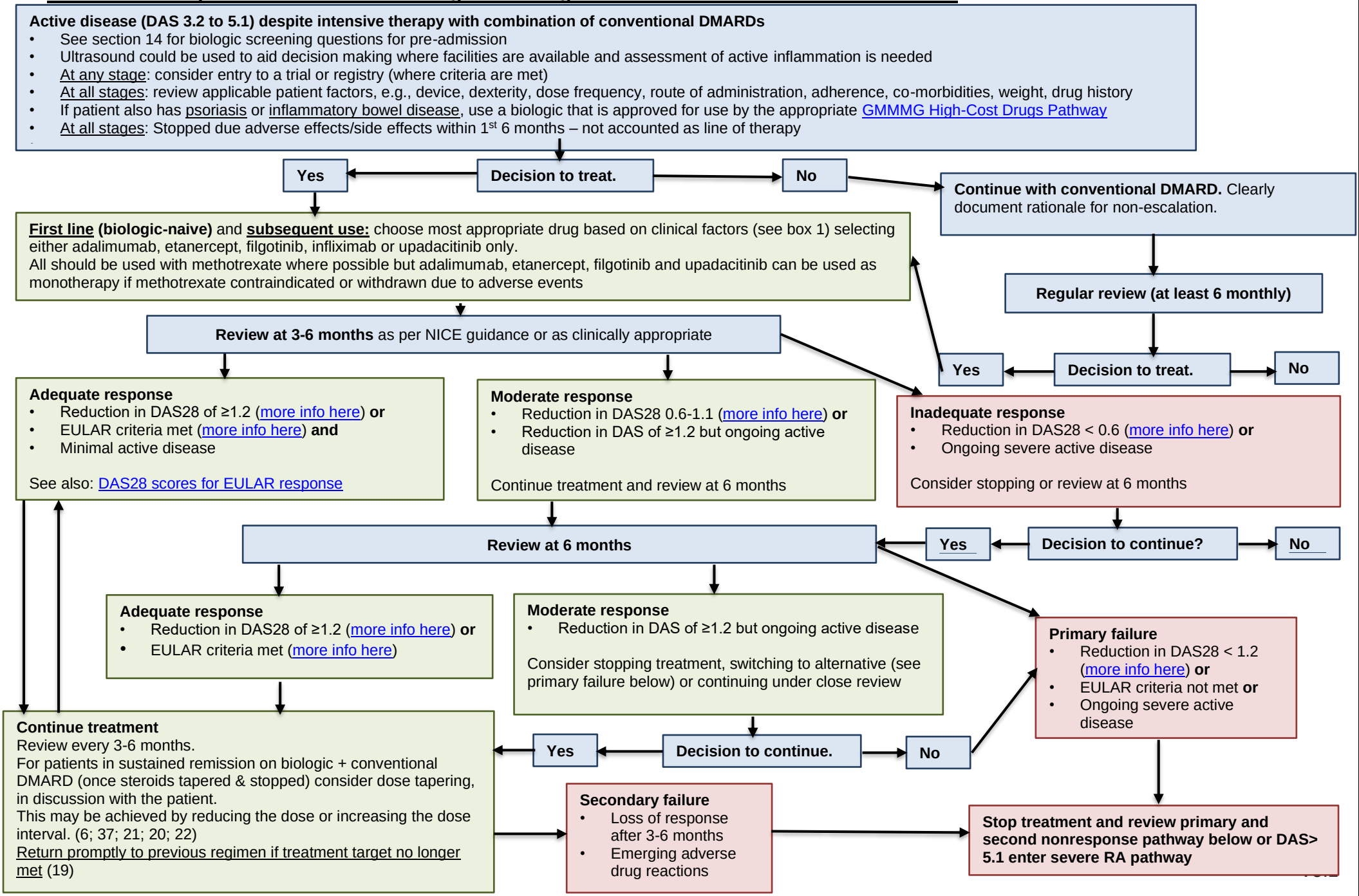
7. GM HCD Pathway for severe RA: second and subsequent high-cost drug in combination with methotrexate



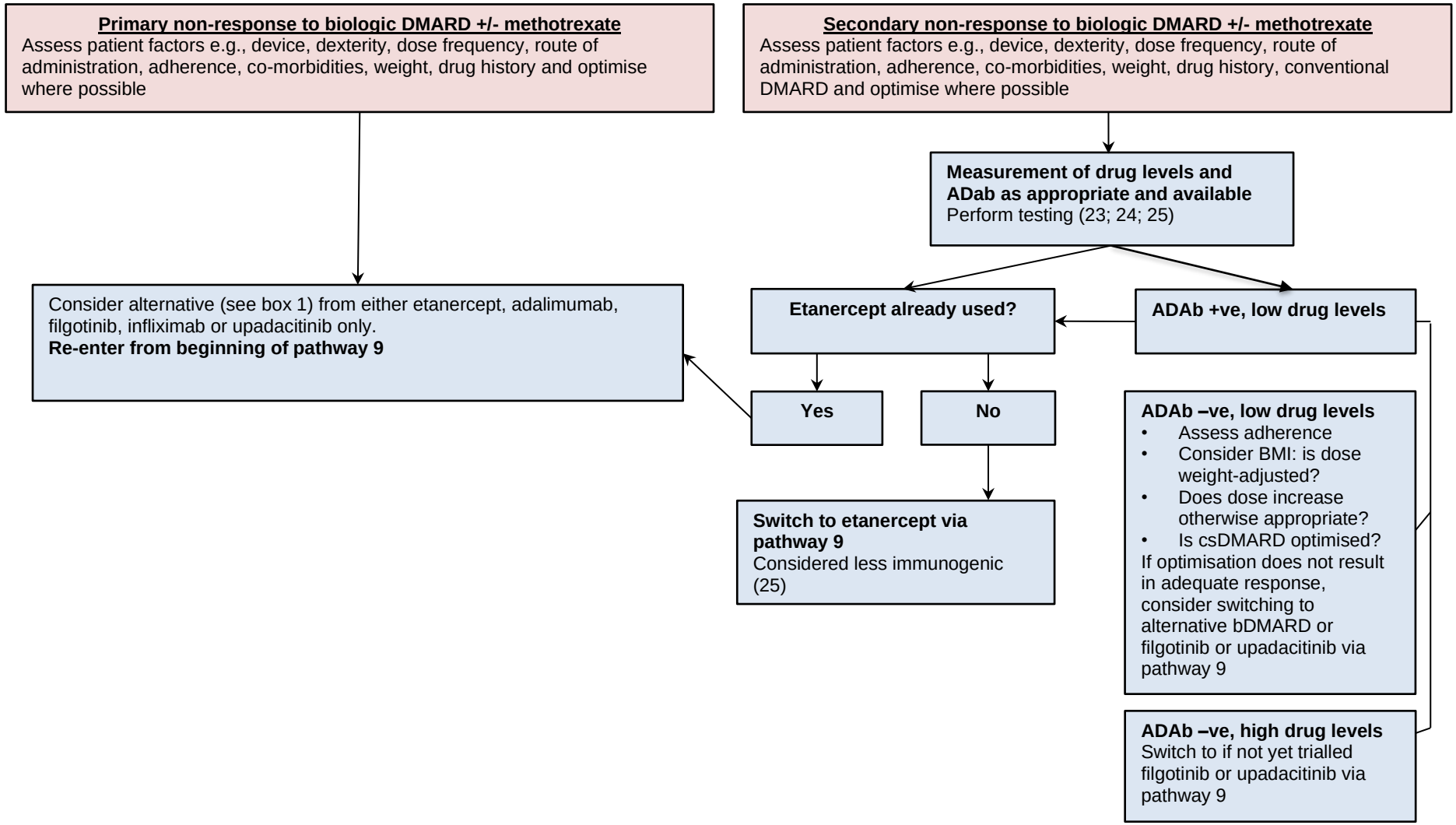
8. GM HCD Pathway for severe RA: use of high-cost drug as monotherapy (no csDMARD or non-methotrexate csDMARD)



9. GM HCD Pathway for rheumatoid arthritis: High-Cost Drug for use in moderate disease DAS 3.2 to 5.1



10. GM HCD Pathway for rheumatoid arthritis in moderate disease DAS 3.2 to 5.1: second and subsequent high-cost drug



11. Biosimilars

GMMMG has approved a Prescribing of high-cost biosimilar biological medicines position statement which makes the following recommendations:

11.1 Initiating treatment with a high-cost drug

- **If more than one treatment is suitable, the least expensive should be chosen** (considering administration costs, dosage and price per dose).
- If the least expensive product is not prescribed, the reasons why must be documented on the Blueteq form where applicable and made available to commissioners if required.
- Where NICE has already recommended the originator high-cost medicine, the same guidance will apply to the biosimilar medicine.
- In line with MHRA guidelines: high-cost drugs, including biosimilars, must be prescribed by brand name to support on-going pharmacovigilance of the individual products.

11.2 Changing from originator to a biosimilar

- 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.
- There is not enough evidence at present to endorse switching between biosimilars brands.

12. Contraindications, special warnings and precautions

a. 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, which is beyond the scope of this guideline. For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis

12.2 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.

13. Pre-biologic screening

Please refer to the checklist provided at the end of the document (section 19), which can be adapted locally if necessary.

b. Tuberculosis

Interferon gamma (gIFN) testing is recommended in patients at risk of TB pre-biologic/JAK treatment. In patients with high index of suspicion/risk of TB consider referring to previously published algorithms for additional screening (7) 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 TB reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). (8) 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 is currently lacking. (8)

c. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic/JAK, particularly rituximab (see: MHRA Drug Safety Update (Dec 2013) Rituximab: screen for hepatitis B virus before treatment)BSR guidance recommends that screening should include: (8)

- Hepatitis B: screen for HBsAg and antibodies to hepatitis B core antigen (anti-HBc) and surface antigen (anti-HBs), 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 bDMARD may be appropriate but should follow a risk/benefit decision made with a hepatologist.

d. HIV Testing

Screening for HIV is recommended for all patients starting a biologic/JAK. NICE Quality Standard QS157 (Sept 2017) recommends young people and adults are offered an HIV test 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 biologic/JAK therapy in HIV positive patients, this should be discussed with an HIV specialist.

13. Special Situations

a. Peri-operative 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.
In all cases rheumatology consultant should be involved. High-cost drugs should be recommenced after surgery when there is evidence of good 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 peri-operative guidelines where applicable.

High-Cost Drug	Dosing Interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One half-life, days	Five half-lives, days
Adalimumab	Every 2 weeks	Week 3	14	70
Abatacept IV	Monthly IV	Week 5	14	70
Abatacept SC	Every week	Week 2	14	70
Certolizumab pegol	Every 2 weeks Every 4 weeks	Week 3 Week 5	14	70
Etanercept	Weekly or Twice Weekly	Week 2	3	15
Filgotinib	Once daily	Week 1 (longer duration of pharmacodynamic activity compared to the half-life)	19 hours	4 days
Golimumab	Every 4 weeks	Week 5	14	70
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9	45
Infliximab SC	Every 2 weeks	Week 3	14	70
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4-7	18	90
Toclizumab IV	Every 4 weeks 4mg/kg 8mg/kg	Week 5	 11 13	 55 65
Tocilizumab SC	Every week	Week 3	13	65
Sarilumab SC	Every 2 weeks			
Baricitinib	Once daily	Week 1 (longer duration of pharmacodynamic activity compared to the half-life)	13 hours	3 days
Tofacitinib	Twice daily	Week 2 (longer duration of pharmacodynamic activity compared to the half-life)	3 hours	15 hours
Tofacitinib MR	Once daily	Week 2 (longer duration of pharmacodynamic activity compared to the half-life)	6 hours	30 hours
Upadacitinib	Once daily	Week 1 (longer duration of pharmacodynamic activity compared to the half-life)	14 hours	3 days

* BSR guidance recommends that IV tocilizumab should be stopped at least 4 weeks prior to surgery, and SC tocilizumab should be stopped at least 2 weeks prior to surgery. (8)
** 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.

b. Pregnancy

There are limited data on the safety of biologic/JAK inhibitors drugs in pregnancy and lactation. 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.

Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks stated in the relevant SPCs after treatment has stopped (see table below). Patients who stop therapy during pregnancy may, if needed, be re-loaded with biological therapy soon after delivery.

Use of a biologic therapy is not necessarily an absolute contraindication during pregnancy or breast-feeding,

but case-by-case risk assessment is required for each patient. Consider certolizumab for first line use in women who are pregnant or breast-feeding, or who are likely to become pregnant during treatment. See SPC for more information.

The British Society of Rheumatology issued guidance on prescribing of drugs in pregnancy and lactation in January 2016. (9) The following is adapted from that guideline, but prescribers should be aware that guidance may change over time as the evidence base evolves.

Drug	Time to continue contraception after treatment cessation (6)	Compatibility with trimesters (9)		
		First	Second	Third
Abatacept	14 weeks	No	No	No
Adalimumab	5 months	Yes	Yes	No
Certolizumab pegol	5 months	Yes	Yes	Yes
Etanercept	3 weeks	Yes	Yes	No
Golimumab	6 months	No data	No data	No data
Infliximab	6 months	Yes	Stop at 16 weeks	No
Rituximab	12 months	No	No	No
Sarilumab	3 months	No data	No data	No data
Tocilizumab	3 months	No	No	No
Baricitinib	1 week (SPC) Effects of JAKi may persist after drug elimination, consider stopping >1 month pre-conception	No data	No data	No data
Tofacitinib	4 weeks	No data	No data	No data
Upadacitinib	4 weeks	No data	No data	No data
Filgotinib	4 weeks	No data	No data	No data

Further information to support decision-making is available from:

- Summaries of Product Characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at http://uktis.org/html/exposures_abc.html or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (http://www.uktis.org/html/reporting.html) UKTIS are commissioned by Public Health England to perform national surveillance of known and emerging human teratogens across the United Kingdom.

Advice and risk assessment for individual patients may also be available by contacting a local Medicines Information service via Trust pharmacy departments.

c. Breast feeding

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

Information on manufacturers' recommendations on use in lactation is available from the individual Summaries of Product Characteristics (available from www.medicines.org.uk). Further information may be available from the Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk and in the BSR guidance on prescribing of drugs in pregnancy and lactation (January 2016).

Advice and risk assessment for individual patients may also be available by contacting a local Medicines Information service via trust pharmacy departments.

d. Vaccination of Infants

If a biologic has been continued in pregnancy after 16 weeks gestation live vaccines should be avoided in the infant until they reach 6 months of age, after which time vaccination should be considered. The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (10)

- Rotavirus - all infants

- Tuberculosis - infants living in areas of the country with incidence ≥40/100,000, and infants with a parent or grandparents born in a country with incidence ≥40/100,000 (11)

Rotavirus is the most common cause of gastroenteritis in infants in the UK. (12) Although there is limited evidence of safety and efficacy in infants with immunosuppression the vaccine may be considered by the treating consultant following careful consideration of the risks and benefits and following specialist consultation as appropriate. This does not include infants with severe combined immune deficiency.

If breastfeeding, the BCG vaccination should not be given until 6 months after finishing breastfeeding. For advice on other live vaccinations following exposure to biologics in breast milk, healthcare professionals should contact the relevant specialist for advice.

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. (9)

14. 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.

a. 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.

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

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 in section 13 above, page 15. For further relevant summaries of products characteristics, www.medicines.org.uk (5)

- the Green Book, https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book (13)
- Specialist advice

Live Vaccine	Brand Name
BCG	Bacillus Calmette-Guerin Vaccine
Nasal Influenza	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	Stamaril®

b. 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. (13)

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

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of high-cost drug treatment, with reference to Department of Health Guidance. (9, 12) During high-cost drug treatment, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once.

15. Data requirements and audit

Full clinical details regarding patients on high-cost drugs disease scores at initiation and continuation, reasons for change of treatment and all previously tried drugs must be made available to commissioners. This is expected to be via Blueteq, where commissioned.
All use of drugs in line with this pathway will be monitored in line with the accompanying monitoring framework. The Greater Manchester Subgroups will provide assurance on the commissioned pathways to the Greater Manchester Medicines Management Group (GMMMG).

a. Blueteq

Blueteq forms which comply with this pathway are available. Where Blueteq has been introduced to the Trust as part of the contractual arrangements, funding approval for the PbR excluded high-cost drugs will be made by meeting the accepted criteria outlined on completion and submission of a Blueteq form.

b. Route of supply

Opportunities to supply biologics (and non-biologic PbRe drugs) via VAT-exempt routes should be maximised where appropriate.

16. Individual Funding Requests (IFR)

- Up to five high-cost drugs for treatment of rheumatoid arthritis will be routinely commissioned, if prescribed in accordance with this pathway. Sixth and subsequent high-cost drugs will require discussion and approval by a multi-disciplinary team comprising at least two consultants (including other specialties as appropriate), a specialist nurse and/or a specialist pharmacist. No limit will be placed on the number of available drugs, but the MDT must be satisfied that continued treatment is in the best interests of the patient. IFRs will not be required but, where available, Blueteq forms must be completed, and MDT approval must be documented. See section 15, above.
- All other treatment options outside of this pathway will require an IFR to be approved prior to treatment being started. When submitting an IFR, exceptionality should be demonstrated; exhausting the treatment options in this pathway does not automatically establish exceptionality.
- IFRs must include details of all previous treatments with responses and reasons for discontinuation.

17. Free of Charge Schemes

All free of charge schemes should be approved in accordance with trust guidance and GMMMG Free of Charge guidance. (13) 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.

18. Research Recruitment

18.1 Clinical trials

Where possible, consideration should be given to entering patients into observational/clinical studies. Some sites host early and later phase clinical trials of biologic therapies, both biologic naïve and biologic experienced. Active trials may be listed on the NIHR website.

18.2 High-cost drug registers

Clinicians are strongly encouraged to offer people with rheumatoid arthritis who are starting treatment with a systemic non-biological or biological drug the opportunity 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/.

19. Checklist for patient screening on selection for high-cost drug agents

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* * 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/Jak inhibitors	**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 [21])*				
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 and funding				
Blueteq form completed/request for funding				
Pregnancy/breastfeeding advice given				
Vaccination advice given				
Patient counselled and educated				
Patient consent to be approached for research				

20. Specific monitoring considerations

See screening questionnaire (section 19, above) for full details of baseline monitoring that should be performed in all patients. 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. (8) Additional monitoring is recommended for some biologics and for the JAK inhibitors, as described below.

20.1 Tocilizumab and sarilumab

<table>
<tr><td colspan="3">FBC (monitoring of absolute neutrophil count [ANC] and platelets) (6; 8)</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:
o IV tocilizumab: before the next scheduled infusion
o SC tocilizumab 3 days before every fourth injection</td></tr>
<tr><td rowspan="9">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) (6; 8)</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 FBC 4-8 weekly for the 1st 6 months then every 12 weeks thereafter. Timing of these tests should ideally be
o IV tocilizumab: the week before the next scheduled infusion
o SC tocilizumab 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 (6; 8)</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. (8)
• 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>

19.1 Rituximab

Serum immunoglobulins (6; 8)	
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.

19.2 JAK inhibitors

19.3.1 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) (6)		
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 10 mg BD: reduce dose to 5 mg BD ○ 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 10 mg BD: reduce dose to 5 mg BD ○ 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	

19.3.2 Baricitinib, Filgotinib, Upadacitinib

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (6)		
Recommended monitoring	• Check FBC at baseline, 4-8 weeks after initiating treatment, and 3-monthly thereafter	
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	
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. Upadacitinib 30 mg once daily is not recommended for patients with severe renal impairment.	

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