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Norfolk and Waveney Integrated Care System

Rheumatoid Arthritis: High-Cost drug Treatment Pathway 2023

Norfolk and Waveney Integrated Care System

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2. Document Control Sheet

Name of document:	Rheumatoid Arthritis: High-Cost drug Treatment Pathway 2023
Description of policy	NWICB high-cost drug pathway for Rheumatoid Arthritis
Version	1
Scope	
Prepared by	Medicine optimisation team With input/advice from specialists at NNUH, QEH & JPH
Impact Assessment (Equalities and Environmental)	
Other relevant approved documents	
Evidence base / Legislation	Level of Evidence: ~~A. based on national research-based evidence and is considered best evidence~~ **B. mix of national and local consensus** ~~C. based on local good practice and consensus in the absence of national research based information.~~
Dissemination	Is there any reason why any part of this document should not be available on the public web site? ~~Yes~~ / **No**
Approved by	N&WICB Therapeutics advisory group
Authorised by	N&WICB Therapeutics advisory group
Review date and by whom	July 2025
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2.1 Revision History

Revision Date	Summary of changes	Author(s)	Version Number
22/07/2022	Draft summation of locally agreed commissioning decisions for RA with supporting information	A. Charlwood, M Sully	0.1
13/10/2022	Added version control, amended as per S. Bingham comments.	As above & specialist input	0.2
08/02/2023	Added summary document, included supporting biologic use information	As above	0.3
18/05/2023	Minor amendments to summary document, update to include MHRA waring	As above	0.4
30/06/2023	Added Adalimumab biosimilar weekly dose escalation as agreed locally. Agreed by TAG.	As above	1

2.2 Approvals

This document requires the following approvals either individual(s), group(s) or board.

Name	Title	Date of Issue	Version Number
Norfolk & Waveney ICB Therapeutics Advisory Group		07/06/2023	1.0

3. Introduction

3.1 Relevant NICE technology Appraisals

Technology Appraisal	Title
TA195	Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
TA225	Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs
TA247	Tocilizumab for the treatment of rheumatoid arthritis
TA375	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
TA415	Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
TA466	Baricitinib for moderate to severe rheumatoid arthritis
TA480	Tofacitinib for moderate to severe rheumatoid arthritis
TA485	Sarilumab for moderate to severe rheumatoid arthritis
TA665	Upadacitinib for treating severe rheumatoid arthritis
TA676	Filgotinib for treating moderate to severe rheumatoid arthritis
TA715	Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed
TA744	Upadacitinib for treating moderate rheumatoid arthritis

*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.

3.2 Pathway scope

This pathway is to be used to guide the initiation and maintenance of high-cost drugs in the management of Psoriatic arthritis and have been written using up to date published NICE Technology Appraisals (TAs) and evidence-based medicine.

The pathway includes:

- Anti-CD20 MAB: Rituximab
- Anti-TNF: Adalimumab, Certolizumab, Etanercept, Golimumab & Infliximab
- CD80 & CD86 APC Inhibitor: Abatacept
- Interleukin-6 inhibitor: Sarilumab & Tocilizumab
- JAK inhibitors (JAKi): Baricitinib, Filgotinib, Tofacitinib & Upadacitinib

3.3 Background

This document is to provide detailed information for treatment of adult patients with active rheumatoid arthritis (RA), defined as disease activity score (DAS28) of >3.1 for moderate, or >5.1 for severe, requiring specialist treatment beyond that of conventional Disease Modifying Anti Rheumatic Drugs (cDMARDs).

The National Institute for Health and Care Excellence (NICE) has published individual Technology Appraisals (TAs) for licensed systemic biological therapies for rheumatoid arthritis. Biologic DMARDs (bDMARDS) including biosimilars and

targeted synthetic DMARDs (tsDMARDs) are locally commissioned and incorporated into the pathway. tsDMARDs – i.e., Janus kinase (JAK) inhibitors oral DMARDs with similar efficacy to biologics.

Any new high-cost drugs or biologics that are approved between pathway updates will be considered for inclusion in this pathway. The use of any new high-cost drugs or biologics prior to inclusion in the pathway should be in accordance with the associated NICE TA. The TAs below are currently included in the pathway.

4. Pathways

Pathway updates will be conducted on the release of new evidence, TAs, or local commissioning changes. The aims of the pathway for both moderate and severe RA is to:

- Illustrate where the use of a particular biologic drug may be preferred over another, based on current safety and efficacy data.
- Promote most appropriate best value biologic therapy by supporting the use of cheaper therapies and biosimilar drugs.
- Advise on use of a biologic, where one treatment line is stopped within one month of initiation due to severe adverse event (e.g., injection site reaction).

5. Options for treatment for Moderate and Severe RA

Options for treatment must be used in line with local and NICE guidance as noted in the agreed pathways should be made with due consideration of the following:

- **Clinical** - The choice of biologic used should, in the first instance, be guided by clinical judgement based on national or local guidance.
- **Best value** - More than one treatment may be suitable, therefore, the overall value proposition offered by the individual medicines (consider administration costs, dosage and price per dose) This may vary because of differences in how the drugs are used and treatment schedules. Best value may be affected by change in drug costs and the cost-effective drug choice may be revised as a result.
- **Biosimilar** - Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.
- **Funding/ commissioning** - Prior approval through Blueteq is required for all non-biosimilar biologics and JAK inhibitors
- **Prescribing** - In line with MHRA guidelines: biologics, including biosimilars must be prescribed by brand name to support on-going pharmacovigilance of the individual products.
- **Pharmacovigilance** is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the black triangle.
- **Patients** prescribed a biologic should be enrolled on to relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.

The companies must supply the treatments as agreed in their patient access schemes.

5.1 Initiating Treatment

The most appropriate treatment should be chosen after discussing the advantages and disadvantages of the available treatments with the patient. For some people the choice will be driven by co-morbidities.

If more than one drug is suitable, consider the differences in how the drugs are administered and their dosing schedules, and choose the best value treatment for the patient (considering administration costs, dose required and price per dose). When the biologic treatment has been selected, the best value biologic/ biosimilar for the patient should be prescribed by brand.

The rationale for choice should be documented as audit of practice and choices may be conducted.

5.2 First line options

5.2.1 Moderate RA DAS28 >3.2 to ≤5.1

Biosimilar anti-TNF Etanercept, Adalimumab, Infliximab, as the likely least costly treatment option where a biologic is required, should be considered

5.2.2 Severe RA DAS >5.1

Biosimilar anti TNF Etanercept, Adalimumab, Infliximab or Rituximab (where anti-TNF is contraindicated or cautioned), as the likely least costly treatment option where a biologic is required, should be considered. Golimumab may also be considered as a best value option

5.2.2.1 Severe RA additional information

Certolizumab is the biologic of choice in women who have severe RA and planning pregnancy, during pregnancy and postnatally when breastfeeding (first three months injection free). Abatacept (SC) with methotrexate has been agreed for restricted use locally as an alternative agent where all other best value products are unsuitable for use first line in Severe RA.

6. Assessing Response and Continuation of treatment

Switching is permitted within NICE during the first 12 weeks of treatment where intolerance or side effects emerge and at this stage will not count as an additional line of treatment. Treatment should be continued only if there is an adequate response measured using European League Against Rheumatism (EULAR) criteria, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

An adequate response is defined as a moderate improvement in DAS28 as per table below, unless otherwise stated in the individual TA.

Current DAS28 Score	DAS28 Improvement		
	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	Good	Moderate	No response
>3.2 and ≤ 5.1	Moderate	Moderate	No response
> 5.1	Moderate	No response	No response

Continue treatment only if there is a moderate response at 6 months after starting therapy. If this initial response is not maintained, stop treatment, and consider alternative treatment as per NICE guidance and locally agreed commissioned pathway for both moderate and severe RA.

6.1 Primary Failure

Patient does not demonstrate a moderate response to therapy in DAS28 (as defined by EULAR in Table 2) following 6 months of treatment.

6.2 Secondary Failure

Patient initially achieves a moderate response to therapy in DAS28 (as defined by EULAR in Table 2) at 6 months post-initiation, which is subsequently not sustained, resulting in failure to maintain a moderate reduction in DAS28.

6.3 Subsequent Treatment

As disease activity is regulated by cytokines, switching between anti TNF agents where one fails over time in:

- **Moderate disease** - The scope for the appraisal in TA715 includes only first-line use of biological DMARDs. Cycling of tumour necrosis factor (TNF)-alpha inhibitors (taking another TNF-alpha inhibitor after a first one) was not considered if a person does not tolerate the first treatment, or if their disease either does not respond or responds inadequately after an initial response. Clinical experts did acknowledge and explained that the cycling of TNF-alpha inhibitors has a place in treating rheumatoid arthritis and that it was appropriate to assume that after the first biological treatment has failed, if the disease progresses to severe, NICE technology appraisal guidance for severe rheumatoid arthritis would be followed
- **Severe Disease** - is likely to regain disease control (cycling) and is standard clinical practice in severe disease. Switching is permitted in primary failure. At any stage in treatment, if more than one treatment is suitable when switching, the least expensive, best value drug should be chosen (taking into account administration costs, dosage and price per dose).

6.3.1 Moderate RA disease

- **JAK inhibitors** Filgotinib or Upadacitinib may be chosen as an alternative to biologics in moderate and severe disease.
- **All use is subject to external audit If the least expensive product is not prescribed, the reasons why should be carefully documented for audit and a prior approval form completed.**

6.3.2 Severe RA disease

- **Rituximab biosimilar** is recommended as an option to anti-TNF in severe disease unless contra-indicated, where first line option for anti-TNF is contra-indicated, has failed or cycling of TNF-alpha inhibitors has been unsuccessful or not considered appropriate. Rituximab may be used with methotrexate or as monotherapy where methotrexate not tolerated or contraindicated.
- Where Rituximab is contraindicated, the best value biologic agent from Abatacept, Tocilizumab, Sarilumab or Golimumab, should be considered (considering administration costs, dosage and price per dose)
- **JAK inhibitors** Filgotinib or Upadacitinib may be chosen as an alternative to biologics in moderate and severe disease and additionally Tofacitinib and Baricitinib are also available in severe disease, where biologics are contra-indicated or not tolerated. The least expensive best value option should be chosen (considering administration costs, dosage, and price per dose)
- **All use is subject to external audit If the least expensive product is not prescribed, the reasons why should be carefully documented for audit and a prior approval form completed.**

6.4 Adalimumab biosimilar weekly dose escalation (local agreement)

As per local agreement (TAG - May 2023), patients on the usual dose of adalimumab 40mg every 2 weeks subcutaneously, who have experienced loss of efficacy with subtherapeutic trough adalimumab levels. Note, the following exclusions apply:

- patients on the originator (Humira)
- patients who have anti-drug antibodies

Published data is limited, however this approach is becoming increasingly used in practice as an intermediate step – the use will be off label in some circumstances (specifically, in combination with methotrexate), and in these cases should be discussed with the patient and be documented in the patient notes.

6.4.1 Ongoing management

The benefits and risks of continued 40 mg weekly therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week, the dosage may subsequently be reduced to 40 mg every other week.

7. MHRA warnings

7.1 Janus kinase (JAK) inhibitors

There have been several MHRA warnings since 2020 for individual JAK inhibitors. In March 2023 the MHRA released information for risk minimisation which has been previously recommended for tofacitinib & upadacitinib, would now apply to all JAK inhibitors. Points of interest[3] include:

- following a review, these risks are considered class effects across JAK inhibitors used for chronic inflammatory disorders and therefore it is advised to avoid prescribing these medicines unless there are no suitable alternatives in patients with the following risk factors:
    - age 65 years or older
    - current or past long-time smoking
    - other risk factors for cardiovascular disease or malignancy
- use caution if prescribing in patients with risk factors for VTE other than those listed above (see below for more details)

It is recommended to read the full guidance here for the full details on caution

8. Treatment Options and Individual Funding Requests (IFR)

The CCG commissions treatment, if prescribed in accordance with these pathways, irrespective of the modes of action of previously tried drugs. Switching is permitted within NICE during the first 12 weeks of treatment where intolerance or side effects emerge and at this stage will not count as an additional line of treatment.

Additional options are not routinely funded and will require the submission of an IFR request where clinical exceptionality can be demonstrated. Further information found on Knowledge Anglia.

Note: Dose escalation outside of local commissioning agreement requires IFR.

9. Blueteq

Blueteq forms are available for use with these pathways as agreed within commissioning decisions. Funding approval for these payments by results excluded high-cost drugs will be granted on completion and submission of these forms for patients meeting the accepted criteria.

10. Changing from originator to a biosimilar where appropriate

Patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. There should be:

- Discussion and agreement with individual patients with an explanation for the reason for changing.
- Change from a biologic originator medicine to a biosimilar for a patient ONLY at the point of prescribing.
- No automatic substitution of a biologic with a biosimilar at the point of dispensing.

11. Route of administration & dose frequency

Biologic treatments are available as IV infusion, subcutaneous injection or oral preparations. Best value treatment options should be selected. SC Tocilizumab and Abatacept are preferred over IV. Once a loading dose has been given, the SC injections are delivered to the patient by Homecare, so VAT is not payable. Infliximab S/C injection is not yet commissioned locally. Rituximab is administered by IV infusion at a minimum 6-month interval and attracts a day case rate.

Drug	Route of administration commissioned	Frequency post loading	Biosimilar available	TA	Blueteq
Abatacept	SC & IV	Every week	No	195,375	Yes
Adalimumab biosimilar	SC injection	Every 2 weeks	Yes	195,375,715	Combined with Etanercept
Baricitinib	Oral	4mg daily	N/A	466	Yes
Certolizumab	SC injection	Every 4 weeks	No	375	Yes
Etanercept biosimilar	SC injection	Twice per week	Yes	195,375,715	Combined with Adalimumab
Filgotinib	Oral	200mg daily	N/A	676	Yes
Golimumab	SC injection	Every 12 weeks	No	225	Yes
Infliximab biosimilar	IV infusion	Every 8 weeks	Yes	195,375	Yes
Rituximab biosimilar	IV infusion	Every 6 months	Yes	195,375	Yes
Sarilumab	SC injection	Every 2 weeks	No	485	Yes
Tocilizumab	IV infusion & SC injection	Every 4 weeks	No	247,375	Yes
Tofacitinib	Oral	5mg BD	N/A	480	Yes
Upadacitinib	Oral	15mg daily	N/A	665,744	Yes - draft

12. Treatment Options for Moderate Rheumatoid Arthritis [DAS28] of >3.2 to ≤5.1

12.1 Biologics and Janus Kinase inhibitors (JAK)

Patients with moderate disease (DAS28 > 3.2 & ≤ 5.1), following an inadequate response to intensive therapy with TWO or more cDMARD therapy, may access the below biologic agents and targeted synthetic DMARDs. The companies are to provide drugs according to the commercial arrangement.

Treatment should be continued only if there is a moderate response compared to baseline measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

- For patients who have an inadequate response i.e., a reduction of DAS28score ≤ 0.6 compared to baseline or adverse effect a switch to an alternative agent, (ideally with a different mode of action)
- If this initial response is not maintained at 6 months, treatment should be stopped.

For patients that respond initially to their first line biologic but have secondary failure after six months of treatment the patient is eligible to switch to an alternative therapy in line with the pathway (see Appendix 1). If the moderate RA pathway fails, when patient has DAS28 >5.1, treat as per Appendix 4.

12.2 Relevant NICE technology appraisals[1]

Ref	Link to relevant NICE technology appraisal
TA676	Filgotinib for treating moderate to severe rheumatoid arthritis
TA715	Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed
TA744	Upadacitinib for treating moderate rheumatoid arthritis

[1] *For full detail of NICE TA specification see Appendix 5*

13. Treatment Options for Severe Rheumatoid Arthritis, DAS28 of >5.1

13.1 Biologics and JAKs

Following an inadequate response to intensive therapy with TWO or more cDMARDs, patients may access the below biologic agents and targeted synthetic DMARDs (see Appendix 2)

- The companies are to provide drugs according to the commercial arrangement
- Treatment should be continued only if there is a moderate response compared to baseline measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.
- For patients who have an inadequate response (i.e., a reduction of DAS28 $\leq$ 0.6 compared to baseline or an adverse effect) switch to an alternative agent, (ideally with a different mode of action)
- If this initial response is not maintained at 6 months, treatment should be stopped.

For patients that respond initially to their first line biologic but have secondary failure after six months of treatment the patient is eligible to switch to an alternative therapy in line with the pathway (see Appendix 1).

13.2 Rituximab – local decision

- September 2010: The TAG supported a business case from the NNUH for use of Rituximab for severe rheumatoid arthritis (DAS28 >5.1) if the following criteria are met:
    - Failure of two DMARDs including methotrexate **AND**
    - contraindication to anti-TNF therapy.
- This was approved by the NHS Norfolk Drug & Therapeutics Commissioning Programme Board in September 2010

14. Perioperative infection risk management

By temporarily discontinuing a patient's biologic medication, the chance of a post-operative infection should be reduced, but this should be carefully weighed against the risk of a peri-operative flare. Consider halting medication 3-5 half-lives before surgery if there is a high chance of infection or if infection could cause substantial harm. As shown in the table below, some biologics need up to 23 weeks to achieve 3-5 half lives.

Locally, there are joint guidelines for the management of interruption of biologic therapies for elective surgery in adults and children, produced by the rheumatology departments across the NWICB, which suggest a shorter interruption of biologic treatment may be appropriate[4]. For further information refer to the guidance linked.

Biologic	Mean half-life as per SPC	Time to stop treatment prior to surgery (3-5 half-lives)	Local guidelines; Time between last dose and surgery
Tofacitinib	3 hours	1 day	Stop 2 days prior to surgery
Baricitinib	12 hours	1.5-2.5 days	Stop 2 days prior to surgery
Filgotinib	15 hours	1.5-3 days	Stop 2 days prior to surgery
Upadacitinib	12 hours	1.5-3 days	No guidance
Etanercept	3 days	9- 15 days	2 weeks
Adalimumab	2 weeks	6-10 weeks	3 weeks
Certolizumab	14 days	6-10 weeks	3 weeks
Golimumab	12 days	5-9 weeks	No guidance
Infliximab	8-9.5 days	4-7 weeks	5, 7 or 9 weeks
Abatacept	14.3 days (IV) 13.1 days (SC)	6-10 weeks (IV/SC)	5 weeks (IV) 2 weeks (SC)
Tocilizumab	16 days (IV) 14 days (SC)	7-11.5 weeks (IV) 6-10 weeks (SC)	5 weeks (IV) 3 weeks (SC)
Sarilumab	21 days	9-15 weeks	4 weeks
Rituximab	22 days	9-16 weeks	4-7 months

Post-operatively, once infection has been ruled out and the wound has healed, treatment should resume. Consider maintaining treatment in situations when there is a low chance of infection or a high risk of illness flare-up. If possible, surgery might be planned for a period when it is anticipated that drug levels will be low.

15. Vaccinations

Prior to initiating biologic treatment, vaccination requirements should be evaluated and updated in accordance with Department of Health guidance.

Do not administer live vaccinations to individuals receiving biologic treatment. Stop biologic medication for at least 12 months prior to administering live vaccinations, including the herpes zoster (shingles) vaccine. Expert opinion suggested, however, that 12 months may not be necessary for all biologics, and where live vaccinations must be considered, expert advice should be sought and/or the individual specifications in the SPC, where timelines are stated explicitly for some of the biologic drugs, should be reviewed. Generally, biologic treatment may be started four weeks after a live vaccination is administered. Consult the drug's SPC and the Green Book for more information.

The Green Book and the clinical risk category 'immunosuppression' should be used to determine immunisation needs during treatment. It is safe to provide inactivated vaccinations simultaneously with biologic treatment. To promote effective immune responses, inactivated vaccines should preferably be delivered at least 2 weeks prior to commencing treatment.

Prior to biologic treatment, patients should obtain yearly influenza vaccination (intramuscular only), pandemic influenza vaccination when suggested, and pneumococcal immunisation. Clinicians should be aware that TNF antagonist monotherapy may result in diminished antibody responses to influenza vaccination, and that TNF antagonists in combination with methotrexate (alone) may result in diminished antibody responses to pneumococcal vaccine.

15.1 New-borns to mothers who have received biological therapy

New-borns (up to 6 months of age) whose mothers received biologic therapy after 16 weeks' gestation. Patients should be counselled about the need of avoiding live immunizations and the potential implications for international travel.

16. Pregnancy

Adalimumab is locally recommended as the first line option for patients who are planning to conceive in the future. Adalimumab biosimilar provides the best value whilst being safe during the first two trimesters. It is vital the patient is aware that they must flag any pregnancy with the responsible clinician, so safety during the third trimester can be managed (either through temporary discontinuation or a switch to Certolizumab).

See the table below for further details on specific biologics in the different stages of pregnancy, information collated from the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding[5], and SPC of the relevant biologic.

Biologic	Compatible with trimester		
	1st	2nd	3rd
Certolizumab	Yes	Yes	Yes
Adalimumab	Yes	Yes	No
Etanercept	Yes	Yes	No
Infliximab	Yes	Stop at 16 weeks	No
Tofacitinib	No	No	No
Upadacitinib	No	No	No
Sarilumab	No, use effective contraceptive methods during and for 3 months following treatment.		
Tocilizumab	No, use effective contraceptive methods during and for 3 months following treatment.		
Abatacept	No, use effective contraceptive methods during and for 14 weeks following treatment.		
Rituximab	No, use effective contraceptive methods during and for 12 months following treatment.		
Baricitinib	No, use effective contraceptive methods during and for 1 week following treatment.		
Filgotinib	No, use effective contraceptive methods during and for 1 week following treatment.		
Golimumab	Data unavailable		

16.1 Breastfeeding

There is little information available regarding the excretion of biologics in breast milk. Immunoglobulins are excreted in human breast milk, so a risk to a child cannot be ruled out. The decision to breastfeed or continue therapy should balance both the benefits of breastfeeding and the benefits of therapy to the mother.

See the table below for further details on specific biologics in breastfeeding, information is taken from the SPC of the relevant biologic. Where no data or recommendation is provided, it would be appropriate to use the "Time to stop treatment prior to surgery" listed in section 11 to determine time between discontinuing treatment and starting breastfeeding.

Biologic	Compatible with Breastfeeding
Adalimumab	Yes
Certolizumab	Yes
Etanercept	Limited data - Balance risk vs benefits
Sarilumab	No data - Balance risk vs benefits
Tocilizumab	No data - Balance risk vs benefits
Baricitinib	No data - Balance risk vs benefits
Abatacept	Wait 14 weeks until after stopping to breastfeed
Infliximab	Wait 6 months until after stopping to breastfeed
Golimumab	Wait 6 months until after stopping to breastfeed
Rituximab	Wait 12 months until after stopping to breastfeed
Filgotinib	No - Contraindicated
Tofacitinib	No - Contraindicated
Upadacitinib	No - Contraindicated

17. Correspondence

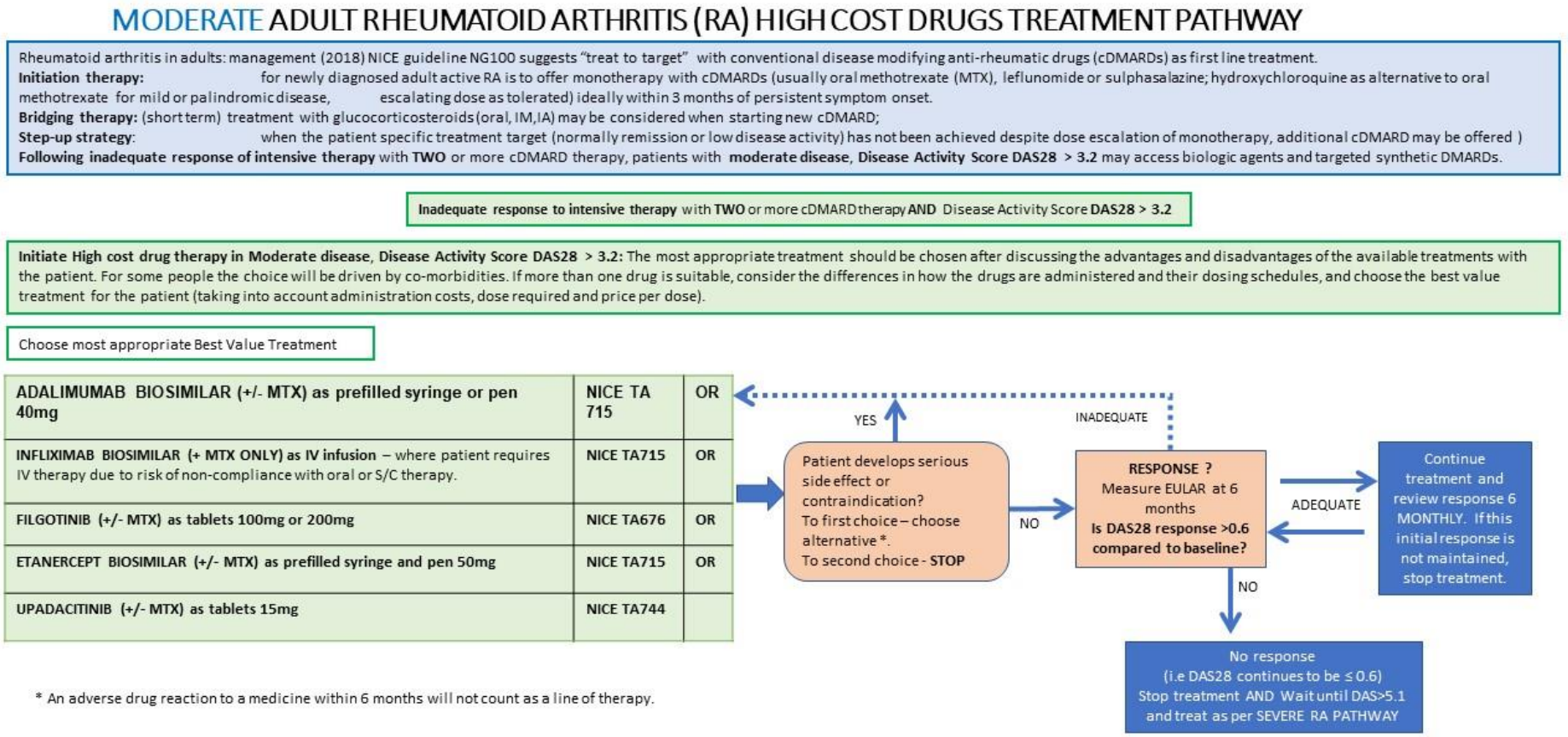
17.1 Information to be included in correspondence from secondary to primary care:

- Main diagnosis/diagnoses
- Date(s) of intervention
- Secondary diagnosis/diagnoses
- Date of last examination, with findings & timing of next planned review/ contact with secondary care
- Current medical therapy including any previous treatments within pathway (including non-biologics)
- Recommended length of current medical therapy

17.2 Information to be included in correspondence from primary to secondary care:

- Date last prescription issued
- All current and recent medications.
- Functional impact e.g., impact on employment, family, and social functioning
- Any newly diagnosed co-morbidities

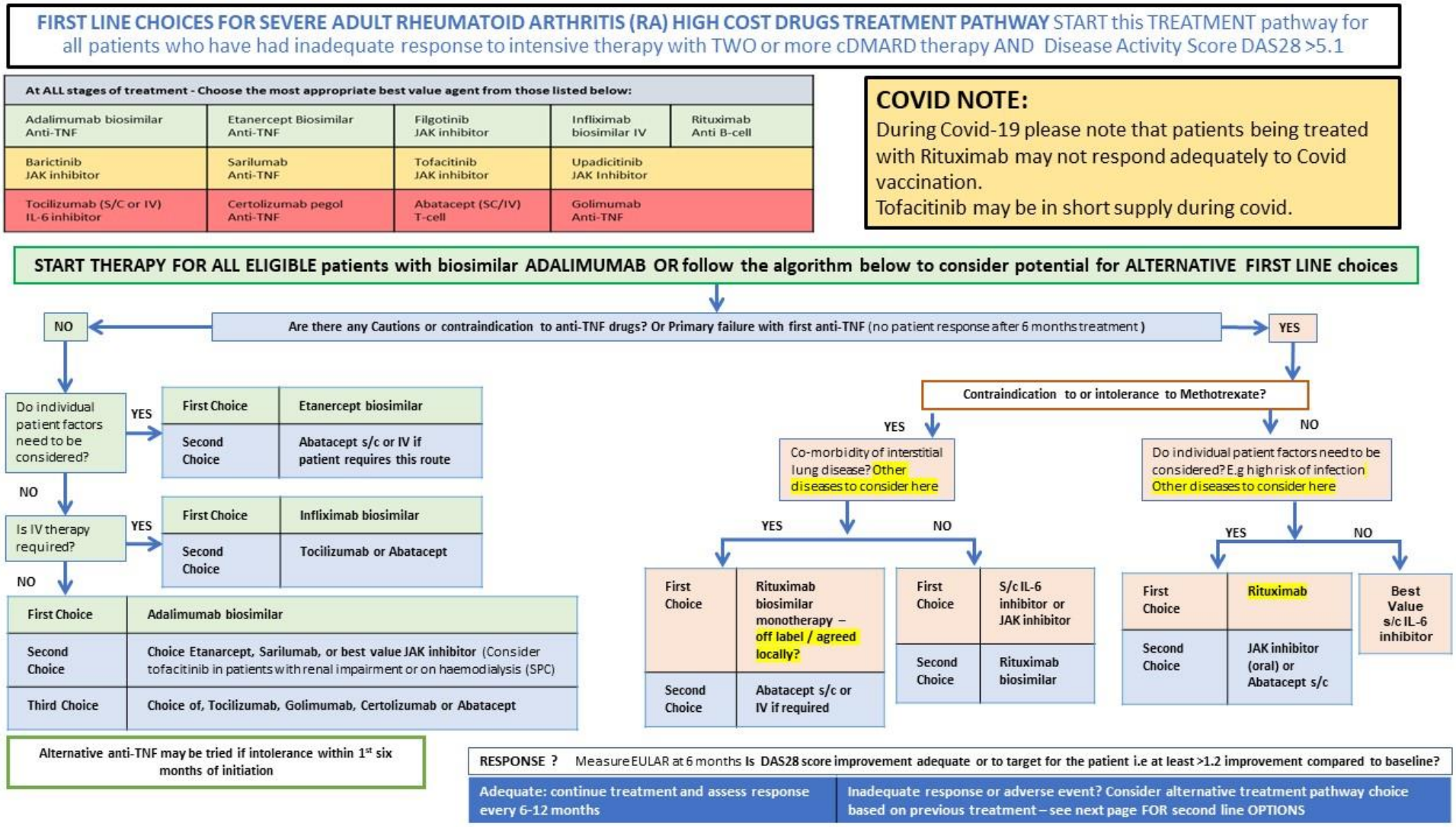
18. Appendix 1: Treatment options for moderate rheumatoid arthritis, DAS28 >3.2 to ≤5.1



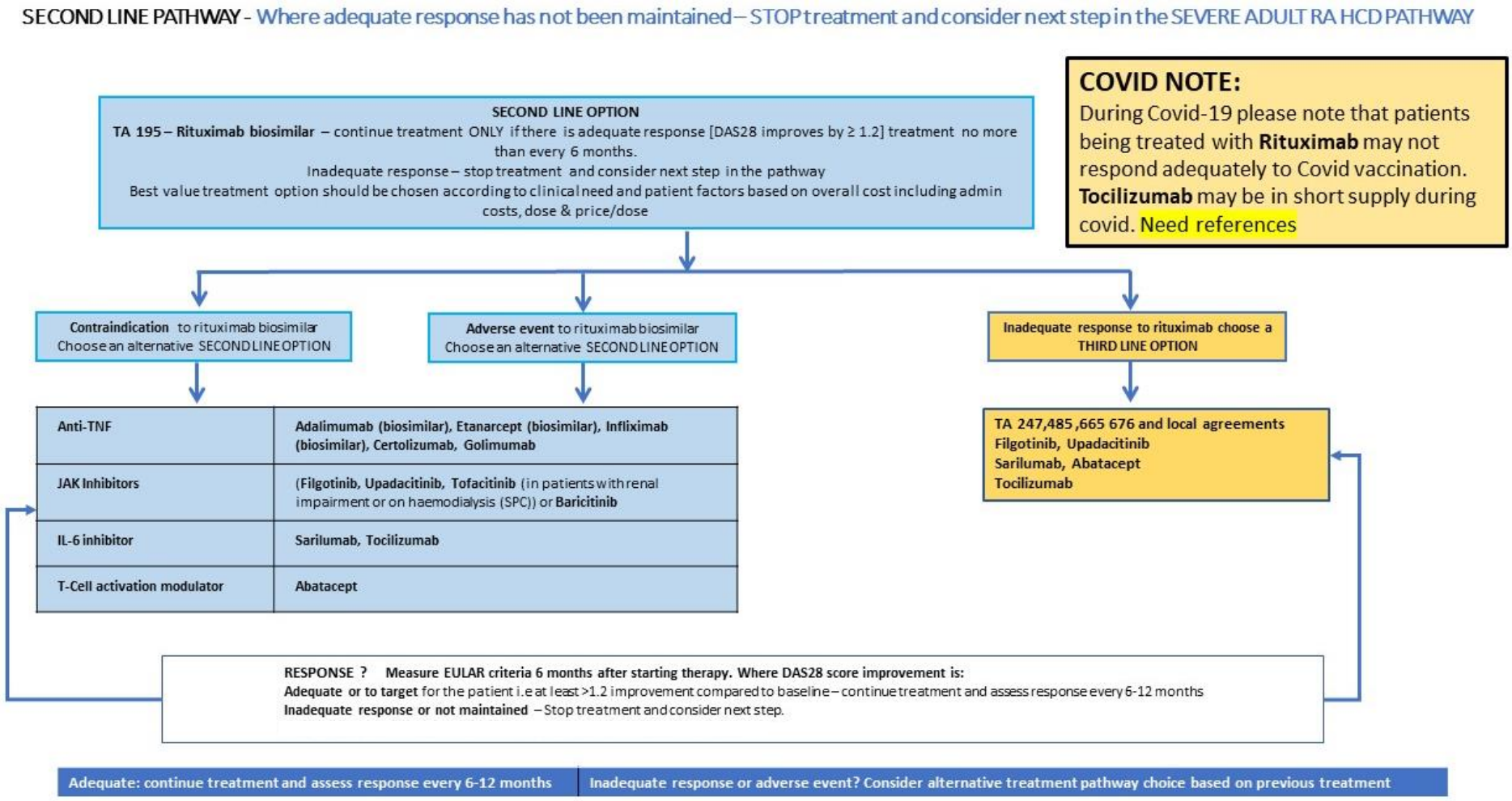
Blueteq; Moderate RA biologic biosimilar initiation does not require blueteq – continuation funding prior approval ONLY is required. Filgotinib and Upadicitinib require blueteq for initiation and continuation
Additional Line of treatment, dose escalation or increase in dose frequency outside of NICE recommendations AND combined biologic treatments are NOT commissioned locally and will require submission of an Individual Funding Request (IFR)

The scope for the appraisal in TA715 includes only first-line use of biological DMARDs. Cycling of tumour necrosis factor (TNF)-alpha inhibitors (taking another TNF-alpha inhibitor after a first one) was not considered if a person does not tolerate the first treatment, or if their disease either does not respond or responds inadequately after an initial response. Clinical experts did acknowledge and explained that the cycling of TNF-alpha inhibitors has a place in treating rheumatoid arthritis and that it was appropriate to assume that after the first biological treatment has failed, if the disease progresses to severe, NICE technology appraisal guidance for severe rheumatoid arthritis would be followed – from NICE TA 715 TNF inhibitor TA and requires local consideration as part of number of therapies followed and when that choice should be made.

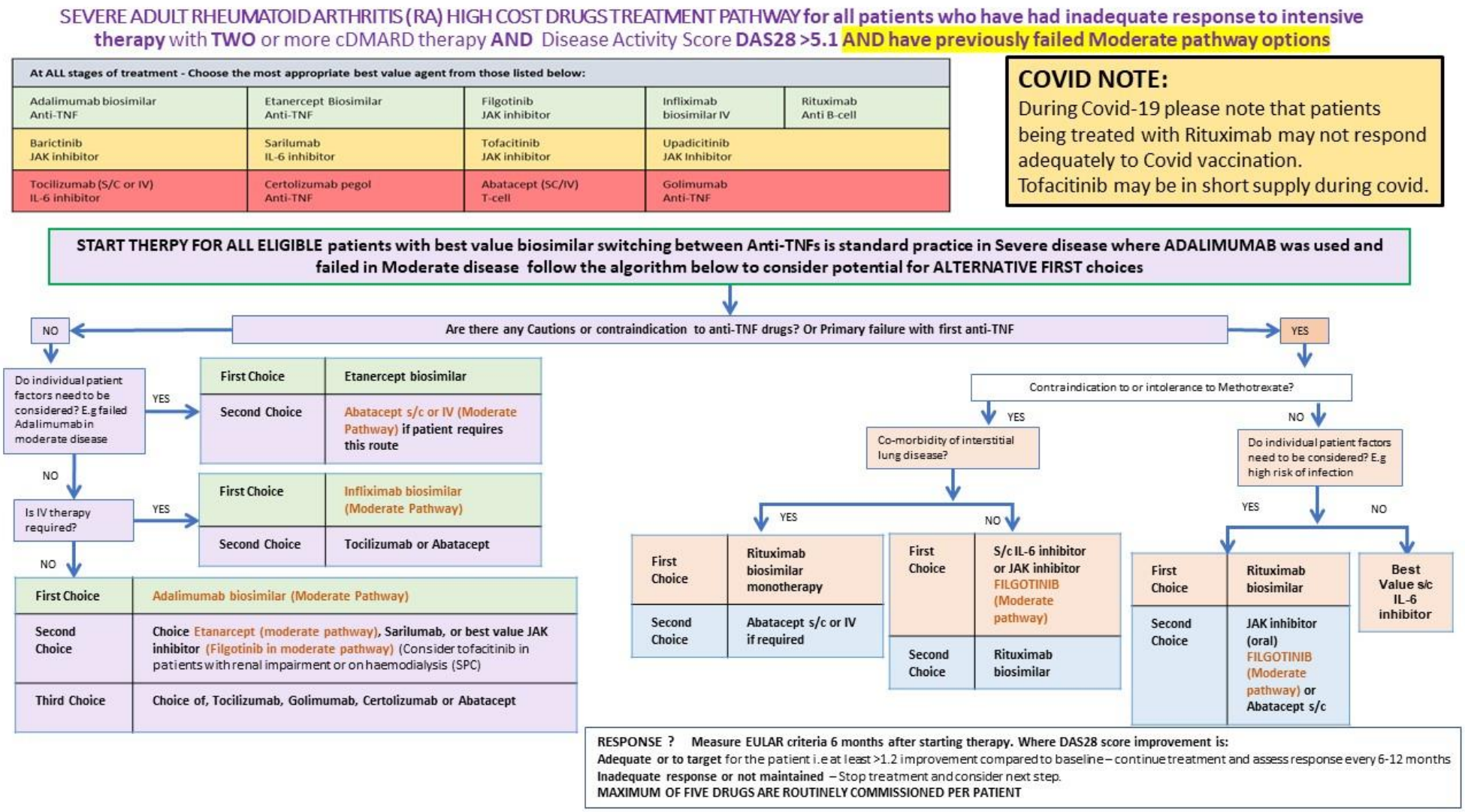
19. Appendix 2: Treatment options for severe rheumatoid arthritis, DAS28 >5.1



20. Appendix 3: Second line options for severe rheumatoid arthritis, DAS28 >5.1



21. Appendix 4: Treatment pathway when moderate rheumatoid arthritis pathway has failed, when DAS28 >5.1



22. Appendix 5: Rheumatoid arthritis high-cost drugs summary

Rheumatoid arthritis high cost drugs summary

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Failure of intensive therapy with 2 or more cDMARDs

- DAS score ≥ 5.1
- 3.2 ≤ DAS score < 5.1

Key	Drug	MoA	RoA	Strength	Frequency	Relative cost	C/I key	DAS score 3.2-5.1 (TA)	DAS score ≥5.1 (TA)	BioSim	MTX required?*	Pregnancy	BrFeed	MHRA
RTX	Rituximab	B cells/CD20	IV	2g	Every 24 weeks		2,3,5,7	-	✓ (195)	✓	-	-	-	-
ADA	Adalimumab	TNFαi	SC	40mg	Every 2 weeks		1,3,4	✓ (715)	✓ (195, 375)	✓	-	T1+2	✓	-
INF	Infliximab	TNFαi	IV	3mg/kg	Every 8 weeks		2,3,4	✓ (715)	✓ (195, 375)	✓	✓	T1	-	-
FGB	Filgotinib	JAK 1&3i	PO	200mg	Once daily		1,5,9	✓ (676)	✓ (676)	✓	-	-	-	-
ETN	Etanercept	TNFαi	SC	50mg	Once weekly		1,3,4	✓ (715)	✓ (195, 375)	✓	-	T1+2	-	-
INF	Infliximab	TNFαi	SC	3mg/kg	Every 8 weeks		2,3,4	-	✓ (676)	✓	✓	T1	-	-
PAD	Upadacitinib	JAK 1i	PO	15mg	Once daily		1,5,8,9	✓ (744)	✓ (665)	-	-	-	-	✓
TFA	Tofacitinib	JAK 1&3i	PO	5mg	Twice daily		1,5,8,9	-	✓ (480)	-	-	-	-	✓
BRB	Baricitinib	JAK 1&2i	PO	4mg	Once daily		1,9	-	✓ (466)	-	-	-	-	✓
SRB	Sarilumab	IL-6i	SC	200mg	Every 2 weeks		1,5	-	✓ (485)	-	-	-	-	-
ABA	Abatacept	T cells CD80/86	IV	125mg	Once weekly		1,5	-	✓ (195, 375)	-	✓	-	-	-
ABA	Abatacept	T cells CD80/86	SC	125mg	Once weekly		1,5	-	✓ (195, 375)	-	✓	-	-	-
CZP	Certolizumab pegol	TNFαi	SC	200mg	Every 2 weeks		1,3,4	-	✓ (375, 415)	-	✓	✓	✓	-
TCB	Tocilizumab	IL-6i	SC	162mg	Once weekly		1,5	-	✓ (247, 375)	-	-	-	-	✓
GOL	Golimumab	TNFαi	SC	50mg	Every 4 weeks		1,3,4	-	✓ (225, 375)	-	✓	-	-	-
TCB	Tocilizumab	IL-6i	IV	162mg	Once weekly		1,5	-	✓ (247, 375)	-	-	-	-	✓

* : Information regarding whether theraputic option can be initiated as monotherapy, or if methotrexate is required in combination. Rituximab can be inititiated as monotherapy, as per local agreement.

Measure EULAR at 6 months
Is DAS28 response >0.6 compared to baseline?

- No → Stop treatment & wait until DAS>5.1, commence severe pathway
- Yes → **Continue treatment and review response 6 MONTHLY.** If this initial response is not maintained, stop treatment.

Measure EULAR at 6 months
Is DAS28 response >1.2 compared to baseline?

- No → Switch to alternative agent with a different mechanism of action.
- Yes → **Continue treatment and review response 6 MONTHLY.** If this initial response is not maintained, stop treatment.

Key - Contraindication

1. Hypersensitivity to active substance, or to any product excipients
2. Hypersensitivity to active substance, to other murine proteins, or to any product excipients
3. NY class 3 4 heart failure
4. Patients with/at risk of severe infections such as tuberculosis sepsis, abscesses, and opportunistic infections
5. Clinically important, active infection (e g active tuberculosis)
6. Active Crohn's disease
7. Patients in a severely immunocompromised state
8. Severe hepatic impairment
9. Pregnancy

Considerations to Support the Use of a Specific Agent

- Patient factors: Device, dexterity, adherence, dose frequency, route of administration, weight, co-morbidities, drug history
  Abatacept: High risk of infection
- **Adalimumab**: Extra articular features/co-existent eg. uveitis (TA383), psoriasis (TA146), IBD (TA 187/329).
- **Certolizumab**: Females of childbearing potential
- **Etanercept**: Risk of activation of latent TB or high risk of infection. Etanercept is less immunogenic than other TNFi, may be a suitable option for patients experiencing secondary failure.
- **Golimumab**: Patient weight >100Kg: PAS permits double dose at the same cost (??)
- **IL-6 inhibitor**: Features of IL-6 mediated disease e.g. high ESR/CRP, anaemia, high ferritin; Consider in monotherapy
- **IV Infusions**: Compliance issues, impaired manual dexterity
- **JAK inhibitor**: Needle phobia. If patient has renal impairment or on haemodialysis, consider Tofacitinib.
- **Rituximab**: Consider 1st line (off-label use) if SLE/CTD overlap, co-existing ILD, haematological malignancy or treated solid malignancy within last 5 years, history of demyelination (EULAR/ACR recommendations). Rituximab with an alternative DMARD or as monotherapy may also be considered.

Published MHRA Warnings for Specific Agents:

- **Tocilizumab** (RoActemra®): rare risk of serious liver injury including cases requiring transplantation (July 2019)
- **All JAK inhibitors:** increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality (April 2023)

Specific JAK inhibitor warnings:

- **Baricitinib** (Olumiant®): risk of venous thromboembolism (March 2020)
- **Baricitinib** (Olumiant®): increased risk of diverticulitis, particularly in patients with risk factors (August 2020)
- **Tofacitinib** (Xeljanz®): new measures to minimise risk of venous thromboembolism and of serious and fatal infections (March 2020)
- **Tofacitinib** (Xeljanz®): new measures to minimise risk of major adverse cardiovascular events and malignancies (October 2021)
- **Upadacitinib** (Rinvoq®): advice for venous thromboembolism (March 2020)

23. Appendix 5: NICE technology appraisal detail

TA195	**Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor** 1. Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months. 2. Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more. 3. Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event. 4. Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event. 5. Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response, 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.
TA225	Overview | Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs | Guidance | NICE 1. Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if: 1.1. it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), **AND** 1.2. the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
TA247	**Tocilizumab for the treatment of rheumatoid arthritis; TA247** 1. Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if: 1.1. the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for TNF inhibitor treatments in the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, specifically the recommendations on disease activity **OR** 1.2. the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab **AND**

	1.3. the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme. 2. People currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet the criteria in 1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop. 3. Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the disease activity score and make any appropriate adjustments.
TA375	**Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed** 1. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if: 1.1. disease is severe, that is, a disease activity score (DAS28) greater than 5.1 **AND** 1.2. disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) **AND** 1.3. the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes. 2. Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in section 1 are met. 3. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. 4. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained. 5. Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules. 6. Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments. 7. People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab or abatacept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA415	**Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor** 1. Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor-alpha (TNF-alpha) inhibitor, only if: 1.1. disease activity is severe **AND** 1.2. rituximab is contraindicated or not tolerated **AND** 1.3. the company provides certolizumab pegol with the agreed patient access scheme. 2. Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF-alpha inhibitor, only if: 2.1. disease activity is severe **AND** 2.2. rituximab therapy cannot be given because methotrexate is contraindicated or not tolerated **AND** 2.3. the company provides certolizumab pegol with the agreed patient access scheme. 3. Continue treatment only if there is at least a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

	4. Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the disease activity score and make any appropriate adjustments.
TA466	**Baricitinib for moderate to severe rheumatoid arthritis** 1. Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if: 1.1. disease is severe (a disease activity score [DAS28] of more than 5.1) **AND** 1.2. the company provides baricitinib with the discount agreed in the patient access scheme. 2. Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if: 2.1. disease is severe (a DAS28 of more than 5.1) **AND** 2.2. they cannot have rituximab **AND** 2.3. the company provides baricitinib with the discount agreed in the patient access scheme. 3. Baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1 or 2 are met. 4. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained. 5. When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.
TA480	**Tofacitinib for moderate to severe rheumatoid arthritis; TA480** 1. Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs), only if: 1.1. disease is severe (a disease activity score [DAS28] of more than 5.1) **AND** 1.2. the company provides tofacitinib with the discount agreed in the patient access scheme. 2. Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot have, other DMARDs, including at least 1 biological DMARD, only if: 2.1. disease is severe (a DAS28 of more than 5.1) **AND** 2.2. they cannot have rituximab **AND** 2.3. the company provides tofacitinib with the discount agreed in the patient access scheme. 3. Tofacitinib can be used as monotherapy for adults who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1.1 or 1.2 are met. 4. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained. 5. When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.
TA485	**Sarilumab for moderate to severe rheumatoid arthritis; TA485** 1. Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if: 1.1. disease is severe (a disease activity score [DAS28] of more than 5.1) **AND** 1.2. the company provides sarilumab with the discount agreed in the patient access scheme. 2. Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if: 2.1. disease is severe (a DAS28 of more than 5.1) **AND** 2.2. they cannot have rituximab **AND**

	2.3. the company provides sarilumab with the discount agreed in the patient access scheme. 3. Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if: 3.1. disease is severe (a DAS28 of more than 5.1) **AND** 3.2. the company provides sarilumab with the discount agreed in the patient access scheme. 4. Sarilumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1 or 2 are met. 5. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained. 6. When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.
TA665	Upadacitinib for treating severe rheumatoid arthritis 1. Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if: 1.1. disease is severe (a disease activity score [DAS28] of more than 5.1) **AND** 1.2. the company provides upadacitinib according to the commercial arrangement. 2. Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if: 2.1. disease is severe (a DAS28 of more than 5.1) **AND** 2.2. they cannot have rituximab **AND** 2.3. the company provides upadacitinib according to the commercial arrangement. 3. Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if: 3.1. disease is severe (a DAS28 of more than 5.1) **AND** 3.2. the company provides upadacitinib according to the commercial arrangement. 4. Upadacitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in points 1, 2 or 3 are met. 5. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, stop treatment if at least a moderate EULAR response is not maintained.
TA676	**Filgotinib for treating moderate to severe rheumatoid arthritis; TA676** 1. Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (DMARDs), only if: 1.1. disease is moderate or severe (a disease activity score [DAS28] of 3.2 or more) **AND** 1.2. the company provides filgotinib according to the commercial arrangement. 2. Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if: 2.1. disease is severe (a DAS28 of more than 5.1) **AND** 2.2. they cannot have rituximab **AND** 2.3. the company provides filgotinib according to the commercial arrangement. 3. Filgotinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if: 3.1. disease is severe (a DAS28 of more than 5.1) **AND** 3.2. the company provides filgotinib according to the commercial arrangement. 4. Filgotinib can be used as monotherapy when methotrexate is contraindicated or if people cannot tolerate it, when the criteria in sections 1, 2 or 3 are met.

	5. Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary from person to person because of differences in how the drugs are taken and treatment schedules. 6. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. If this initial response is not maintained, stop treatment. 7. When using the DAS28, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any adjustments they consider appropriate.
TA715	**Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed** **Technology appraisal guidance [TA715] Published: 14 July 2021** 1. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if: 1.1. disease is severe, that is, a disease activity score (DAS28) greater than 5.1 **AND** 1.2. disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) **AND** 1.3. the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes. 2. Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in section 1 are met. 3. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. 4. After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained. 5. Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules. 6. Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments.
TA744	Upadacitinib for treating moderate rheumatoid arthritis 1. Upadacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (DMARDs), only if: 1.1. disease is moderate (a disease activity score [DAS28] of 3.2 to 5.1) **AND** 1.2. the company provides upadacitinib according to the commercial arrangement. 2. Upadacitinib can be used as monotherapy when methotrexate is contraindicated or if people cannot tolerate it, when the criteria in section 1.1 are met. 3. If more than 1 treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary because of differences in how the drugs are used and treatment schedules. 4. Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. If this initial response is not maintained, stop treatment. 5. Take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments.