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ELISA testing for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis

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Plain English summary

Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disease that typically affects synovial joints (such as those in the hands and feet), causing swelling, stiffness, pain and progressive irreversible joint destruction. Disease can also occur outside the joints, affecting other organs, including the lungs, heart and eyes.

In RA, too much of a protein called tumour necrosis factor (TNF)-α is produced in the body, causing inflammation, pain and damage to the bones and joints, and is manifested with increasing disability and reduced quality of life.

Physicians commonly prescribe different TNF-α inhibitors to treat severe RA. The TNF-α inhibitors block the action of TNF-α and, therefore, reduce inflammation.

Although these drugs can help many people with RA, there are some people whose disease does not respond to treatment (primary non-responders), and many people whose disease first responds to treatment find that their disease stops responding over time (secondary non-responders).

The loss of response may be caused by a number of factors including the presence of antibodies to the drugs, and fluctuations in circulating drug levels.

Anti-drug antibodies can be elicited by the drugs during therapy as a response by the human immune system to these medications. These anti-drug antibodies have been shown to reduce drug levels.

ELISA tests can be used for measuring the drug levels and anti-drug antibody levels in serum/plasma of patients treated with TNF-α inhibitors**.**

It is expected that therapeutic monitoring of TNF-α inhibitors using ELISA tests might be useful in the treatment of RA for primary and secondary loss of response to therapy and in the optimisation of dosages for those who are already responding. The ELISA tests will be

conducted in addition to current clinical practice in the UK, i.e. clinical assessment and monitoring using a composite score such as the Disease Activity Score (DAS) 28.

Therapeutic drug monitoring of TNF-α inhibitors for RA is not routine in most clinical practices in the UK, or at least does not use biochemical assays to quantify the level of drug or antibodies to the drug in a patient's body. There are neither gold standards nor guidelines available to monitor these drugs.

This technology assessment will identify and synthesise research evidence on outcomes and costs of six alternative ELISA kits/processes:

- Promonitor test (Grifols - Progenika)
- IDKmonitor enzyme-linked immunosorbent assay (ELISA) kits (Immundiagnostik/BioHit Healthcare)
- LISA-TRACKER ELISA kits (Theradiag)
- RIDASCREEN (R-Biopharm)
- MabTrack ELISA kits (Sanquin) and
- Sanquin Diagnostic Services (testing service using validated ELISAs)

for assessing response to anti-TNF treatments, and their clinical and cost effectiveness compared to standard-of-care when treatment decisions are based on clinical judgement and regular monitoring using a composite score such as DAS28.

The study will be conducted by Peninsula Technology Assessment Group (PenTAG).

1 Background

1.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that can result in substantial morbidity, impaired physical activity, and poor quality of life, leading to a reduced life expectancy. RA typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease and can affect the whole body, including the lungs, heart and eyes. RA is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive.

RA is associated with substantial costs both direct (drug acquisition and hospitalisation) and indirect (due to reduced productivity). It is estimated that approximately one-third of people stop work within two years because of the disease, and this prevalence increases thereafter.

1.1.1 Epidemiology

Rheumatoid arthritis affects approximately 0.8% of the population, or approximately 580,000 people in England. Of these, approximately 15% have severe disease. It is about two- to four-times more prevalent in women than in men. It can develop at any age, with around three-quarters of all new diagnoses in working-age people.

1.1.2 Risk factors

Among the factors that may increase the risk of rheumatoid arthritis are gender, advanced age, regular smoking and obesity.

1.1.3 Management

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. Early recognition of symptoms and diagnosis is key to a more successful patient outcome. Early review allows faster initiation of treatment and suppression of inflammation.

Treatment for RA usually includes: non-steroidal anti-inflammatory drugs which reduce pain, fever and joint swelling/inflammation; and disease modifying anti-rheumatic drugs (DMARDs).

DMARDs may be broadly classified as conventional, biologic or synthetic. Conventional DMARDs (cDMARDs) include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Biologics include, but are not limited to, tumour necrosis factor (TNF) inhibitors. There are targeted synthetic DMARDs used for RA such as the Janus kinase inhibitor tofacitinib.

1.1.3.1 Biologic DMARDs

Biologic DMARDs have diverse modes of action that either inhibit the effects of TNF (infliximab, adalimumab, etanercept, certolizumab pegol, and golimumab), block the anti-interleukin 6 (IL-6) receptor (tocilizumab), deplete B cells (rituximab), or interfere with T-cell costimulatory signaling (abatacept).

TNF-α is a cell signalling protein that promotes inflammatory responses. Dysregulation of TNF-α production can contribute to inflammatory diseases, such as RA. TNF-α inhibitors are given to people with RA disease to inhibit TNF-α production and suppress the inflammatory response. The anti-TNF agents have proven effective at reducing signs and symptoms and slowing progression of RA. In addition to differences in method of administration and dosing schedule, these drugs have important molecular differences that may affect immunogenicity and long-term clinical efficacy.

A substantial proportion of RA patients (up to 30%) fail to respond to the first biologic drug. Recent findings indicate that lack of clinical response to biologics may be related with lowering serum drug levels. Studies have shown that patients receiving either adalimumab or infliximab developed neutralizing antibodies against the drugs, contributing to a loss of therapeutic response.

Due to inadequate therapeutic response, clinicians often escalate or intensify the drug dose, which increases drug treatment costs, patient inconvenience, and risk of adverse events (e.g. infusion reactions and infections), without necessarily offering additional clinical benefit.

For people with newly diagnosed rheumatoid arthritis, DMARDs slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation. The main aim of management in early disease is to suppress disease activity and induce disease remission, prevent loss of function, control joint damage, maintain pain control and enhance self-management. In established disease, management should address complications and associated comorbidity; and the impact of the condition on the patient's quality of life.

Several biologic drugs - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept - all in combination with methotrexate, are recommended by NICE for treating RA if disease is severe (i.e. a disease activity score of 28 joints - DAS28 - is greater than 5.1), and disease has not responded to intensive therapy with a combination of conventional DMARDs (Source: TA375, NICE guidance [1]). The NICE guidance TA375 states that treatment should be continued only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After initial response within 6 months, treatment should be withdrawn if a moderate EULAR response is not maintained. Treatment should start 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.

Adalimumab, etanercept, certolizumab pegol or tocilizumab can also be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met [1].

Adalimumab, etanercept, infliximab, rituximab and abatacept are recommended by NICE for adults with severe rheumatoid arthritis who have tried other DMARDs but cannot tolerate them or they haven't worked well enough (Source: TA195, NICE guidance [2]).

1.1.3.1.1 Biologics pathways

Two treatment pathways related to biologics were identified during a pilot search. They are described below.

1.1.3.1.1.1 Biologic drugs pathways reported by NHS Kingston

There are no nationally endorsed and published treatment pathways for treating people with RA with biologics. However, a clear example of a treatment pathway based on NICE RA commissioning algorithm (*with local adaptation*) is reported by NHS Kingston [3]. Two biologics pathways are presented: "Pathway A: Biologics used with methotrexate", and "Pathway B: Biologics used without methotrexate" (Figs 1-3).

Figure 1: Treatment pathways reported by NHS Kingston

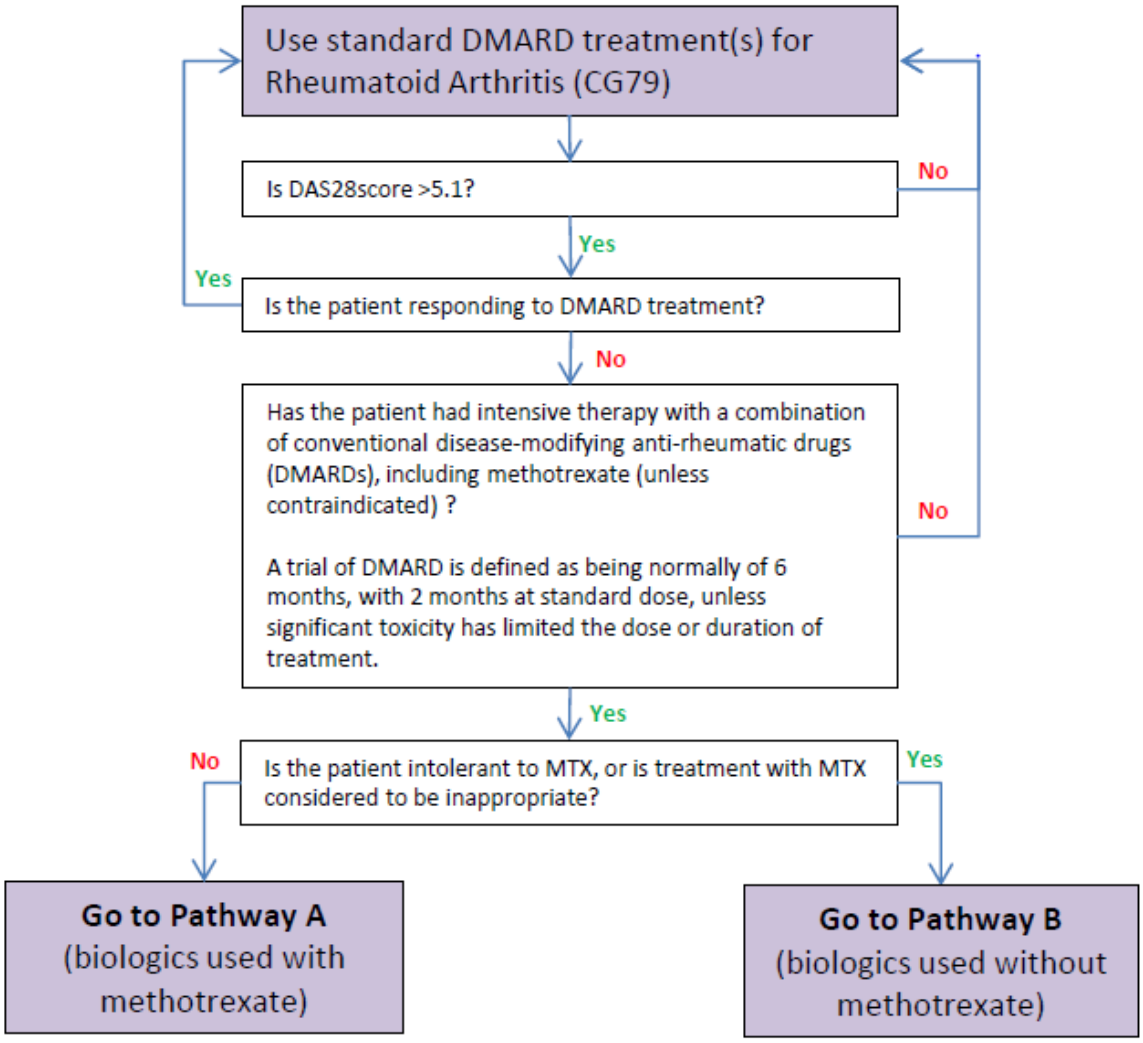


Figure 2: Pathway A

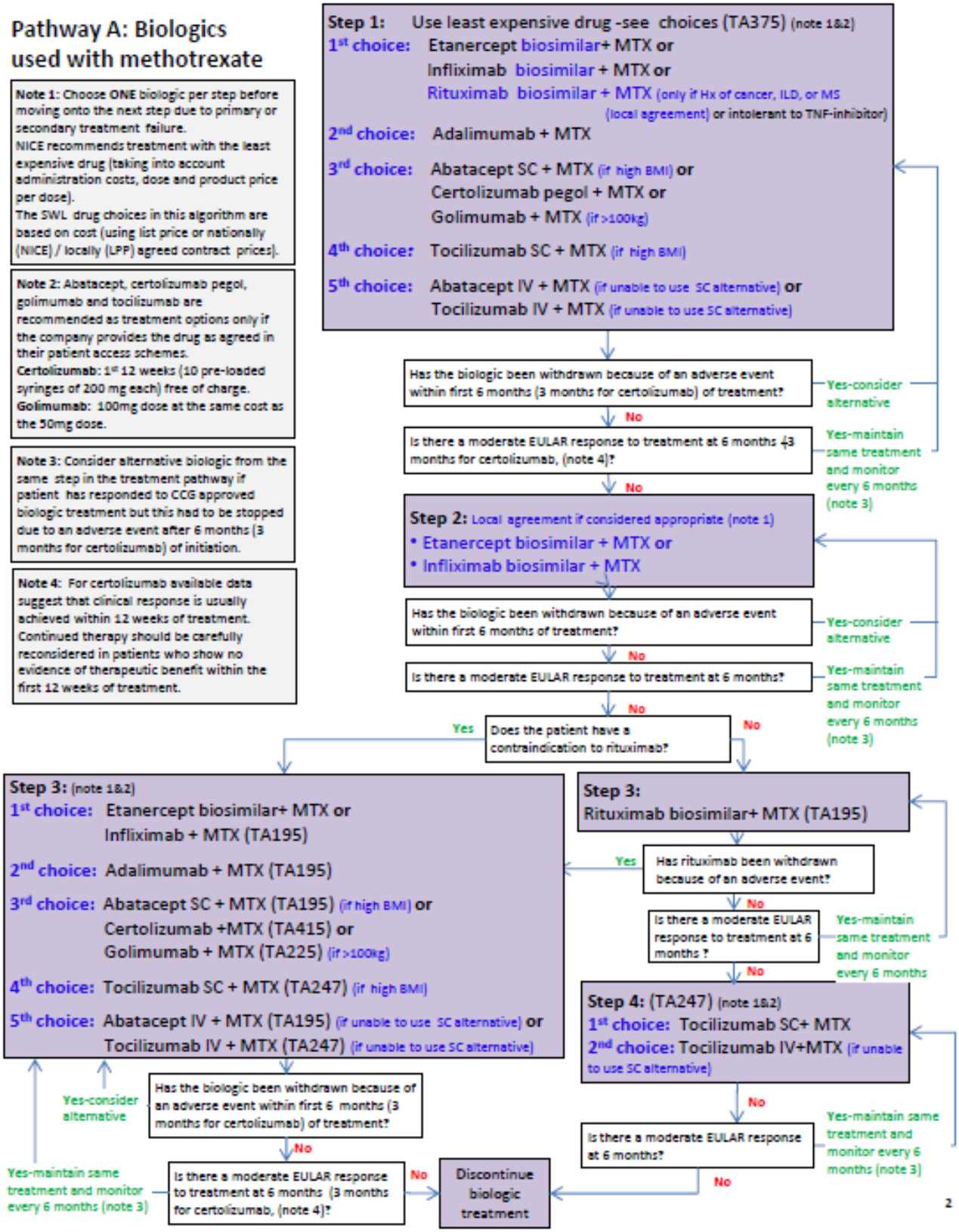
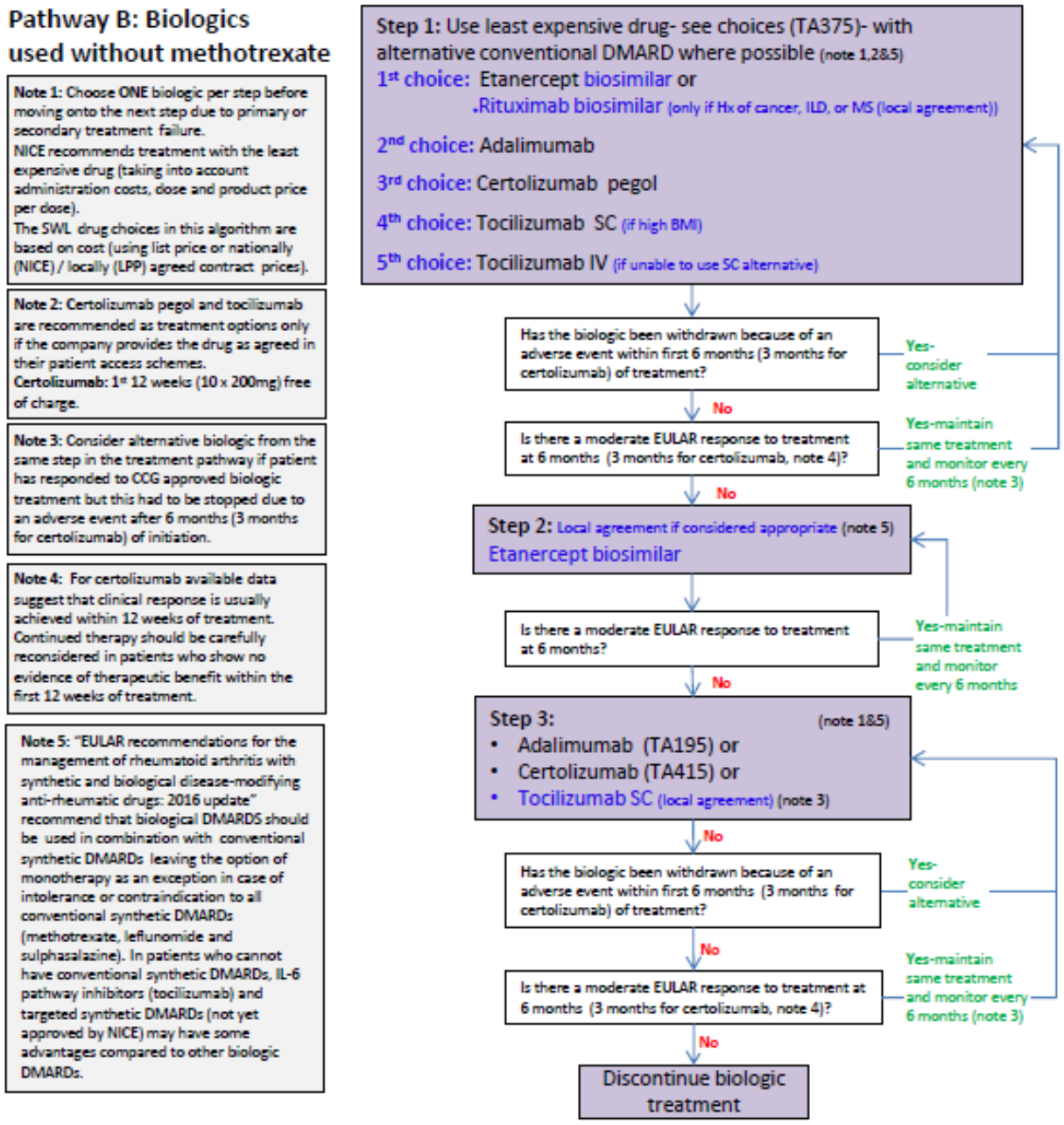


Figure 3: Pathway B



1.1.3.1.1.2 Biologic drugs pathways reported by Greater Manchester Medicines Management Group

Another example of a biologic drug care pathways for people with rheumatoid arthritis has been reported by Jani et al. (2017) [4] (refer to Appendix 1 for details).

1.2 Using tests to monitor treatment response to biologics in RA

1.2.1 Diagnosis of RA

American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) developed classification criteria for RA, which can help a physician-made diagnosis. The criteria attribute points based on the number of tender or swollen joints. There has to be at least one joint with clinical synovitis. Laboratory tests are also included: rheumatoid factor, anti-cyclic citrullinated peptide antibody and acute phase reactants. However, antibody positivity and elevated acute phase reactants are not essential to make the diagnosis. A total score of more than 6 points is considered definite RA. For patients with long-standing disease, they can be classified as having rheumatoid arthritis if they previously fulfilled the diagnostic criteria (Table 1).

Table 1: ACR/EULAR 2010 rheumatoid arthritis classification criteria

Joint distribution (0–5)	
1 Large joint	0
2–10 Large joints	1
1–3 Small joints (large joints not counted)	2
4–10 Small joints (large joints not counted)	3
>10 Joints (at least one small joint)	5
Serology 0–3	
Negative RF *and* negative ACPA	0
Low positive RF *or* low positive ACPA	2
High positive RF *or* high positive ACPA	3
Symptom duration	
<6 weeks	0
>6 weeks	1
Acute phase reactants	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1

RF = rheumatoid factor; ACPA = anti-citrullinated protein (anti-CCP) antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

1.2.2 Current approaches to treatment response assessment

1.2.2.1 DAS28

Treatment decisions for RA are currently typically based on clinical judgement and regular monitoring using a composite score such as the disease activity score 28 (DAS28), which combines clinical examination of joints, measurement of biochemical markers of inflammation in the blood and subjective assessments of disease activity. The Disease Activity Score (DAS), its modified version, the DAS28, and the DAS-based EULAR response criteria are well-known measures of disease activity in rheumatoid arthritis (RA).

The DAS28 is a composite score derived from the following measures:

- Clinical examination of 28 joints to count how many joints are tender to the touch (TEN28) and/or swollen (SW28)

- Blood markers of inflammation, e.g. erythrocyte sedimentation rate (ESR) or C reactive protein (CRP)
- Subjective assessment (SA) on a scale of 0-100 made by the patient regarding disease activity in the previous week.

These measures are used in a mathematical formula to produce the overall disease activity score:

DAS28 = 0.56 TEN280.5 + 28* SW280.5 + 0.70 * ln (ESR) + 0.014 * SA*

A DAS28 of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission.

The DAS28 can be used to classify both the disease activity of the patient and the level of improvement estimated within the patient.

1.2.2.2 EULAR

The EULAR response criteria is a classified response criteria which classifies the patients individual as non-responder, moderate or good responders dependent on the change and the level of the DAS28 score (Table 2).

Table 2: Definition of the EULAR response criteria using the DAS28 score

DAS28 at endpoint	Improvement in DAS28 ≤ 1.2	Improvement in DAS28 > 0.6 and ≤ 1.2	Improvement in DAS28 ≤ 0.6
≤3.2	good	moderate	none
>3.2 and ≤5.1	moderate	moderate	none
>5.1	moderate	none	none

1.2.3 Assays

Assays are used to measure free drug levels and free anti-drug antibody levels. The LISA-TRACKER, IDKmonitor, RIDASCREEN, MabTrack, Promonitor enzyme-linked immunosorbent assay (ELISA) kits and ELISAs used by Sanquin Diagnostic Services are intended for measuring the levels of TNF-α inhibitors and antibodies against TNF-α inhibitors in the blood of people having TNF-α-inhibitor treatment for RA disease.

There are no gold standard assays for anti-TNF-α agents or for antibodies to anti-TNF-α agents that might provide a robust basis for comparisons between the performances of different assays. ~~According to US Medical Insurance assessments 'candidate' assays have been insufficiently investigated to establish any as a gold standard and, the evidence is incomplete on how these different assays may compare in practice.~~

Therapeutic drug monitoring of drug levels in the blood for biological drugs in RA is not routine in most clinical practices in the UK. Such tests are performed only in a few laboratories. There are no guidelines available to monitor these drugs, and no agreed algorithm for the translation of the test results into coherent plans for patient management according to test outcome.

It is expected that therapeutic monitoring of TNF-α inhibitors might be useful in the treatment of RA for primary and secondary loss of response to anti-TNF-α therapy and in the optimisation of dosages for those who are already responding.

The anti-TNF-α and anti-drug antibody assays are most frequently administered just before the next administration of the anti-TNF-α agent. This is to allow measurement of a 'trough' level of the drug. For patients whose response to therapy has waned, the results of the tests are frequently dichotomised using a cut-off assay result. Thus, on the basis of anti-TNF-α assays, patients are classified as having therapeutic levels of anti-TNF-α or sub-therapeutic levels, and on the basis of anti-drug antibody assay results they are classified as having clinically significant levels of anti-drug antibodies or insignificant levels. Such classifications yield four categories of patient for whom different explanations of failed response are possible. Algorithms have been developed prescribing treatment pathways and/or further diagnostic tests based on such classification.

1.2.3.1 Promonitor

Promonitor (Grifols–Progenika) is a portfolio of assays that measure drug levels (etanercept, infliximab, infliximab biosimilars, adalimumab, golimumab) and their correlating anti-drug antibodies (anti-etanercept, anti-infliximab, anti-adalimumab, anti-golimumab). Promonitor ELISA kits are manufactured by Proteomika and distributed in the UK by Grifols UK. There are 8 Promonitor ELISA kits relevant to this assessment (Table 3): 4 of these kits measure the levels of free anti-drug antibodies and 4 kits measure the levels of free TNF-α inhibitor.

Table 3: Promonitor kits

Promonitor-IFX (infliximab levels)
Promonitor-Anti-IFX (anti-infliximab antibody levels)
Promonitor-ADL (adalimumab levels)
Promonitor-Anti-ADL (anti-adalimumab antibody levels)
Promonitor-ETN (etanercept levels)
Promonitor-Anti-ETN (anti-etanercept antibody levels)
Promonitor-GLM (golimumab levels)
Promonitor-Anti-GLM (anti-golimumab antibody levels)

Source: Progenika [5]

The kits consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards, controls and ELISA cover films. The ELISAs are laboratory-based tests. They can be done manually or run on an automated ELISA processor.

1.2.3.2 IDKmonitor ELISA kits (Immundiagnostik/BioHit Healthcare)

IDKmonitor ELISA kits are manufactured by Immundiagnostik AG and distributed in the UK by Biohit Healthcare Ltd. There are 10 IDKmonitor ELISA kits relevant to this assessment (Table 4): 4 kits measure the levels of free TNF-α inhibitor, 4 kits measure the levels of free anti-drug antibodies, and 2 kits measure the levels of total anti-drug antibodies (free antibodies and antibodies bound to the drug).

Table 4: IDKmonitor ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent
IDKmonitor infliximab drug level ELISA (K9655)	Free[1] infliximab (Remicade, Remsima, Inflectra)	Monoclonal anti-infliximab antibody	Peroxidase labelled antibody
IDKmonitor adalimumab drug level ELISA (K9657)	Free[1] adalimumab	Monoclonal anti-adalimumab antibody	Peroxidase labelled antibody
IDKmonitor etanercept drug level (K9646)	Free[1] etanercept	Monoclonal anti-etanercept antibody	Peroxidase labelled antibody
IDKmonitor golimumab drug level ELISA (K9656)	Free[1] golimumab	Monoclonal anti-golimumab antibody	Peroxidase labelled antibody
IDKmonitor infliximab free ADA, ELISA (K9650)	Free[1] anti-infliximab antibodies	Infliximab $F(ab)_2$ fragments	Peroxidase labelled infliximab
IDKmonitor adalimumab free ADA, ELISA (K9652)	Free[1] anti-adalimumab antibodies	Adalimumab $F(ab)_2$ fragments	Peroxidase labelled adalimumab
IDKmonitor etanercept free ADA, ELISA (K9653)	Free[1] anti-etanercept antibodies	Etanercept $F(ab)_2$ fragments	Peroxidase labelled etanercept
IDKmonitor infliximab total ADA, ELISA (K9654)	Total[2] anti-infliximab antibodies	Streptavidin	N/A
IDKmonitor adalimumab total ADA, ELISA (K9651)	Total[2] anti-adalimumab antibodies	Streptavidin	N/A
IDKmonitor golimumab free ADA, ELISA (K9649)	Free[1] anti-golimumab antibodies	Golimumab $F(ab)_2$ fragments	Peroxidase labelled golimumab

[1] Free TNF-α inhibitor is drug that is unbound to antibody, and free anti-drug antibodies are those that are unbound to drug
[2] Total anti-drug antibodies include both unbound (free) antibodies and those bound to TNF-α inhibitor

The kits consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards (drug level ELISAs only) and controls. The ELISA tests are laboratory-based. They can be done manually or run on an automated ELISA processor.

1.2.3.3 LISA-TRACKER ELISA kits (Theradiag)

LISA-TRACKER ELISA kits are manufactured by Theradiag. There are 10 CE marked LISA-TRACKER ELISA kits (Theradiag) that are potentially relevant to the scope (Table 5). Five of these kits measure the levels of free anti-drug antibodies and 5 kits measure the levels of free TNF-α inhibitor. LISA-TRACKER Duo kits are also available that include assays to measure the levels of both free anti-drug antibodies and TNF-α inhibitor.

Table 5: LISA-TRACKER ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent
LISA-TRACKER Adalimumab	Free[1] adalimumab	TNF-α	Biotinylated anti-human IgG antibody
LISA-TRACKER Certolizumab	Free[1] certolizumab	TNF-α	
LISA-TRACKER Etanercept	Free[1] etanercept	TNF-α	
LISA-TRACKER Infliximab	Free[1] infliximab	TNF-α	
LISA-TRACKER Golimumab	Free[1] golimumab	TNF-α	
LISA-TRACKER anti-Adalimumab	Free[1] anti-adalimumab antibodies	Adalimumab	Biotinylated adalimumab
LISA-TRACKER anti-Certolizumab	Free[1] anti-certolizumab antibodies	Certolizumab	Biotinylated certolizumab
LISA-TRACKER anti-Infliximab	Free[1] anti-infliximab antibodies	Infliximab	Biotinylated infliximab
LISA-TRACKER anti-Etanercept	Free[1] anti-etanercept antibodies	Etanercept	Biotinylated etanercept
LISA-TRACKER anti-Golimumab	Free[1] anti-golimumab antibodies	Golimumab	Biotinylated golimumab

[1] Free TNF-α inhibitor is drug that is unbound to antibody, and free anti-drug antibodies are those that are unbound to drug

The LISA-TRACKER ELISA kits consist of pre-coated strips of microtitre plate (96 wells), reagents, wash buffer, standards and controls. All tests are laboratory based assays. They can be run simultaneously or individually on any manual or automated standard ELISA-based processor platform.

1.2.3.4 RIDASCREEN (R-Biopharm)

The RIDASCREEN enzyme linked immunoassays are manufactured by R-Biopharm. There are 4 CE marked RIDASCREEN ELISAs potentially relevant to the scope (Table 6). All are laboratory based assays. Two of the kits measure levels of free TNF-α inhibitor and 2 kits measure the levels of free anti-drug antibodies. The RIDASCREEN ELISAs are commercialised versions of the KU Leuven in-house ELISAs, and are marketed as apDia ELISA kits in the Benelux area of Europe.

Table 6: RIDASCREEN ELISA kits

Name	Detects	Microplate pre-coat	Secondary reagent
RIDASCREEN ADM Monitoring	Free[1] adalimumab	TNF-α	Peroxidase conjugated monoclonal antibody

Name	Detects	Microplate pre-coat	Secondary reagent
RIDASCREEN IFX Monitoring	Free[1] infliximab (Remicade, Remsima, Inflectra)	TNF-α	Peroxidase conjugated monoclonal antibody
RIDASCREEN Anti-ADM Antibodies	Free[1] antibodies to adalimumab	Adalimumab	(1) Biotin conjugated infliximab. (2) Peroxidase conjugated streptavidin
RIDASCREEN Anti-IFX Antibodies	Free[1] antibodies to infliximab	Infliximab	(1) Biotin conjugated infliximab. (2) Peroxidase conjugated streptavidin

[1] Free TNF-α inhibitor is drug that is unbound to antibody, and free anti-drug antibodies are those that are unbound to drug

1.2.3.5 MabTrack ELISA kits and Sanquin Diagnostic Services

Sanquin is a laboratory in the Netherlands and it provides laboratory test services including testing for TNF-α inhibitors using ELISA based assays. It also provides CE marked ELISA kits for local laboratory testing for adalimumab and infliximab levels and their correlating anti-drug antibodies. The kits available to purchase are called MabTrack ELISA kits. There are 4 CE marked ELISA kits available that are relevant to the scope (Table 7): 2 for testing free drug levels and 2 for their correlating free anti-drug antibodies. In addition, a testing service using validated ELISAs is available for etanercept and its correlating anti-drug antibodies, golimumab drug levels and certolizumab drug levels. Testing is performed at the Sanquin laboratories in the Netherlands. Radioimmunoassays that measure drug levels or anti-drug antibodies are outside of the scope of this assessment.

Table 7: MabTrack ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent
MabTrack level adalimumab M2910	Free[1] adalimumab	TNF-α	Peroxidase-labeled monoclonal anti-adalimumab antibody
MabTrack level infliximab M2920	Free[1] infliximab (Remicade, Remsima, Inflectra)	TNF-α	Peroxidase-labeled monoclonal anti-infliximab antibody
MabTrack ADA adalimumab M2950	Free[1] antibodies to adalimumab	Adalimumab	Peroxidase-labelled adalimumab
MabTrack ADA infliximab M2960	Free[1] antibodies to infliximab	Infliximab	Peroxidase-labelled infliximab

[1] Free TNF-α inhibitor is drug that is unbound to antibody, and free anti-drug antibodies are those that are unbound to drug

The MabTrack ELISA kits consist of pre-coated strips of microtitre plate (96 wells), reagents, wash buffer, standards or calibrators, controls and ELISA cover films.

1.3 Current Guidelines

In January 2018, NICE published draft guidance on the management of RA in adults. The final guideline is due to be published in July 2018.

1.3.1 NICE's draft guideline on rheumatoid arthritis

The draft guideline states that active RA in adults should be treated with the aim of achieving a target of remission or low disease activity (treat-to-target) [6]:

"A treat-to-target strategy is a strategy that defines a treatment target (such as remission or low disease activity) and applies tight control (for example, monthly visits and respective treatment adjustment) to reach this target. The treatment strategy often follows a protocol for treatment adaptations depending on the disease activity level and degree of response to treatment."

The draft guideline advocates starting treatment with just one conventional (non-biologic) DMARD (cDMARD) drug instead of a combination of cDMARDs. Further cDMARDs should be added if treatment targets are not met despite dose escalation [6].

As stated in the draft guideline [6], in adults with active RA, C-reactive protein (CRP) and disease activity using a composite score such as DAS28 should be measured monthly until the target of remission or low disease activity is achieved. A review appointment should be considered 6 months after achieving treatment target (remission or low disease activity) to ensure that the target has been maintained.

An annual review should be offered to all adults with RA to:

- assess disease activity and damage, and measure functional ability (using, for example, the Health Assessment Questionnaire [HAQ])
- check for the development of comorbidities, such as hypertension, ischaemic heart disease, osteoporosis and depression
- assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung or eyes
- organise appropriate cross referral within the multidisciplinary team
- assess the need for referral for surgery
- assess the effect the disease is having on a person's life

The draft guideline does not discuss the use of biological DMARDs for RA such as TNF-α inhibitors.

1.3.2 Test-based treatment recommendations for RA

In our scoping searches, recommendations by NHS Greater Glasgow and Clyde on biologic drug monitoring have been identified [7]. This document provides guidance on testing for infliximab and adalimumab drug levels and neutralising antibodies. An overview of recommendations is presented in Appendix 2.

According to these recommendations, tests for the therapeutic monitoring of TNF-α inhibitors and antibodies to TNF-α inhibitors may be done in two ways:

- Concurrent testing: tests for TNF-α-inhibitor drug levels and antibodies to TNF-α inhibitors are performed at the same time.

- Reflex testing: the test for TNF-α-inhibitor drug levels is conducted first and the result used to guide follow-up testing by the laboratory without a further request from the treating clinician. If the drug is undetectable, testing for antibodies to the TNF-α inhibitor would be done. If TNF-α inhibitor is present in the sample, then testing for antibodies would not be done.

2 Decision problems

2.1 Purpose of the decision to be made

The purpose of this work is to provide NICE with the most up to date evidence on the effectiveness and cost-effectiveness of alternative testing and monitoring approaches using ELISAs for assessing TNF-α inhibitor levels and antibodies to TNF-α inhibitors levels in people with RA in the UK.

The 'decision problem' is in fact potentially (i.e. relevant empirical data allowing) a number of discrete decision problems, because:

- There are 15 alternative patient target populations for whom different testing/monitoring strategies might be deemed cost-effective (this is because there are 5 different TNF-α inhibitors, multiplied by the 3 specific circumstances in which such circulating drug and drug anti-body testing is deemed to be clinically appropriate: primary non-response, secondary non-response, remission/low disease activity
- Also, depending on which TNF-α inhibitor a patient is taking, there are between 2 and 6 alternative testing kits/diagnostic services, plus the alternative of current clinical judgement with use of composite treatment response scores (DAS28, EULAR)

If data permit, the treatment effect data will be pooled and an average effect will be estimated.

NB. Empirical data permitting, other potential variations in the mode of provision of treatment monitoring (e.g. concurrent vs reflex testing on antibodies; free vs total drug/antibody testing) might be explored through supplementary scenario analyses, rather than as part of the main reference case analyses.

2.2 Clear definition of the interventions

The interventions to be evaluated are biochemical ELISA testing kits for measuring the level of TNF-α inhibitor or antibodies to TNF-α inhibitor, typically in the period immediately before administration of their next dose (i.e. trough levels), conducted in addition to current clinical practice in the UK, i.e. clinical assessment and monitoring using a composite score such as DAS28.

There are six companies providing different test kits or testing services for up to five TNF-α inhibitors or the antibodies to those TNF-α inhibitors (see below and Table 8).

Promonitor ELISA kits (Grifols - Progenika):

- Promonitor-ADL-1DV
- Promonitor-ANTI-ADL-1DV
- Promonitor-ETN-1DV
- Promonitor-ANTI-ETN-1DV
- Promonitor- IFX-1DV

- Promonitor-ANTI-IFX-1DV
- Promonitor-GLM-1DV
- Promonitor-ANTI-GLM-1DV

IDKmonitor ELISA kits (Immundiagnostik/BioHit Healthcare):

- IDKmonitor Adalimumab drug level
- IDKmonitor Adalimumab free ADA
- IDKmonitor Adalimumab total ADA
- IDKmonitor Etanercept drug level
- IDKmonitor Etanercept free ADA
- IDKmonitor Infliximab drug level
- IDKmonitor Infliximab free ADA
- IDKmonitor golimumab drug level
- IDKmonitor golimumab free ADA

LISA-TRACKER ELISA kits (Theradiag):

- LISA-TRACKER Adalimumab (LTA002)
- LISA-TRACKER anti-Adalimumab (LTA003)
- LISA-TRACKER Duo Adalimumab (LTA005)
- LISA-TRACKER Certolizumab (LTC002)
- LISA-TRACKER anti-Certolizumab (LTC003)
- LISA-TRACKER Duo Certolizumab (LTC005)
- LISA-TRACKER Etanercept (LTE002)
- LISA-TRACKER anti-Etanercept (LTE003)
- LISA-TRACKER Duo Etanercept (LTE005)
- LISA-TRACKER Infliximab (LTI002)
- LISA-TRACKER anti-Infliximab (LTI003)
- LISA-TRACKER Duo Infliximab (LTI005)
- LISA-TRACKER Golimumab (LTG002)
- LISA-TRACKER anti-Golimumab (LTG003)

RIDASCREEN (R-Biopharm):

- RIDASCREEN ADM monitoring

- RIDASCREEN anti-ADM antibodies
- RIDASCREEN IFX monitoring
- RIDASCREEN anti-IFX antibodies

MabTrack ELISA kits (Sanquin)

- MabTrack level adalimumab M2910
- MabTrack ADA adalimumab M2950
- MabTrack level infliximab M2920
- MabTrack ADA infliximab M2960

Sanquin Diagnostic Services (testing service using validated ELISAs)

- Adalimumab drug levels
- Certolizumab drug levels
- Etanercept drug levels
- Etanercept anti-drug antibodies
- Golimumab drug levels
- Infliximab drug levels

2.3 Populations

People with rheumatoid arthritis who are being treated with a TNF-α inhibitor (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab), and:

- have achieved treatment target (remission or low disease activity) or,
- experience a primary non-response or,
- experience a secondary non-response

There are therefore 15 alternative patient target populations for whom different testing/monitoring strategies might be deemed cost-effective (this is because there are 5 different TNF-α inhibitors, multiplied by the 3 specific circumstances in which such circulating drug and drug anti-body testing is deemed to be clinically appropriate: primary non-response, secondary non-response, remission/low disease activity).

2.4 Place of the intervention in the treatment pathway(s)

There are three clinical scenarios in which the assays described in Section 2.2 may be used:

- **Remission/low disease activity**: Testing for drug levels and anti-drug antibodies 6 to 12 months after achieving treatment target (remission or low disease activity) to check whether continued treatment at the same dose is appropriate

- **Primary non-responders** (defined as those who have little to no improvement in clinical signs and symptoms initially and as treatment continues), and
- **Secondary non-responders** (people with an initial response to a TNF-α inhibitor followed by loss of efficacy).

  Testing could help clinicians and patients to understand the reasons why there is a non-response or loss of response. It could also indicate whether non-response could be because treatment non-adherence.

2.5 Relevant comparator

~~For any given patient with RA, who is taking a particular TNF-α inhibitor and who is experiencing either remission or non-response, there are between 2 and 6 testing kits/services available to assess circulating drug levels and drug anti-body levels.~~

If data permit, within each patient group as defined in 2.3~~this way~~, the ELISA testing kits will be compared against each other and against the drug treatment monitoring using clinical judgement composite scores such as DAS28.

2.6 Key factors to be addressed

There is unpredictability in the action of TNF-α inhibitors in rheumatoid arthritis patients and subjective outcomes are often used to guide TNF-α inhibitor therapy. Promonitor test or other alternative tests can be used to monitor treatment response to TNF-α inhibitors in patients with rheumatoid arthritis. ~~However, it is unclear about~~ The clinical impact of using these tests for monitoring response to TNF-α inhibitors in rheumatoid arthritis patients, especially in terms of improvement on patients' disease activity and health related quality of life, will be assessed. The main challenge relates to the availability of relevant high-quality evidence.

3 Report methods for assessing the outcomes arising from the use of the interventions

This project will assess the clinical effectiveness of using tests for monitoring response to TNF-α inhibitors in rheumatoid arthritis patients. The following key objective is proposed:

- To perform a systematic review of the clinical effectiveness of tests for monitoring response to TNF-α inhibitors in patients with rheumatoid arthritis

3.1 Inclusion criteria

The inclusion criteria for clinical effectiveness reviews are as follows:

3.1.1 Population

The eligible population will be patients with rheumatoid arthritis who are being treated with a TNF-α inhibitor (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab), and:

- have achieved treatment target (remission or low disease activity) or,
- experience a primary non-response or,
- experience a secondary non-response

3.1.2 Interventions

ELISA test kits or diagnostic services used to monitor response to TNF-α inhibitor treatments for rheumatoid arthritis patients will be eligible for inclusion. These tests run on an enzyme-linked immunosorbent assay (ELISA) technology platform, are used to measure drug levels (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab) or their anti-drug antibodies (anti-etanercept, anti-infliximab, anti-adalimumab, anti-certolizumab pegol, and anti-golimumab). A serum sample is needed to perform an ELISA test.

Eligible ELISA tests can be run with or without automation platforms and may be used with any ELISA platform or the Tritutus and SQII platforms. Each test only needs to be run once, potentially allowing for high throughput. The test should be intended for monitoring purpose to predict treatment response to biologic therapies in rheumatoid arthritis patients.

The ELISA testing kits or diagnostic services shown below will be included (see also Table 8).

Promonitor ELISA kits (Grifols-Progenika):

- Promonitor-ADL-1DV
- Promonitor-ANTI-ADL-1DV
- Promonitor-ETN-1DV
- Promonitor-ANTI-ETN-1DV
- Promonitor-GLM-1DV
- Promonitor-ANTI-GLM
- Promonitor- IFX-1DV

- Promonitor-ANTI-IFX-1DV

IDKmonitor ELISA kits (Immundiagnostik/BioHit Healthcare):

- IDKmonitor adalimumab drug level
- IDKmonitor adalimumab free ADA
- IDKmonitor adalimumab total ADA
- IDKmonitor etanercept drug level
- IDKmonitor etanercept free ADA
- IDKmonitor golimumab
- IDKmonitor golimumab free ADA
- IDKmonitor infliximab drug level
- IDKmonitor infliximab free ADA
- IDKmonitor infliximab total ADA

LISA-TRACKER ELISA kits (Theradiag):

- LISA-TRACKER Adalimumab (LTA002)
- LISA-TRACKER anti-Adalimumab (LTA003)
- LISA-TRACKER Duo Adalimumab (LTA005)
- LISA-TRACKER Certolizumab (LTC002)
- LISA-TRACKER anti-Certolizumab (LTC003)
- LISA-TRACKER Duo Certolizumab (LTC005)
- LISA-TRACKER Etanercept (LTE002)
- LISA-TRACKER anti-Etanercept (LTE003)
- LISA-TRACKER Duo Etanercept (LTE005)
- LISA-TRACKER Golimumab (LTG002)
- LISA-TRACKER anti-Golimumab (LTG003)
- LISA-TRACKER Duo Gloimumab (LTG005)
- LISA-TRACKER Infliximab (LTI002)
- LISA-TRACKER anti-Infliximab (LTI003)
- LISA-TRACKER Duo Infliximab (LTI005)

RIDASCREEN ELISA kits (R-Biopharm)

- RIDASCREEN ADM monitoring
- RIDASCREEN anti-ADM antibodies

- RIDASCREEN IFX monitoring
- RIDASCREEN anti-IFX antibodies

MabTrack ELISA kits (Sanquin)

- MabTrack level adalimumab M2910
- MabTrack ADA adalimumab M2950
- MabTrack level infliximab M2920
- MabTrack ADA infliximab M2960

Sanquin Diagnostic Services (testing service using validated ELISAs)

- Adalimumab drug levels
- Certolizumab drug levels
- Etanercept drug levels
- Etanercept anti-drug antibodies
- Golimumab drug lelves
- Infliximab drug levels

The use of both free and total anti-drug antibody assays for these tests will be assessed, depending on the availability of assessment data relating to both assays.

The intervention tests will be used in addition to current clinical practice (clinical assessment and monitoring using a composite score such as DAS28).

3.1.3 Comparator

Standard care for people with RA where treatment decisions are based on clinical judgements and other measures (e.g. DAS28), without measuring circulating drug levels and anti-drug antibodies by ELISA tests.

3.1.4 Outcomes

3.1.4.1 Clinical outcomes

The following outcomes will be included:

- Number of inconclusive results
- Time to result
- Number, direction and magnitude of dose changes
- Frequency of dose adjustment (e.g. dose reduction) due to monitoring response
- Frequency of treatment switch to an alternative biologic
- Discontinuation of ineffective therapy
- Patient related outcomes:
    - Change in disease activity
    - Rates of disease response, relapse and remission
    - Duration of response, relapse and remission

- Rates of hospitalisation
- Rates of surgical intervention
- Adverse effects of treatment such as infections
- Health related quality of life

The following types of report will be excluded: editorials and opinions; case reports; reports focusing only on technical aspects of the technologies (such as technical descriptions of the testing process). Studies with a sample size of 20 or less will be excluded due to inadequate statistical power. For studies that include rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients, we will only include studies with at least 70% of rheumatoid arthritis patients. The relevance of any studies that include less than 70% rheumatoid arthritis patients will be discussed with clinical experts, and we will contact study authors to try and get subgroup data for rheumatoid arthritis patients. We will select the most recent or most complete report in cases of multiple reports for a given study or when we cannot exclude the possibility of overlapping populations.

3.1.4.2 Cost-effectiveness outcomes

For the review of cost effectiveness, the outcomes to be assessed for interventions and comparators are the cost and/or cost-effectiveness of an intervention or comparator.

3.2 Study design

For the review of clinical effectiveness, clinical trials (including both randomised and nonrandomised controlled trials) that evaluated clinical effectiveness outcomes of using the intervention tests to monitor treatment response in rheumatoid arthritis patients who received TNF-α inhibitor therapies (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) will be included. We will also include observational studies that evaluated the clinical effectiveness of the intervention tests to monitor treatment response in rheumatoid arthritis patients, providing they report any of those relevant clinical outcomes for this assessment (see Section 3.1.4.1). The primary clinical outcomes will be patient related outcomes including improvement on disease activity and health related quality of life.

3.3 Search strategy

The search strategy, which will identify both evidence on effectiveness and cost-effectiveness will comprise the following main elements:

- Searching of electronic databases;
- Contact with experts in the field;
- Scrutiny of bibliographies of retrieved papers (citation chasing);
- Follow-up on mentions of potentially relevant HTAs;
- Checking progress of on-going trials mentioned in key prior systematic reviews

The main electronic databases of interest will be:

- Medline & Medline in Process (OVID)
- Embase (OVID)
- PsycINFO (OVID)
- HMIC (OVID)
- Econlit (EBSCO)

- Cinahl (EBSCO)
- Web of Science (ISI)
- The Cochrane Library (ALL)
- BIOSIS (Thomson Reuters)
- NRR (National Research Register)
- Web of Science Proceedings
- Current Controlled Trials
- Clinical Trials.gov
- FDA website
- EMEA website
- Cochrane Register of Diagnostic Test Accuracy Studies (CRDTAS)

Searches will be limited to human only populations; there will be no search filters applied for study design or date. As these technologies are still very new, we will search for observational studies as well as for clinical trials and will include cohort and case-control studies in our searches.

Study design search filters will be used to identify studies reporting costs, economics, utilities and the development of decision models. The searches will be developed and implemented by a trained information specialist and will be piloted by the review team prior to agreeing the final search syntax. This final syntax will be clinically approved by our clinical experts prior to the searches being run.

Scoping searches for this review have yielded 1229 results in Medline (without study or language filters) - see Appendix 3 for search strategy.

3.4 Study selection strategy

Two reviewers will screen independently the titles and abstracts (if available) of all reports identified by the search strategy. Full text copies of all studies deemed to be potentially relevant will be obtained and two reviewers will independently assess them for inclusion. Any disagreements will be resolved by consensus or arbitration by a third reviewer.

3.5 Data extraction strategy

A data extraction form will be developed and piloted. One reviewer will independently extract details from full text studies of study design, participants, intervention and outcome data. The data extraction will be checked by another reviewer. Any disagreements will be resolved by consensus or arbitration by a third reviewer.

For studies reporting clinical event outcomes we will extract data on these as numbers of patients experiencing the specified outcome. For studies reporting continuous outcomes we will extract data on these as mean and standard deviation. Mean differences, relative risks or odds ratios (with 95% confidence intervals) will be extracted from comparative studies, where reported. Results adjusted for potential confounding factors will be extracted preferentially.

For studies in which only a subgroup of patients will be included in the review, we will extract, analyse and present data for this subgroup only. If some data are unclear or missing, we will attempt to contact study authors to obtain additional data.

3.6 Quality assessment strategy

One reviewer will independently assess the quality of all included studies in terms of risk of bias. The Cochrane risk of bias tool for randomised studies and the Cochrane (ROBINS-1) tool for non-randomised studies will be used and adapted as appropriate. The quality assessment will be checked by another reviewer. Any disagreements will be resolved by consensus or arbitration by a third reviewer.

3.7 Methods of analysis/synthesis

3.7.1 Clinical-effectiveness review

For clinical effectiveness outcomes, meta-analyses will be performed when outcomes are reported consistently for analyses to be feasible. Otherwise, results will be synthesised in a narrative fashion. Where meta-analyses are performed, data will be pooled using standard random-effects DerSimonian-Laird meta-analyses. Data analyses will be conducted in Stata software. Studies that include 20 patients or less will be excluded from the analyses.

3.7.2 Exploration of heterogeneity

For clinical effectiveness outcomes, where possible, statistical heterogeneity will be assessed using the I^2 statistic. Subgroup analyses and sensitivity analyses will be performed to explore heterogeneity where feasible. Potential sources of heterogeneity will be taken into account for the interpretation of the results.

We will perform the following subgroup analyses to explore potential sources of heterogeneity:

- A subgroup of patients who have achieved treatment target (remission or low disease activity)
- A subgroup of patient who have experienced a primary non-response
- A subgroup of patient who have experienced a secondary non-response

We will also consider other factors such as different time of testing and testing method (e.g. reflex vs. concurrent) to explore potential sources of heterogeneity.

3.7.3 Sensitivity analysis

For clinical effectiveness outcomes, sensitivity analyses will be performed to explore robustness of the results according to study quality based on results from the Cochrane risk of bias tool. Sensitivity analyses will also be performed by excluding studies with a sample size (<50 patients).

Where participants from several studies are recruited from the same cohorts, we will include data from only one study with the most reliable reporting in the analyses.

4 Report methods for synthesising evidence of cost-effectiveness

4.1 Identifying and systematically reviewing published cost-effectiveness studies

A search of the literature for published economic evaluations, cost and quality of life (utility) studies will be performed. The search strategy for cost effectiveness will be based on the strategy for the clinical effectiveness review.

4.1.1 Population, intervention, comparators, outcomes and study designs

As described in Sections 3.1 and 3.2 except that study designs will include economic evaluations and comparative cost analyses. Economic evaluation sub-types that will be included are: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses, cost-minimisation analyses, cost-consequence analyses, or cost-offset analyses.

For the review of economic evaluations, studies can be based on trials, other data sources (e.g. registries), decision models, or systematic reviews of existing economic evaluations. If set in the NHS, studies must report costs and/or resource use. If not set in the NHS, studies must report incremental costs and/or resource use, as well as incremental effectiveness outcomes. Studies not reporting incremental outcomes but reporting sufficient information for these to be calculated will also be included.

4.1.2 Search strategy

As described in Section 3.3

4.1.3 Study selection strategy

As described in Section 3.4

4.1.4 Data extraction and quality assessment

Data will be extracted to capture all the key information relation to study aims, approach (model-based, trial-based, other), interventions and comparators, outcomes, types of resource use included, time horizon, perspective, discounting, results (per comparator and incremental) and the assessment of uncertainty.

Where studies do not conduct a full incremental cost-effectiveness analysis (e.g. if they perform a cost–consequences analysis), but it is possible to conduct an incremental analysis based on reported results, this will be done. Currency conversion will not be performed, but an indication will be given of purchasing-power-parity exchange rates, and if currency- or country-specific cost-effectiveness thresholds are supplied by the authors these will also be reported (in the original currency).

Quality assessment of full economic evaluations will be conducted using the CHEC criteria list (Evers et al 2005 [8]) for assessing the quality of economic evaluations.

4.1.5 Evidence synthesis

The evidence of cost-effectiveness will be summarised and synthesised primarily using tables and text (i.e. narrative synthesis) to describe the findings, validity and relevance of the included studies to the present decision problem and the UK healthcare context.

4.2 Development of a health economic model

A health economic model will be developed to assess the cost-effectiveness of using ELISA tests relative to the alternatives and standard care. Costs will be included from the NHS and Personal Social Services perspective. Among the cost consequences to be measured are the costs of testing, treatments received by RA patients, and healthcare costs. Assay/test costs will include those of test kits, staff time to perform test, and staff training (if not covered by the companies) or cost of testing service including sample transport. A discount rate of 3.5% will be applied both for costs and QALYs. Cost-effectiveness results will be presented as incremental cost-effectiveness ratios (ICERs) of incremental costs to incremental QALYs. The lifetime time horizon may be used to reflect the chronic nature of RA.

The approach will be to develop a model of cost effectiveness of ELISA testing for therapeutic drug monitoring in RA, using an existing model as a starting point or, where an appropriate model does not exist, develop a de novo health economic model. The decision on whether an appropriate model exists will be informed by the systematic review of cost-effectiveness studies. The economic analysis will adhere to the NICE Diagnostic Assessment Programme Manual [9].

The effectiveness of the alternative testing kits will be estimated from published studies identified in the systematic review of clinical effectiveness. Model parameters will generally be taken from the systematic reviews of cost effectiveness and a systematic search of the literature of utility values. Supplemental reviews may be done to address specific additional parameter requirements for the model. Given that there may be a large number of model parameters, it cannot be guaranteed that these will be systematic reviews. However, if an existing systematic review is available, that will be used, or if not, the approach to the review will be as systematic as possible, particularly with respect to documentation of the approach taken.

Costs for the model will be obtained from NHS Reference Costs, the Personal Social Services Research Unit (PSSRU), the British National Formulary (BNF) and any other relevant sources of data identified.

Utility values will preferably be obtained from literature or by clinical expert elicitation in the absence of published estimates.

If data permit, we will compare the following ELISA kits with each other (Table 8):

- Promonitor
- IDKmonitor ELISA kits
- LISA-TRACKER ELISA kits
- RIDASCREEN
- MabTrack ELISA kits
- Sanquin Diagnostic Services

Given available evidence, comparisons will also be made between relevant treatment response monitoring technologies and the comparator.

Table 8: ELISA kits for detecting free TNF-α inhibitor and free anti-drug antibody levels

		Promonitor	IDKmonitor	LISA-TRACKER	RIDASCREEN	MabTrack	Sanquin Diagnostic Services
Adalimumab	drug	X	X	X	X	X	X
	antibody	X	X[1]	X	X	X	
Etanercept	drug	X	X	X			X
	antibody	X	X	X			X
Infliximab	drug	X	X[1]	X	X	X	X
	antibody	X	X	X	X	X	
Golimumab	drug	X	X	X			X
	antibody	X	X	X			
Certolizumab pegol	drug			X			X
	antibody			X			

[1] Test for total anti-drug antibodies is also available. Total anti-drug antibodies include both unbound (free) antibodies and those bound to TNF-α inhibitor.

Treatments will include TNF-α inhibitors: adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab. If data permit, the treatment effect data will be pooled and an average effect will be estimated.

The following comparisons will be conducted as scenario analyses where possible:

- Concurrent versus reflex testing
- Testing for free (unbound) compared with total levels of drug or antibody

4.2.1 Exploration of uncertainty

The effect of uncertainty in parameter values upon the cost-effectiveness will be explored through univariate sensitivity analyses and probabilistic analyses if feasible and potentially informative. Alternative testing algorithms will be explored in scenario analyses based on available data.

5 Handling information from the companies

All data submitted by the company(s) will be considered if received by the EAG no later than 17h September, 2018. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data provided and specified as such will similarly be highlighted in yellow and underlined.

6 Competing interests of authors

All authors confirm that they have no potential competing interests.

7 Timetable/milestones

Milestone	Date to be completed
Draft protocol	15 June, 2018
Final protocol	5 July, 2018
Progress report	3 October, 2018
Draft assessment report	3 December, 2018
Final assessment report	3 January, 2019

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Abbreviations

cDMARD	conventional DMARD
DAS	disease activity score
DMARDs	disease modifying anti-rheumatic drugs
EAG	External Assessment Group
ELISA	enzyme-linked immunosorbent assay
EULAR	European League Against Rheumatism
ICER	incremental cost-effectiveness ratio
NICE DSU	National Institute for Health and Care Research Decision Support Unit
PenTAG	Peninsula Technology Assessment Group
QALYs	quality-adjusted life-years
RA	rheumatoid arthritis
TNF	tumour necrosis factor

Appendix 1. Biologic drugs pathways reported by Greater Manchester Medicines Management Group

Figure 4: Pathway for first choice biologic

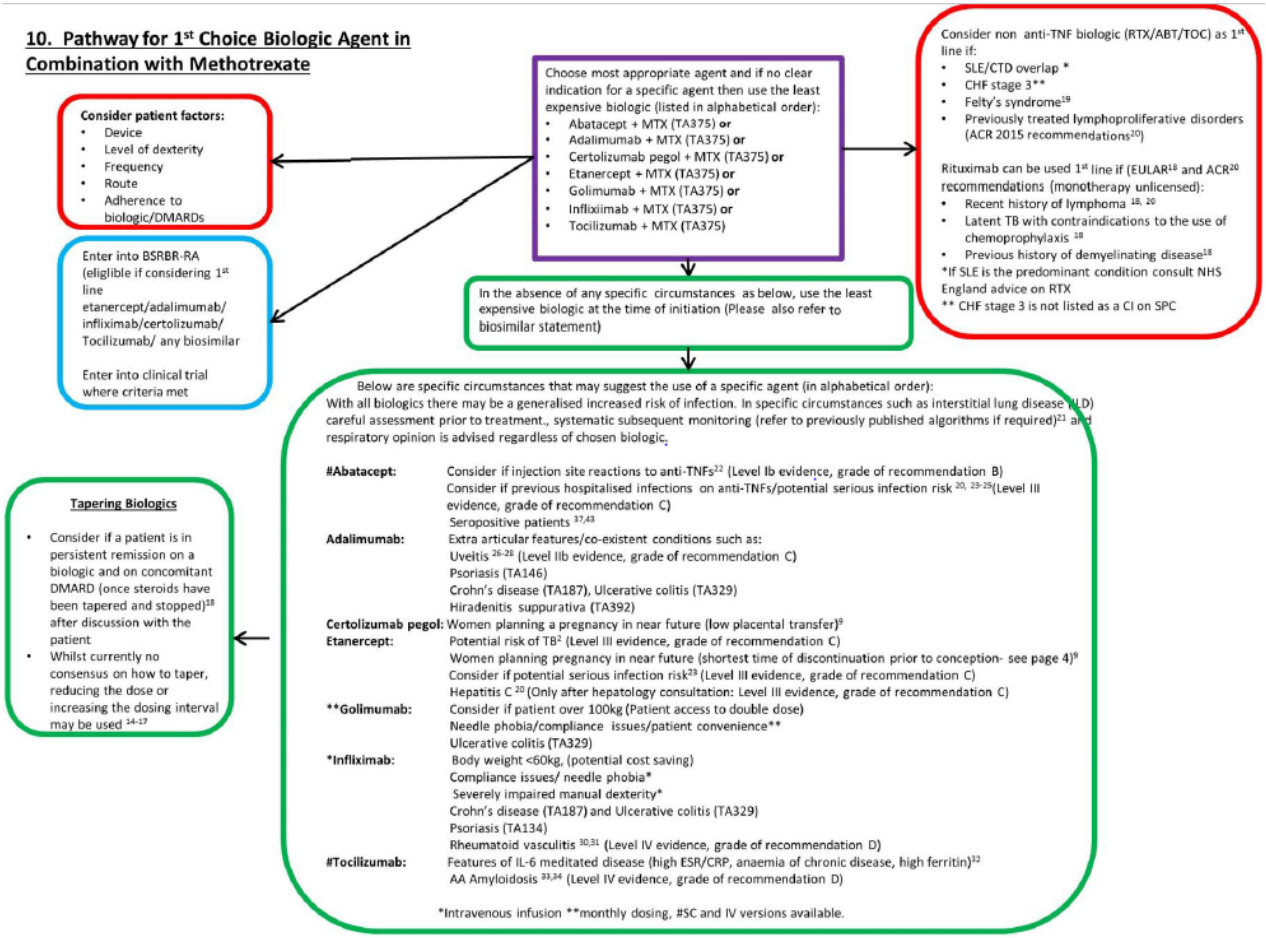


Figure 5: Pathway for primary non-responders to biologic agent in combination with methotrexate

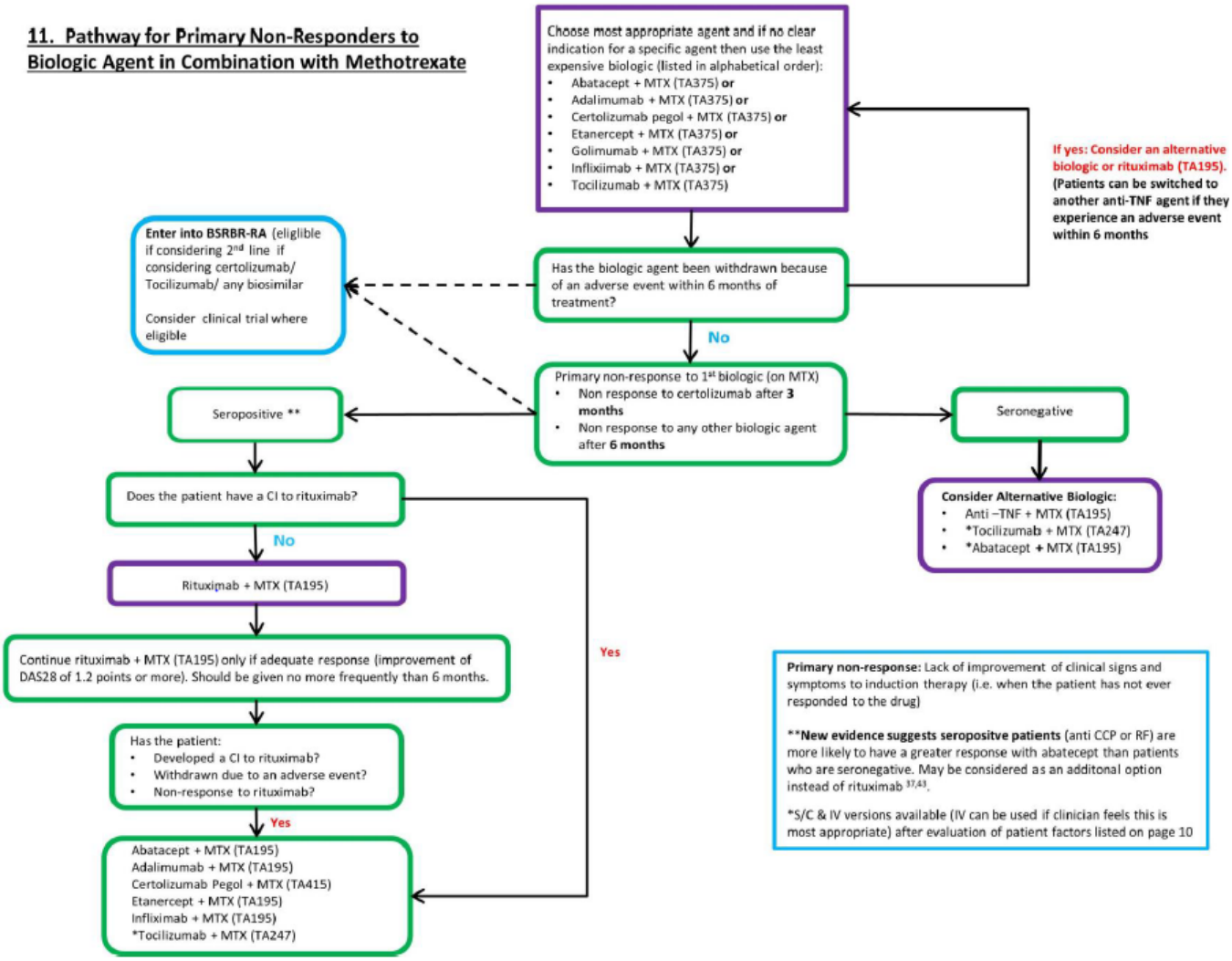


Figure 6: Pathway for secondary non-responders to biologic agent in combination with methotrexate

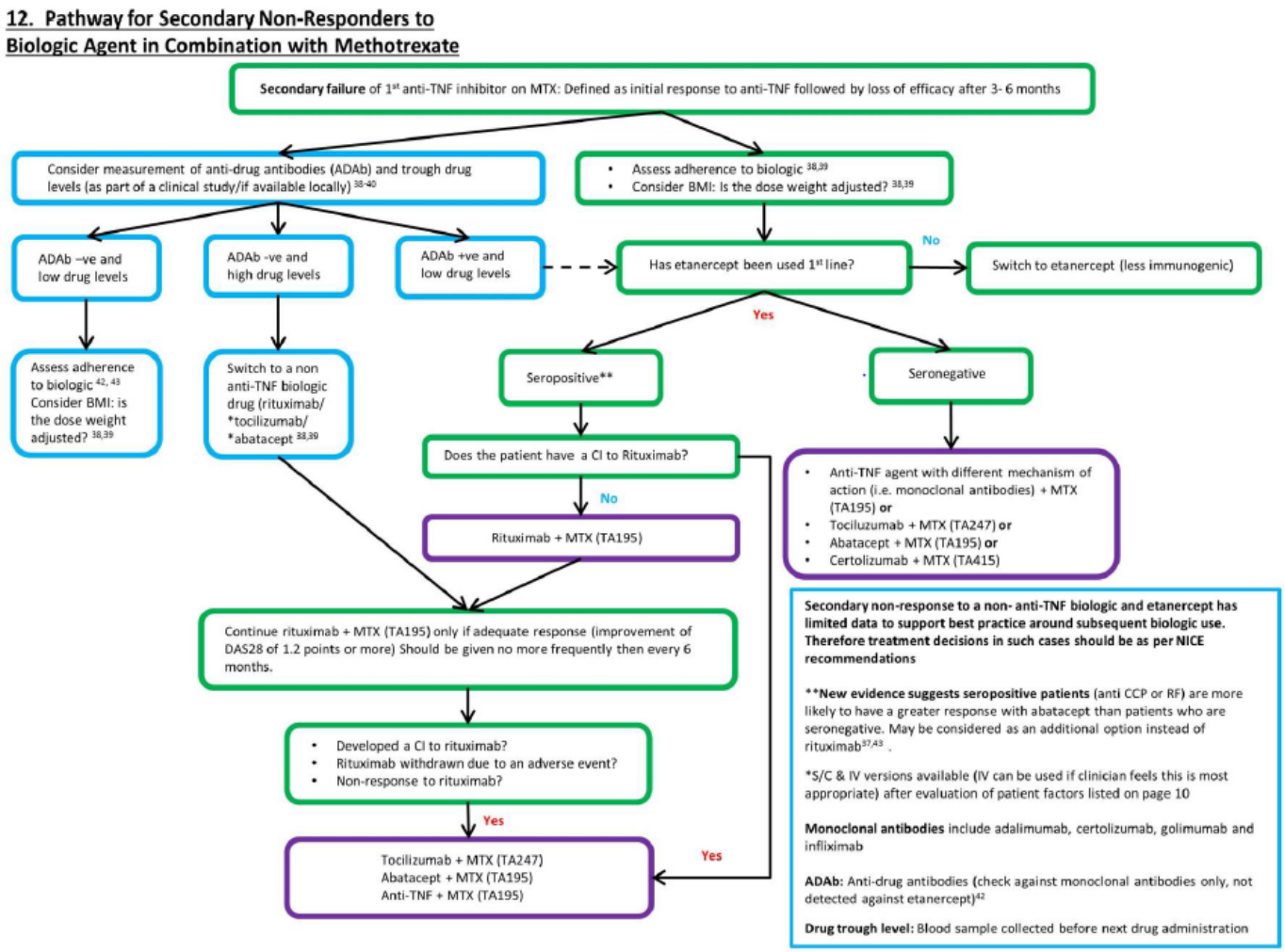
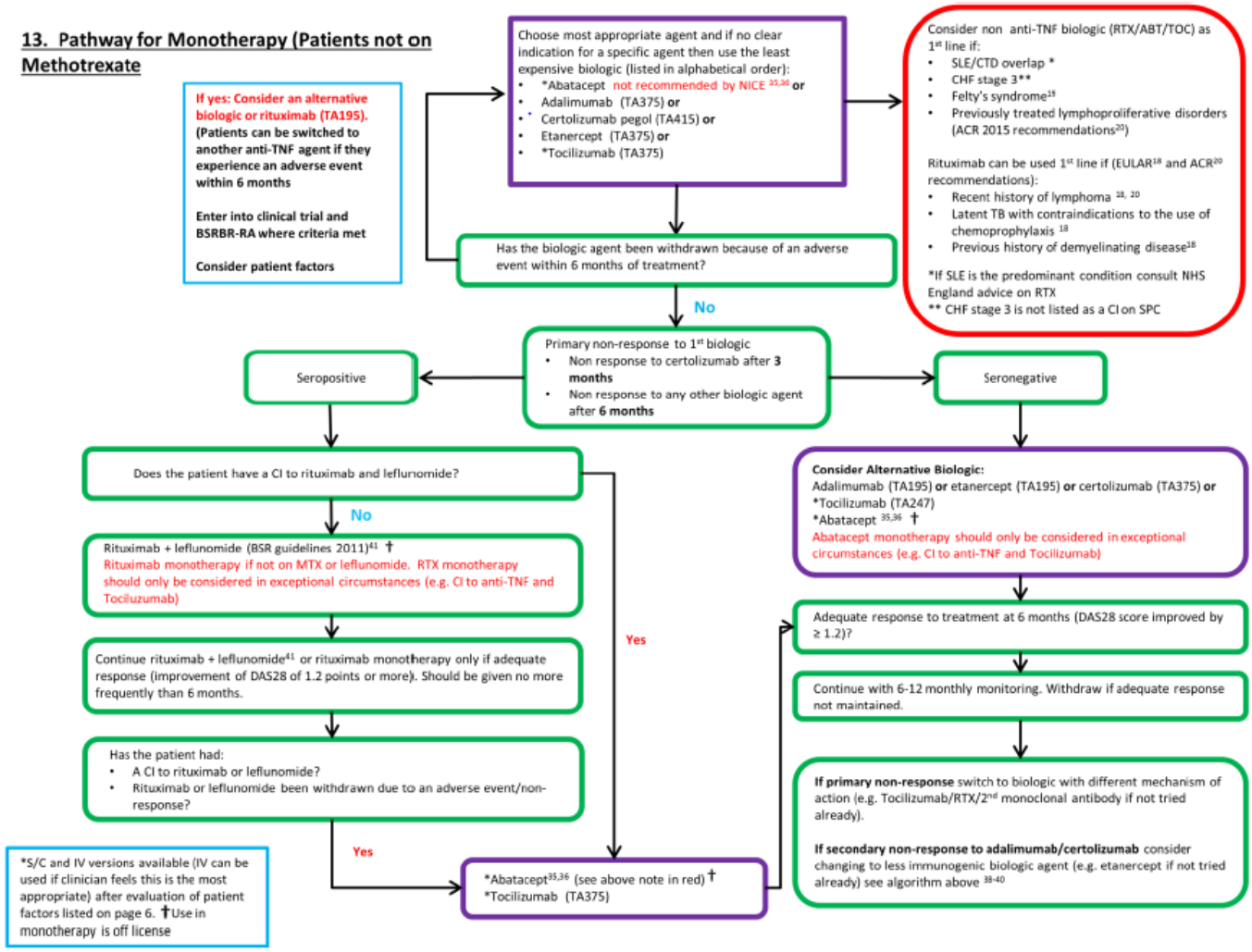


Figure 7: Pathway for monotherapy in patients not on methotrexate



Appendix 2. Recommendations by NHS Greater Glasgow and Clyde

Serum sample required for trough level should be taken pre-infusion for infliximab and no earlier than 3-5 days prior to injection date for adalimumab. Test results are interpreted as follows (Table 9, Figure 8 and Figure 9):

- Levels below the lower limit suggest secondary failure of response or poor compliance. Presence of neutralising antibody may be present in the former.
- Levels above the upper limit suggest overtreatment.

Table 9: Interpretation

Analyte	Lower limit of assay	Upper limit of measurement	Units
Adalimumab	0.4	14	ug/mL
Infliximab	0.3	14	ug/mL

Figure 8: Interpretation: 3-6/12 after initiation of therapy to guide drug dose/infusion time interval

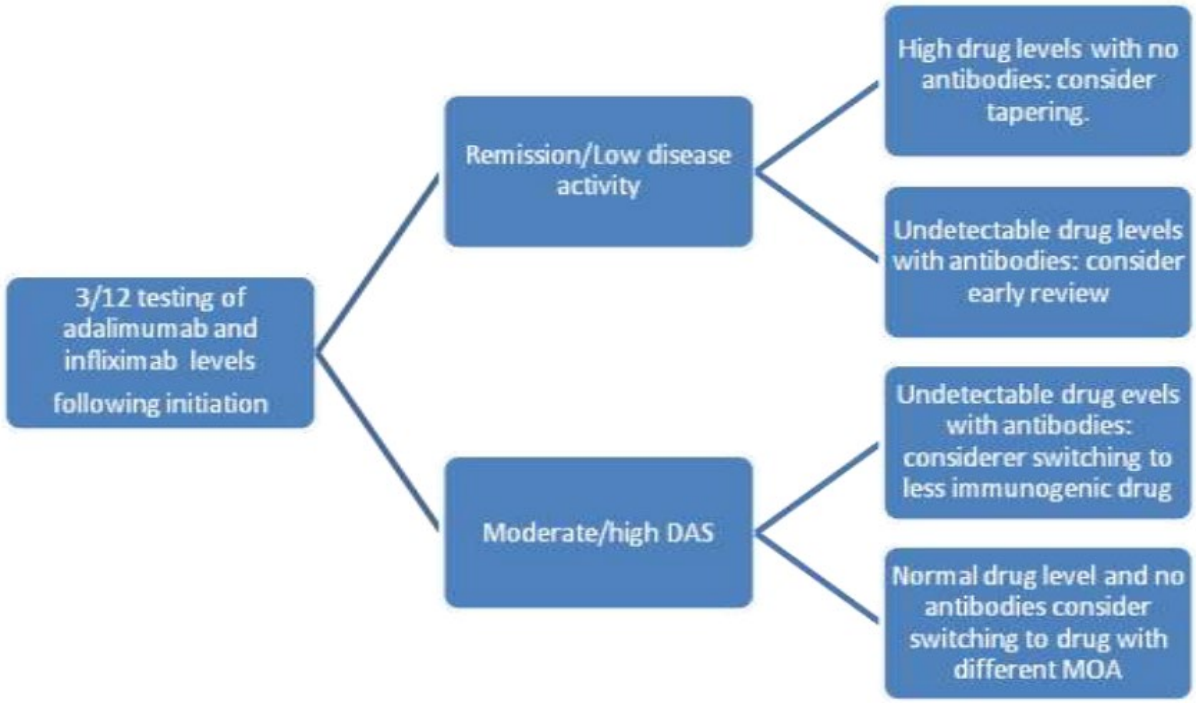
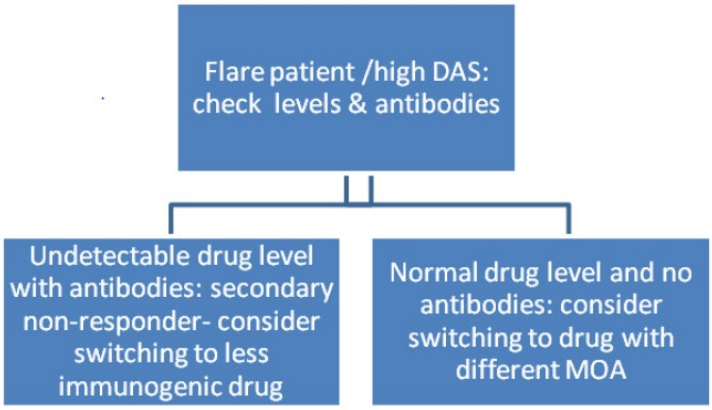


Figure 9: Interpretation: anti-TNF failure of response



Interpretation: considering dose reduction

- High/normal drug levels confer favourable likelihood of success.
- Undetectable drug levels with presence of antibodies suggest drug is not required for the patient's remission. Consider stopping therapy.

Appendix 3. Draft search strategy (Medline only)

1	((anti-TNF$ or antiTNF$ or TNF$) adj2 inhibitor$).kw.	56
2	anti$ tumo?r$ necrosis$ factor$.kw.	199
3	Tumor Necrosis Factor-alpha/	114483
4	exp Antibodies, Monoclonal/	212502
5	anti$ drug$ antibod$.kw.	116
6	etanercept.mp. or ETANERCEPT/	7451
7	adalimumab.mp. or ADALIMUMAB/	6489
8	infliximab.mp. or INFLIXIMAB/	12613
9	or/1-8	322969
10	exp Enzyme-Linked Immunosorbent Assay/	142093
11	(immundiagnostik$ or immunodiagnostik$ or immunediagnostik$).tw.	24
12	(proteomika$ or promonitor$).tw.	14
13	enzyme$ link$ immunoassay$.tw.	3281
14	enzyme$ link$ immuno$ assay$.tw.	80260
15	ELISA$.tw.	147633
16	or/10-15	251345
17	exp Arthritis, Rheumatoid/	105191
18	RA.mp.	65393
19	Rheumarthrit*.tw.	3
20	((Rheumatoid* or rheumatic*) adj3 (arthrit* or polyarthrit*)).tw.	95714
21	17 or 18 or 19 or 20	161963
22	9 and 16 and 21	1229

Appendix 4. Details of EAG and clinical advisors

Name	Institution	Role/expertise
TAR team		
Martin Hoyle	PenTAG, UEMS	Professor of Heath Technology Assessment; Project Director until 29th June, 2018
Stuart Logan	PenCLAHRC, UEMS	Director; Project Director after 29th June, 2018
Irina Tikhonova	PenTAG, UEMS	Research Fellow; cost-effectiveness lead and overall project lead
Huiqin Yang	PenTAG, UEMS	Senior Research Fellow; clinical effectiveness lead and network meta-analysis
Mohsen Rezaei Hemami	PenTAG, UEMS	Research Fellow; economic modelling
Segun Bello	PenTAG, UEMS	Postdoctoral Research Associate; systematic reviewer
Sophie Robinson	PenTAG, UEMS	Information Specialist; information science
Jaime Peters	PenCLAHRC, UEMS	Senior Research Fellow; economic modelling
Sophie Dodman	PenTAG, UEMS	Research Assistant; systematic reviewer
Andriy Kharechko	PenTAG, UEMS	Postdoctoral Research Associate; economic modelling
Sue Whiffin	ESMI, UEMS	Senior Administrator; project coordinator
Jenny Lowe	ESMI, UEMS	Administrator; document retrieval
Clinical advisors		
Richard Haigh	RD&E Hospital	Consultant Rheumatologist
Meghna Jani	University of Manchester	NIHR Clinical Lecturer in Rheumatology
Timothy McDonald	RD&E Hospital, UEMS	Consultant Clinical Scientist & Clinical Associate Professor

PenTAG, Peninsula Technology Assessment Group; RD&E, the Royal Devon and Exeter; UEMS, University of Exeter Medical School