NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis

The National Institute for Health and Care Excellence (NICE) is producing guidance on using enzyme-linked immunosorbent assay (ELISA) tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services) in rheumatoid arthritis in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the diagnostics assessment report and corresponding erratum and addenda).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

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- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on the use of ELISA tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services) in rheumatoid arthritis in the NHS in England. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics assessment programme manual.

Key dates:

Closing date for comments: 4 April 2019

Second diagnostics advisory committee meeting: 16 April 2019

1 Recommendations

1.1 Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis. The ELISA tests covered by this guidance are Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services.

1.2 Laboratories currently using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis should do so as part of research and further data collection (see sections 5.3 and 5.21).

1.3 Further research is recommended on the clinical effectiveness of using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis (see sections 5.22, 6.1 and 6.2).

Why the committee made these recommendations

Tumour necrosis factor (TNF)-alpha inhibitors can be an effective treatment option for severe rheumatoid arthritis that does not respond to conventional therapy. Therapeutic monitoring of TNF-alpha inhibitors could help to optimise their use, improving management of the condition and outcomes that are important for people with rheumatoid arthritis. These include how long their disease is in remission, the rate of flares and relapse, and health-related quality of life.

The clinical effectiveness evidence for ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis is not robust, although there are some positive trends. The key INGEBIO study is of poor quality and is not generalisable to NHS practice.

Results of the economic model based on INGEBIO are uncertain. So, although the tests show some promise, they are not recommended for routine use in the NHS. Further research would be valuable.

2 Clinical need and practice

The problem addressed

2.1 Tumour necrosis factor (TNF)-alpha inhibitors are recommended as treatment options for people with severe rheumatoid arthritis (disease activity score [DAS28] greater than 5.1) whose disease does not respond to intensive conventional therapy (a combination of conventional disease-modifying antirheumatic drugs [DMARDs]).

2.2 In some people, the disease does not respond to treatment with TNF-alpha inhibitors or stops responding over time. This can be related to the formation of antibodies to TNF-alpha inhibitors and

fluctuations in circulating TNF-alpha inhibitor levels. Therefore, laboratory tests that measure the levels of these antibodies and the circulating drug could help clinicians understand the reasons for non-response (for example, to exclude poor adherence) and guide decisions on which treatment to offer next. Currently, although there is considerable interest in therapeutic drug monitoring, treatment decisions are usually based on clinical judgement alone.

2.3 Therapeutic monitoring of TNF-alpha inhibitors could also potentially benefit people whose rheumatoid arthritis has a sustained response to these drugs and who could be considered for dose reduction of their TNF-alpha inhibitor. Reducing the dose of TNF-alpha inhibitor is expected to lower the risk of unnecessary side effects such as serious infections, and lower the cost of treatment, without having a negative effect on outcomes. Currently, dose reduction is not routine NHS practice and if carried out, it is usually based only on clinical assessment and patient history.

2.4 The purpose of this assessment is to evaluate the clinical effectiveness and cost effectiveness of using enzyme-linked immunosorbent assay (ELISA) tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services) to measure circulating drug levels and antidrug antibodies for monitoring response to TNF-alpha inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol and golimumab) in people with rheumatoid arthritis who:

- have reached their treatment target (remission or low disease activity)
- have disease that has not responded to TNF-alpha inhibitors (primary non-response)
- have disease that has stopped responding to TNF-alpha inhibitors (secondary non-response).

The condition

2.5 Rheumatoid arthritis is a chronic systemic autoimmune disease, primarily causing inflammation, pain and stiffness (synovitis) in the joints. It affects approximately 0.8% of the population (around 500,000 people in the UK; Symmons et al. 2002). The disease affects about 2 to 3 times more women than men.

2.6 The course of rheumatoid arthritis varies considerably from person to person, but often results in substantial morbidity, impaired physical activity, poor quality of life, and reduced life expectancy. It is marked by relapses (when the disease flares up) and remission (when there are few or no signs or symptoms). Rheumatoid arthritis is currently incurable, and people will remain on treatment for the rest of their lives.

The care pathways

2.7 Initial diagnosis and management of rheumatoid arthritis, including monitoring of treatment response, are covered in the NICE Pathway on rheumatoid arthritis and the following NICE guidance:

- Rheumatoid arthritis in adults: management (2018) NICE guideline NG100.
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016) NICE technology appraisal guidance 375.
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010) NICE technology appraisal guidance 195.

2.8 People with active rheumatoid arthritis should have treatment with the aim of disease remission or low disease activity. Monitoring

treatment response allows treatment adjustments to be made. In current clinical practice, the DAS28 and the European League Against Rheumatism (EULAR) response classification system (which is based on the DAS28) are most commonly used to monitor disease activity.

2.9 People with rheumatoid arthritis whose disease does not respond to intensive conventional therapy (a combination of conventional DMARDs), and whose disease is severe (DAS28 greater than 5.1), may have treatment with biological therapy, including the TNF-alpha inhibitors adalimumab, etanercept, infliximab, certolizumab pegol and golimumab.

2.10 Treatment with a TNF-alpha inhibitor should only be continued if there is an adequate response (using EULAR criteria) 6 months after starting therapy. Treatment should be withdrawn if an adequate EULAR response is not maintained.

2.11 Currently, monitoring response to TNF-alpha inhibitors is usually based only on clinical assessment and patient history. A monitoring review appointment generally takes place 6 months after reaching the treatment target (remission or low disease activity) to ensure that the target has been maintained. Monitoring should continue every 6 to 12 months to assess disease activity, treatment response, functioning, quality of life, comorbidities, complications and the need for surgery, and to arrange multidisciplinary referrals.

2.12 Treatment options for people whose disease does not respond to treatment with TNF-alpha inhibitors or stops responding over time include switching to another TNF-alpha inhibitor or switching to treatment with a different mechanism of action.

2.13 Currently, dose reduction of TNF-alpha inhibitors in people whose disease is in sustained remission or has low disease activity is not

part of routine NHS practice in England and is not covered in NICE guidance. However, dose reduction is already being done in some centres. Also, the EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs recommend reducing the dose of biological DMARDs if a person's disease is in persistent remission after reducing their dose of glucocorticoids, especially if this treatment is combined with a conventional DMARD.

2.14 Adding therapeutic monitoring of circulating TNF-alpha inhibitor levels and antidrug antibodies to the current monitoring of response to TNF-alpha inhibitors could help inform treatment decisions for people with rheumatoid arthritis.

3 The diagnostic tests

3.1 The assessment compared 6 intervention tests (enzyme-linked immunosorbent assay [ELISA] tests; Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and in-house tests used by Sanquin Diagnostic Services) with 1 comparator (standard care). These ELISA tests are intended to be used for measuring the levels of tumour necrosis factor (TNF)-alpha inhibitors and antibodies to TNF-alpha inhibitors in the blood of people having TNF-alpha inhibitor treatment for rheumatoid arthritis.

3.2 Single or duplicate ELISA tests may be done. Testing can be concurrent or reflex, and can include testing of free or total antibody levels:

- Concurrent testing: tests for TNF-alpha inhibitor drug levels and antibodies to TNF-alpha inhibitors are done at the same time.
- Reflex testing: the test for TNF-alpha inhibitor drug levels is done first. If the drug is undetectable, testing for antibodies to the TNF-alpha inhibitor would be done without a further request

from the treating clinician. If TNF-alpha inhibitor is present in the sample, then testing for antibodies would not be done.

- Testing of free antibody levels: the test measures the levels of antidrug antibodies that are unbound to drug.
- Testing of total antidrug antibody levels: the test measures levels of both unbound (free) antidrug antibodies and those bound to TNF-alpha inhibitor.

The interventions

3.3 The ELISA tests are all similar and consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards or calibrators, and controls. The tests are done either manually or on an automated ELISA processor in a laboratory.

Table 1 Summary of the ELISA kits and tests relevant to this assessment

ELISA kits and tests relevant to this assessment	Manufacturer and UK distributor
Promonitor; 8 CE-marked ELISA kits, 4 measuring the levels of circulating TNF-alpha inhibitor (adalimumab, etanercept, infliximab or golimumab) and 4 measuring the levels of corresponding free antidrug antibodies.	Proteomika, distributed by Grifols UK
IDKmonitor; 10 CE-marked ELISA kits, 4 measuring the levels of free TNF-alpha inhibitor (adalimumab, etanercept, infliximab or golimumab), 4 measuring corresponding levels of free antidrug antibodies and 2 measuring the levels of total antidrug antibodies (against adalimumab or infliximab).	Immundiagnostik, distributed by BioHit Healthcare Ltd.
LISA-TRACKER; 10 CE-marked ELISA kits, 5 measuring the levels of free TNF-alpha inhibitor (adalimumab, certolizumab pegol, etanercept, infliximab or golimumab) and 5 measuring the corresponding levels of free antidrug antibodies. LISA-TRACKER Duo kits are also available that include assays to measure the levels of both free antidrug antibodies and TNF-alpha inhibitor.	Theradiag, distributed by Cambridge Life Sciences Ltd.
RIDASCREEN; 4 CE-marked ELISA kits, 2 measuring the levels of free TNF-alpha inhibitor (adalimumab or infliximab) and 2 measuring the corresponding levels of free antidrug antibodies. They are commercial versions of the KU Leuven in-house ELISAs, and are marketed as apDia ELISA kits in the Benelux area of Europe.	R-Biopharm

MabTrack; 4 CE-marked ELISA kits; 2 measuring the levels of free TNF-alpha inhibitor (adalimumab and infliximab) and 2 measuring the corresponding levels of free antidrug antibodies. They are commercial versions of the Sanquin in-house ELISAs	Sanquin
Sanquin Diagnostic Services ELISA tests. Validated ELISAs are available for adalimumab, infliximab, golimumab, etanercept and certolizumab and their corresponding antidrug antibodies.	Test service provided by Sanquin Diagnostic Services, a laboratory in the Netherlands.

The comparator

3.4 The comparator for this assessment is treatment decisions based on clinical judgement only, without measuring the levels of TNF-alpha inhibitor or antibodies to TNF-alpha inhibitor.

4 Evidence

The diagnostics advisory committee (section 9) considered evidence on enzyme-linked immunosorbent assay (ELISA) tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and tests used by Sanquin Diagnostic Services) for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors in rheumatoid arthritis from several sources. Full details of all the evidence are in the committee papers.

Clinical effectiveness

4.1 The external assessment group (EAG) did a systematic review of the evidence on ELISA tests to monitor the levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol and golimumab) in people with rheumatoid arthritis who:

- have reached their treatment target (remission or low disease activity)
- have disease that has not responded to TNF-alpha inhibitors (primary non-response)

- have disease that has stopped responding to TNF-alpha inhibitors (secondary non-response).

4.2 Evidence on the following outcomes was of interest in the clinical effectiveness review:

- Decision impact – how the test influences decision making in terms of the proportion of people having treatment modifications such as TNF-alpha inhibitor dose reduction or switching to another treatment.
- Clinical utility – the ability of the prospective use of the test (through treatment modification) to affect outcomes for people with rheumatoid arthritis such as duration of time in remission, rate of flares, relapse, or health-related quality of life.

4.3 The EAG included only studies in which at least 70% of people had rheumatoid arthritis, but this inclusion criterion was subsequently relaxed because of the low number of studies retrieved. The EAG found no studies that met the initial criterion, and 2 studies (reported in 4 sources) that met the relaxed inclusion criterion, that is the 2 studies were done in a mixed population of people with rheumatic diseases, rather than specifically in rheumatoid arthritis. Both studies were done in Spain, in people whose rheumatoid arthritis had reached the treatment target (remission or low disease activity). One was a non-randomised controlled study (INGEBIO; Gorostiza et al. 2016, Arango et al. 2017, Ucar et al. 2017) and the other an observational cohort study (Pascual-Salcedo et al. 2013).

4.4 The EAG also considered a study by l'Ami et al. (2017), in people with rheumatoid arthritis. It did not meet the inclusion criteria of the systematic review because it did not specify that people were in remission or had low disease activity at study enrolment. But from the description of the inclusion and exclusion criteria, most people had disease that met this criterion.

4.5 The EAG found 1 ongoing Norwegian multicentre randomised controlled trial (NOR-DRUM) that is evaluating the effect of therapeutic monitoring of infliximab in people with different inflammatory diseases, including rheumatoid arthritis, compared with standard care. Enrolment for NOR-DRUM started in March 2017, with an expected primary completion date of March 2020 and study completion date of March 2022.

INGEBIO non-randomised controlled study

4.6 INGEBIO was a prospective, non-randomised, non-inferiority, multicentre pragmatic study. It assessed the efficacy and cost of implementing therapeutic monitoring to guide treatment decisions in people with different rheumatic diseases taking adalimumab. The comparator was standard care, in which treatment decisions (including dose reduction) were based on clinical judgement only.

4.7 It recruited a mixed population of 169 people with rheumatoid arthritis (n=63; 37%), psoriatic arthritis (n=54; 32%) and ankylosing spondylitis (n=52; 31%). They had treatment with adalimumab and had remained clinically stable for at least 6 months (Ucar et al. 2017).

4.8 In the study, everyone had therapeutic monitoring using Promonitor adalimumab and anti-adalimumab antibody kits, but test results were only revealed to clinicians in the intervention arm. They were not obliged to follow any therapeutic algorithm based on the test results but could use it to inform their judgement on treatment. In contrast, therapeutic monitoring test results were not revealed to clinicians in the control arm. This reflected standard care in Spain where treatment decisions are based on clinical judgement only, without knowing the drug levels and antidrug antibodies of people with rheumatoid arthritis.

4.9 The frequency of testing was once every 2 to 3 months. People were assessed for up to 18 months for change in disease response and health-related quality of life outcomes.

4.10 Results were reported in 3 conference abstracts. Baseline characteristics and 18-month clinical outcomes reported in INGEBIO are presented in table 2. Ucar et al. (2017) reported intention-to-treat analysis, whereas Arango et al. (2017) reported 'per-protocol' analysis, which excluded 19 people who were lost to follow up. In the intention-to-treat analysis:

- A total of 35.8% of people in the intervention group and 36.7% in the control arm (standard care) had their adalimumab doses reduced.
- The mean duration of remission was 344 days in the intervention group and 329 days in the control group.
- The rate of flares per patient-year was 0.463 in the intervention group and 0.639 for the control group, with a rate difference of −0.176 (95% confidence interval [CI] −0.379 to 0.0289).
- There was a non-statistically significant reduction in the risk of flares in the intervention group compared with the control group (incidence rate ratio 0.7252, 95% CI 0.4997 to 1.0578).
- Median time to the first flare was 145 days in the intervention group and 136.5 days in the control group.
- Quality of life (EQ-5D-5L) was statistically significantly better in the intervention group at visits 2 (p=0.001) and 3 (p=0.035) compared with the control group; EQ-5D-5L remained higher in the intervention group throughout the 18-month follow-up period, although the difference was not statistically significant at other visits.

Table 2 Baseline characteristics and 18-month clinical outcomes reported in INGEBIO

	Ucar et al. 2017 (intention-to-treat population)		Arango et al. 2017 (per-protocol population)	
Outcome	**Intervention arm (n=109)**	**Control arm (n=60)**	**Intervention arm (n=98)**	**Control arm (n=52)**
Baseline characteristics				
Proportion of people in remission (%)	73.4	83.3	71.4	82.7
Proportion of people with low disease activity (%)	26.6	16.7	28.6	17.3
Median trough adalimumab levels (mg/litre)	5.3	5.5	5.04	5.76
Clinical outcomes				
Mean follow up (days)	499	505	530.8	544.6
Proportion of people on reduced dose, % (number)	35.8 (39/109)	36.7 (22/60)	35.7 (35/98)	34.6 (18/52)
Rate of flares per patient-year	0.463	0.639	0.463	0.639
Mean duration of remission (days)	344	329	362	360
Mean duration of remission or low disease activity (days)	NR	NR	460	475
Median time to first flare (days)	145	136.5	145	136.5

Notes: The rate of flares per patient-year reported in Ucar et al. (2017) is the same as in Arango et al. (2017) even though these sources reported outcomes for different numbers of people and different follow-up periods. This could be because of an error in 1 of the abstracts.

The difference in duration of follow up between the 2 abstracts is most likely because of the exclusion of 19 people who were lost to follow up (and so had a shorter follow-up time) rather than a longer data collection period.

Abbreviations: NR, not reported

4.11 Using ROBINS-I criteria, INGEBIO was judged to be at serious risk of bias, because of baseline imbalance in disease activity between the intervention and control groups. Also, the findings may not be generalisable to the UK rheumatoid arthritis population because the study was done in Spain (dose reduction of TNF-alpha inhibitors is

part of standard care in Spain but not in the UK) and enrolled a mixed population of people with rheumatic diseases.

Observational study by Pascual-Salcedo et al. (2013)

4.12 This was a single-centre observational study of daily clinical practice comparing clinical outcomes in 88 people (43 rheumatoid arthritis and 45 spondyloarthritis) who had treatment with TNF-alpha inhibitors (infliximab, adalimumab and etanercept) before and after introducing therapeutic monitoring of TNF-alpha inhibitors (capture ELISA by Sanquin). Inclusion and exclusion criteria were not reported in the conference abstract.

4.13 All people were in remission or had low disease activity (people with rheumatoid arthritis had a disease activity score [DAS28] less than 3.2) throughout the 7 years analysed (2006 to 2012; therapeutic monitoring of TNF-alpha inhibitors introduced in 2010). However, it is not clear from the conference abstract whether people were required to be in remission or have low disease activity throughout the entire period as 1 of the study inclusion criteria, or whether this was reported as 1 of the study outcomes in everyone who had therapeutic monitoring.

4.14 After introducing therapeutic monitoring of TNF-alpha inhibitors, the mean drug administration interval was statistically significantly longer ($p<0.001$), and the mean weekly dose statistically significantly lower (approximately 20% reduction; $p<0.001$) than before the introduction of therapeutic monitoring for all 3 TNF-alpha inhibitors.

4.15 Everyone had stable clinical activity in both periods. In people with rheumatoid arthritis, the mean (± standard deviation, SD) DAS28 score was 2.31±0.52 after introducing therapeutic monitoring of

TNF-alpha inhibitors, compared with 2.51±0.85 in the first period (p=0.061).

Additional study by l'Ami et al. (2017)

4.16 The study was an open-label, randomised, parallel-group, non-inferiority trial done in the Netherlands. It assessed clinical outcomes in people with rheumatoid arthritis with high serum adalimumab concentrations (above 8 mg/litre) who had dose-interval prolongation, compared with people who continued standard dosing.

4.17 The trial considered consecutive people with rheumatoid arthritis who had treatment for at least 28 weeks and had no indication for adjustment of adalimumab treatment, discontinuation or a scheduled surgery in the next 6 months. A total of 55 people were randomised and 54 included for analyses.

4.18 The mean DAS28-ESR scores after 28 weeks decreased by 0.14 (SD 0.61) in the interval prolongation group and increased by 0.30 (SD 0.52) in the continuation group. The difference in the mean change in DAS28 scores was 0.44 (95% CI 0.12 to 0.76; p=0.01) in favour of the prolongation group.

4.19 The authors concluded that the frequency of adalimumab dosing can be safely extended without the loss of disease control. However, considering the small sample size and comparable median adalimumab doses at week 28 in both groups, the EAG did not include this study in the economic assessment.

Cost effectiveness

Systematic review of cost-effectiveness evidence

4.20 The EAG identified 5 studies investigating the cost effectiveness of ELISA tests used to measure drug levels and antidrug antibodies

for monitoring response to TNF-alpha inhibitors. Three studies were model-based economic evaluations (cost-effectiveness models) and 2 were observational (Pascual-Salcedo et al. 2013 reported costs and Arango et al. 2017 reported costs and quality-adjusted life years [QALYs]; both reported in abstract form only).

4.21 In INGEBIO (see sections 4.6 to 4.11 for study details), the mean QALYs during the 18-month follow-up period were 1.076 in the control (standard care) group and 1.145 in the intervention group (therapeutic monitoring of TNF-alpha inhibitors; gain of 0.069 QALYs compared with control; Arango et al. 2017). The average per patient-year costs of adalimumab were €10,665 in the control group and €9,856 in the intervention group (a cost saving of €808 [8% of cost]). Other healthcare costs were not reported.

4.22 In the observational study by Pascual-Salcedo et al. (2013; see sections 4.12 to 4.15 for study details), introduction of therapeutic monitoring of TNF-alpha inhibitors resulted in lower monthly acquisition costs of TNF-alpha inhibitors, compared with the monthly costs of the drugs before monitoring. The monthly cost saving was €92 per person on infliximab (assuming a mean weight of 70 kg), €324 per person on adalimumab, and €257 per person on etanercept.

4.23 Krieckaert et al. (2015) considered the cost effectiveness of a personalised treatment algorithm in people with rheumatoid arthritis taking adalimumab in the Netherlands. This was based on clinical response and drug levels (in-house ELISA tests, Sanquin) at 6 months of treatment, compared with standard care. The study population included all people who had treatment for 6 months, regardless of disease response. It was reported that for 272 people starting adalimumab treatment over the period of 3 years, a test-based treatment strategy would add 3.84 QALYs and save

€2.5 million in total healthcare costs (with €2.3 million saving in drug costs) and approximately €15,000 in productivity costs.

4.24 Laine et al. (2016) assessed the cost effectiveness of routine monitoring of serum drug concentrations and antidrug antibodies in people with rheumatoid arthritis who had TNF-alpha inhibitors (adalimumab and infliximab), compared with standard care in Finland. Routine monitoring of both drug and antibody levels was estimated to be cost saving, assuming that it would improve treatment decisions for 2.5% to 5% of people who would otherwise have non-optimal treatment for 3 to 6 months in the standard care scenario.

4.25 Gavan (PhD thesis 2017; personal communication with the EAG) assessed the cost effectiveness of using ELISA testing (no test specified) for monitoring people with rheumatoid arthritis taking adalimumab. The analysis considered 10 different testing scenarios and 2 scenarios in which adalimumab doses were halved without prior testing. Routine adalimumab testing (either drug levels alone or drug levels plus antidrug antibodies) was generally cost effective compared with current practice, but was unlikely to be cost effective relative to dose reduction (without testing) for people in remission.

Economic analysis

4.26 The EAG developed a de novo economic model designed to estimate the health and economic outcomes of adding therapeutic monitoring of TNF-alpha inhibitors to usual practice to guide treatment decisions in people with rheumatoid arthritis who had reached treatment target (remission or low disease activity). The 2 primary analyses were based on the INGEBIO results, so they considered Promonitor kits for measuring adalimumab drug and antibody levels.

- The first analysis was based on the intention-to-treat INGEBIO results reported in a conference abstract by Ucar et al. (2017).
- The second analysis was based on the INGEBIO results reported in a conference abstract by Arango et al. (2017), which excluded 19 people who were lost to follow up.

4.27 The EAG did 2 separate types of economic analyses: incremental cost effectiveness ratio (ICER) analysis, and threshold analysis. The latter estimated the cost of TNF-alpha inhibitor testing in which the test-based treatment has no net monetary benefit at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained, taking into consideration the major components of differential costs and QALYs.

4.28 Exploratory analyses were done to assess the health and economic outcomes of the Promonitor tests to measure drug levels and antidrug antibodies for TNF-alpha inhibitors other than adalimumab (that is, infliximab and etanercept). These assumed similar clinical effectiveness across the TNF-alpha inhibitors and similar performance of the Promonitor test kits used for measuring the drug and antibody levels of all TNF-alpha inhibitors.

4.29 Economic analyses for ELISA tests other than Promonitor were not done because of the lack of evidence to inform the models.

4.30 Economic assessment for the population with primary or secondary non-response was not possible because of the lack of evidence.

Model structure

4.31 The time horizon was 18 months, as defined by the observational period in INGEBIO. Cost and health outcomes were not extrapolated into the future because of the lack of long-term evidence, so external validation of extrapolated outcomes was not

feasible. Therefore, no discounting was applied to estimated costs and QALYs, and mortality was not modelled.

4.32 Because of the short time horizon, a simple model was created. For both primary analyses it was assumed that people could be in 1 of 2 health states. However, definitions of health states in each analysis differed because different outcomes were reported in each conference abstract:

- Ucar et al. (2017) reported time in remission; the model assumed that people would be in the remission health state or the active disease health state (low to high disease activity).
- Arango et al. (2017) reported time in remission or low disease activity; the model assumed that people would be in the remission or low disease activity health state, or the active disease health state (moderate to high disease activity).

The duration of time in each health state was based on the INGEBIO results.

Key assumptions

4.33 At the beginning of the model time horizon, a proportion of people had their doses reduced in both intervention and control groups, as in INGEBIO. This was based either on the clinical assessment only (control group) or clinical assessment and therapeutic monitoring test results (intervention group).

4.34 The dose of adalimumab was reduced by increasing the interval between doses from 2 to 3 weeks (that is, by spacing doses).

4.35 A proportion of people in both the intervention and control groups had flares, as reported in INGEBIO. In INGEBIO, flare rates in the intervention and control arms were not stratified further according to the dose (full or reduced). Therefore, within each arm, the EAG

applied the same rate of flares to all people, regardless of their dose.

4.36 The full dose of adalimumab was restored in all people on reduced doses when their disease flared (based on the mean time to first flare derived from INGEBIO).

4.37 All people who were switched back to the full dose continued on the full dose for the rest of the model time horizon. The disutility of the flare and the cost of managing the flare were applied for the duration of the flare (7 days in the primary analyses).

4.38 The rates of serious adverse events in people on full and tapered doses were 3 per 100 and 2 per 100 patient-years, respectively.

Model inputs

4.39 The model was populated with data from INGEBIO, and supplemented with information from secondary sources.

4.40 Costs considered in the economic evaluation included the costs of testing, the costs of treatments taken by people with rheumatoid arthritis, and healthcare costs, from the perspective of the NHS and personal social services.

4.41 The costs of testing comprised those of the test kits, staff time to perform the test and staff training, the cost of the testing service and sample transport. In the primary analyses, it was assumed that tests for trough drug and antibody levels would be done at the same time (concurrent testing), each sample would be tested once (single testing), and testing would be done once a year. Based on the information submitted by Grifols, the assay cost was £8.75 per sample.

4.42 Adalimumab acquisition costs were based on the Humira list price in the British national formulary (BNF; £9,187). However, biosimilar

versions of adalimumab are available in the UK. Because the actual prices paid by the NHS are confidential and subject to regional tendering processes, the EAG assumed a hypothetical minimum cost of adalimumab of £1,000 in the threshold analysis. Also, the EAG did one-way deterministic sensitivity analyses to explore the effect of an up to 80% discount on the adalimumab BNF list price on the ICER.

4.43 Treatment wastage was assumed to be £370 per patient-year in people on a full dose; it was reduced proportionally to the reduction in dose.

4.44 Adalimumab is self-administered (usually at home), and, therefore, the administration cost was assumed to be zero.

4.45 The annual per-patient costs of managing health states were:

- Ucar et al. (2017) analysis: remission, £11,409 and active disease (low to high activity), £18,889.
- Arango et al. (2017) analysis: remission or low disease activity, £13,489 and active disease (moderate to high activity), £22,143.

4.46 The costs associated with flare management were £423 per flare for diagnostic investigations and £68 per month for treatment (excluding the cost of biological DMARDs).

4.47 The cost of managing an adverse event was £1,622.

4.48 QALYs were estimated from the duration of time in each of the 2 health states, the rates and duration of flares and adverse events, and the corresponding utility values from published literature (see table 3).

Table 3: Model inputs: utilities

Assumption	Estimate	Source
Remission	0.718	Estimated from health assessment questionnaire scores for different health assessment questionnaire bands reported by Radner et al. (2014)
Low disease activity or active disease	0.568[1]	
Remission or low disease activity	0.665[1]	
Active disease	0.483	
Disutility of flare[2]	0.140	Markusse et al. 2015
Disutility of adverse events[3]	0.156	NICE technology appraisal guidance 375, Oppong et al. (2013)

Notes: [1] Computed from a weighted average health assessment questionnaire score for the low, moderate and high disease activity health states reported by Radner et al. (2014) and mapped to EQ-5D values following Malottki et al. (2011).

[2] Rates of flares were based on the INGEBIO study. In the primary analyses, duration of flare was assumed to be 7 days.

[3] In the primary analyses, the rates of adverse events in people on full and reduced doses were 3 per 100 and 2 per 100 patient-years, respectively. Duration of adverse event was assumed to be 28 days.

Cost-effectiveness results: primary analyses

4.49 In the economic analysis based on data from Ucar et al. (2017), therapeutic monitoring of TNF-alpha inhibitors dominated standard care (that is, testing was more clinically effective and cheaper than standard care), producing a cost saving of £260 and a gain of 0.007 QALYs.

4.50 When the analysis was based on data from Arango et al. (2017), the opposite effect was seen; the testing strategy was dominated by standard care (that is, standard care was more clinically effective and cheaper than testing), with a £361 increase in costs and a loss of 0.007 QALYs.

4.51 However, when the Arango et al. analysis was based on additional information provided by Grifols (outcome data on time in remission rather than time in remission or low disease activity; mean number

of days in remission: 362 days in the therapeutic monitoring group compared with 360 days in the standard care group), the results were in line with those of the analysis based on Ucar et al. (2017; that is, therapeutic monitoring of TNF-alpha inhibitors dominated standard care).

4.52 The results of the threshold analyses were in line with the results of the ICER analyses, that is, when clinical inputs from Ucar et al. (2017) or additional data from Grifols were used, the testing strategy could be considered cost effective. To be considered cost effective at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained, the overall cost of testing (assay cost, cost of the testing service and sample transport) would have to be lower than:

- £430 and £479, respectively (Ucar et al. 2017)
- £194 and £205, respectively (Arango et al. 2017; additional data from Grifols).

In comparison, an annual total cost of testing of £132 was assumed in the primary cost–utility analysis, so in both analyses the testing strategy could be considered cost effective.

However, using the results from the Arango et al. (2017) conference abstract, there would be no cost at which testing could become cost effective.

Cost-effectiveness results: scenario analyses

4.53 Sensitivity analyses were done to explore the effect of the following parametric and structural uncertainties on the model outcomes:

- differences in costs and QALYs are related to differences in rates of flares only (that is, when the effect of health states and adverse events is not considered)

- the tapering strategy (dose halving: adalimumab 40 mg every 4 weeks rather than every 3 weeks assumed in primary analyses [and compared with every 2 weeks for standard dosing])
- the total cost of treatment wastage (£0 rather than £370 assumed in the primary analyses)
- the duration of flare (19 days instead of 7 days)
- the proportion of people with flares who increase their TNF-alpha inhibitor dose (55% or 0% instead of 100%)
- the health state utility values (Ucar et al. remission: 0.496; low disease activity or active disease: 0.302; Arango et al. remission or low disease activity: 0.496; active disease: 0.302)
- the disutility of flare (0.085 or 0.116)
- the frequency of testing (twice per year rather than once per year assumed in the primary analyses)
- the cost of testing (including the effect of excluding the cost of the initial phlebotomy appointment, the effect of testing in duplicate, and the effect of reflex testing using 2 assumptions of the proportion of people with low drug levels: 4.7% (the lower bound) and 35.8% [the upper bound])

4.54 In all except 1 scenario analysis based on data from Ucar et al. (2017), the intervention dominated standard care (that is, testing was more clinically effective and cheaper than standard care).

4.55 In all but 1 scenario analysis based on data from Arango et al. (2017) standard care dominated the intervention (that is, standard care was more clinically effective and cheaper than testing).

4.56 When the effect of flares only was modelled (that is, the effect of health states and adverse effects was not considered), the ICERs were £72,645 per QALY gained in the analysis based on Ucar et al. (2017) and £8,804 per QALY gained in the analysis based on Arango et al. (2017).

Cost-effectiveness results: deterministic sensitivity analyses

4.57 Sensitivity analyses on the cost of adalimumab (20% to 80% discount) did not change the conclusions of the primary analyses. In all analyses based on Ucar et al. (2017), testing dominated standard care, whereas in all analyses based on Arango et al. (2017), standard care dominated testing.

4.58 Additional deterministic sensitivity analyses were done for the analyses based on data from Arango et al. (2017):

- Percentage of people who had their dose of biological treatment reduced (+20% in the intervention arm and −20% in the control arm).
- Flare rate (−20% in the intervention arm and +20% in the control arm).
- Difference between the time in the remission or low disease activity health state (+10% in the intervention arm and −10% in the control arm [that is +1.5 days and −1.5 days, respectively]).
- Costs of managing health states (−20%).

In all analyses standard care dominated the intervention (that is, standard care was more clinically effective and cheaper than testing).

Exploratory analyses for etanercept and infliximab

4.59 The cost effectiveness of therapeutic monitoring of TNF-alpha inhibitors (Promonitor) in people with rheumatoid arthritis who had treatment with etanercept and infliximab and who had reached treatment target (remission or low disease activity) was explored in scenario analyses.

4.60 The analyses assumed similar clinical effectiveness across the TNF-alpha inhibitors and similar performance of the Promonitor test kits for measuring the drug and antibody levels of all TNF-alpha

inhibitors. The analysis used all the assumptions from the primary analyses of adalimumab, except drug acquisition and administration costs of the TNF-alpha inhibitors. The information on the actual costs to the NHS of the TNF-alpha inhibitors was not available to the EAG. Therefore, the list prices of the biological treatments were assumed: £9,327 for Enbrel (etanercept), £8,394 for Erelzi (etanercept), and £5,164 for Flixabi or Renflexis (infliximab), assuming no vial wastage.

4.61 For both exploratory analyses, the intervention (therapeutic monitoring) dominated standard care (that is, the testing strategy was more clinically effective and cheaper than standard care) when data from Ucar et al. (2017) were used. When data from Arango et al. (2017) were used, standard care dominated the intervention (that is, standard care was more clinically effective and cheaper than the testing strategy).

5 Committee discussion

Clinical need and practice

5.1 A clinical expert explained that rheumatoid arthritis has a devastating effect on a person's quality of life and that almost 1 in 3 people stop work within 2 years of diagnosis. The patient experts commented that active disease and flares have the biggest effect on their lives and they constantly fear their recurrence. The committee noted that there is no standard definition of flare. Further research to better define it would be beneficial but may be challenging because of the variability in disease presentation. The committee also heard that 'low disease activity' covers a wide range of disease presentations, and people with rheumatoid arthritis can continue to have pain even when their joints are not visibly swollen.

5.2 The committee heard that tumour necrosis factor (TNF)-alpha inhibitors can be an effective treatment option for severe rheumatoid arthritis that has not responded to conventional therapy, but some people have disease that does not respond or loses response to TNF-alpha inhibitors. Based on British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) data, approximately 50% of people who have TNF-alpha inhibitors stop within the first 4 years, because of lack of efficacy and adverse events such as severe infections. The committee concluded that managing rheumatoid arthritis is complex and that new tests to optimise the use of TNF-alpha inhibitors could improve management of the condition and so improve outcomes and quality of life for people with rheumatoid arthritis.

5.3 The committee noted that therapeutic monitoring of TNF-alpha inhibitors is more established in inflammatory bowel disease. It was informed that companies who make TNF-alpha inhibitors may offer to cover the cost of the enzyme-linked immunosorbent assay (ELISA) kits if a trust switches to their drug. The committee concluded that because testing is already being done and may be provided free of charge, clinicians may potentially have access, therefore it was important to consider whether testing in rheumatoid arthritis is appropriate.

5.4 The committee discussed treatment options for people with rheumatoid arthritis whose treatment target (remission or low disease activity) with TNF-alpha inhibitors had been reached. The clinical experts explained that, in the UK, most people continue their treatment at the standard dose, that is, their dose is not reduced. But the committee was also informed that an increasing number of trusts do reduce the dose of TNF-alpha inhibitor (based on clinical judgement) for these people. These trusts would have quick access policies in place for people reducing their dose, so

that they can return to clinic should their disease need to be reassessed or treatment adjusted.

5.5 The committee considered the potential value of therapeutic monitoring of TNF-alpha inhibitors in people with rheumatoid arthritis whose treatment target (remission or low disease activity) had been reached. The committee noted that compared with no dose reduction, therapeutic monitoring could help inform clinicians who could reduce their dose of TNF-alpha inhibitor without loss of efficacy. Lower doses could mean a lower risk of side effects, such as serious infections, and lower costs for TNF-alpha inhibitors. The committee noted that compared with dose reduction based on clinical judgement only, therapeutic monitoring may have limited effect on the average dose of TNF-alpha inhibitor and rates of adverse events. However, it could help to better inform clinicians who can reduce their dose without loss of efficacy, and so lead to a lower rate of relapse and flares. In this scenario, therapeutic monitoring may have less effect on the average doses of biological treatments or rates of adverse events.

5.6 A patient expert explained that therapeutic monitoring of TNF-alpha inhibitors can reassure people with rheumatoid arthritis who wish to consider reducing their dose. They explained that people may be uneasy about reducing their dose of TNF-alpha inhibitor, fearing they may have disease recurrence or a flare as a result. The committee concluded that therapeutic monitoring of TNF-alpha inhibitors could potentially reassure people with rheumatoid arthritis about reducing their dose more than when their dose is reduced based on clinical judgement alone.

Clinical effectiveness

5.7 The committee reviewed the available evidence on the clinical effectiveness of using ELISA tests for therapeutic monitoring of

TNF-alpha inhibitors in people with rheumatoid arthritis. The committee noted that there was no evidence available for people with disease that has not responded to TNF-alpha inhibitors or has stopped responding to TNF-alpha inhibitors. It also noted that the evidence for people whose treatment target had been reached was limited and of poor quality. The committee was aware that no UK studies had been identified and there was no evidence for the IDKmonitor, LISA-TRACKER and RIDASCREEN ELISA tests.

5.8 The committee was concerned that the results of the INGEBIO study may not be generalisable to the NHS. This was because of differences in the healthcare settings between Spain and the UK, and the lack of an explicit algorithm for guiding clinicians in how the results of testing should be interpreted and how they affect treatment. A patient expert explained that a warm climate has a favourable effect on symptoms, so there could be some differences in disease presentation between Spain and the UK. The committee noted that, because both treatment groups were enrolled at the same study sites, climate should not affect the results. Also, the committee was aware that the rate of dose reduction of TNF-alpha inhibitors based on clinical judgement alone (standard care) and the rate of dose reduction based on clinical judgement plus therapeutic monitoring of TNF-alpha inhibitors was similar in both study arms. The committee recalled that dose reduction based on clinical judgement is not routine practice in the NHS (see section 5.4). It concluded that INGEBIO may not be generalisable to clinical practice in the NHS.

5.9 The committee considered other limitations of INGEBIO. It noted that the study findings were presented as abstracts only and that the external assessment group (EAG) was not able to confirm whether a full-text peer-reviewed publication is in preparation. The committee was also aware that the study had a non-randomised

design with no adjustment for baseline imbalance in disease activity between groups. Also, there were unclear differences in clinical outcomes between the intention-to-treat analysis and the analysis that excluded 19 people who were lost to follow up. The committee noted that the study enrolled a mixed population of people with different rheumatic diseases, with only 37% of people having rheumatoid arthritis. The clinical experts explained that rheumatic diseases have different rates of immunogenicity and therapeutic ranges but algorithms to interpret test results should be similar across these diseases. The committee noted a trend towards reduction in the rate of flares with therapeutic monitoring but the difference was not statistically significant. Also, the committee noted that the rates of flares in INGEBIO were not stratified by dose and so did not provide information as to whether doses of TNF-alpha inhibitors can be reduced without loss of efficacy. The committee noted that without this dose-relationship information, the differences seen in INGEBIO could simply be caused by chance. The committee concluded that the clinical outcomes reported were uncertain.

5.10 The committee considered the single-centre observational study by Pascual-Salcedo et al. (2013) and the small randomised controlled trial by l'Ami et al. (2017). It discussed its doubts about the generalisability of the Spanish observational study to the NHS because of differences in healthcare setting, the lack of a control group and enrolling people with mixed rheumatic diseases. The committee noted that l'Ami et al. enrolled a small number of people, had a short follow-up time, and the median doses of TNF-alpha inhibitor (adalimumab) in both treatment groups were not statistically significantly different at the end of the study. The committee also noted that l'Ami et al. only randomised people with high blood levels of TNF-alpha inhibitor. It did not provide any

information on treatment choices and outcomes for people with lower levels of TNF-alpha inhibitor. The committee concluded that the 2 studies had important limitations, but they provided some support that therapeutic monitoring could help reduce doses of TNF-alpha inhibitors without negatively affecting clinical outcomes (that is, without a subsequent increase in disease activity).

5.11 The committee considered the analytical validity of the tests. A clinical expert explained that there is no formal external quality assurance scheme for measuring levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors, but some laboratories take part in sample-exchange schemes as a form of quality assurance. Work on assuring the quality of ELISA tests for therapeutic monitoring of TNF-alpha inhibitors is ongoing and is most advanced for infliximab, for which the World Health Organization international calibration standards have been developed. These were shown to improve the consistency of results between different laboratories. A clinical expert explained that despite this progress there is variability between results generated by the different ELISA tests, and between different laboratories, especially for TNF-alpha inhibitors other than infliximab. The committee concluded that there is potential uncertainty in the analytical performance of the ELISAs.

5.12 The committee noted that studies on the clinical validity of measuring levels of TNF-alpha inhibitors (that is, studies looking at correlation between test results and health state such as remission or active disease) were not included in the assessment. It concluded that considering the very limited and poor-quality direct evidence on the clinical utility of ELISA tests (that is, information showing how treatment decisions informed by ELISA test results affect outcomes for people with rheumatoid arthritis), information on the clinical validity of ELISA tests could be beneficial. However, this information would not be able to confirm their clinical utility.

Cost effectiveness

5.13 The committee considered the choice of model structure. It recalled the uncertainties associated with INGEBIO (see sections 5.8 and 5.9), which provided the main clinical inputs for the model. Because of this, the committee agreed with the choice of a simple modelling approach. It concluded that the model results were of limited value because of a lack of robust clinical data.

5.14 The committee discussed differences between the 2 sources of clinical data from INGEBIO for the 2 primary analyses and noted both were conference abstracts. It was aware that the Ucar et al. intention-to-treat analysis reported time in remission, whereas Arango et al. excluded people lost to follow up and reported time in remission or low disease activity pooled together. Consequently, health states were defined differently in the 2 primary analyses: remission compared with active disease (low to high disease activity) in the first analysis, and remission or low disease activity compared with active disease (moderate to high disease activity) in the second analysis. In the Ucar et al. intention-to-treat analysis, the mean duration of remission in the intervention group was slightly longer than in the control group. But in the analysis by Arango et al. the mean duration of remission or low disease activity in the intervention group was slightly shorter than in the control group. It noted that this resulted in the testing strategy dominating standard care when data from Ucar et al. were used, and standard care dominating the testing strategy when data from Arango et al. were used. The committee agreed that in the EAG's model based on INGEBIO, the time spent in each health state was a key driver of the cost-effectiveness results. Differences in the time spent in the different health states between the 2 primary analyses accounted for the contrasting results. The committee also noted that if the comparator in the model was no dose reduction it would

be likely that the amount of drug would be a key driver of the cost-effectiveness results, and not the time spent in each health state.

5.15 The committee noted that the costs of managing health states appeared to be high. Also, the cost difference between managing disease in remission and low disease activity was high, considering these disease states are managed similarly in clinical practice. The EAG explained that the costs used in the model were based on published UK data. The committee concluded that there was uncertainty around the cost difference between managing different health states in rheumatoid arthritis, but given the lack of clinical evidence, exploration of the uncertainty in the costs of managing health states was of limited value.

5.16 The committee noted that the rates of adalimumab dose reduction in INGEBIO were similar in the 2 treatment groups. As a result, the model did not provide information on whether therapeutic monitoring could offer cost savings to the NHS on the acquisition costs of adalimumab compared with the current practice of no dose reduction (see sections 5.4 and 5.5). The committee also noted that the similar rates of dose reduction in both groups explained why the results were not sensitive to changes in the acquisition price of adalimumab, even when discounts of up to 80% were considered. The committee agreed that in the NHS, rates of dose reduction and biosimilar prices are expected to affect the cost effectiveness of therapeutic monitoring of TNF-alpha inhibitors. The committee was aware that in Gavan's cost-effectiveness modelling, based on the BSRBR-RA data, therapeutic monitoring of TNF-alpha inhibitors was generally cost effective compared with no dose reduction, but was unlikely to be cost effective relative to dose reduction based on clinical judgement. The committee concluded that the EAG model may not be representative of NHS practice, in which dose reduction of TNF-alpha inhibitors is not routinely done.

5.17 The committee acknowledged that the rates of flares in INGEBIO were not stratified by dose and so the relationship between adalimumab dose and the rate of flares was not captured in the model. It concluded therefore, that the model may not accurately reflect the experience of people with rheumatoid arthritis in the NHS whose dose of TNF-alpha inhibitors is reduced.

5.18 The committee noted that the cost of a phlebotomy appointment appeared to be high but clinical experts explained that it likely represents the true cost of an outpatient phlebotomy appointment. They commented that although people with rheumatoid arthritis taking TNF-alpha inhibitors (especially those also taking methotrexate) have frequent monitoring, an additional phlebotomy appointment may be needed to measure trough drug levels. This additional appointment would not be needed if drug levels of TNF-alpha inhibitors could be measured at any time in the administration cycle. The EAG did a sensitivity analysis assuming no additional phlebotomy appointment. The committee concluded that this had a limited effect on the model results.

5.19 The committee discussed the limitations of the economic model. It agreed that although the clinical studies for therapeutic monitoring of TNF-alpha inhibitors show promising results, the degree of uncertainty in the clinical evidence was too high for it to be able to use the incremental cost-effectiveness ratios (ICERs) for decision making. It considered that the scope of any further revisions to the assumptions in the modelling would be limited without more robust clinical data. The committee noted other evidence gaps such as:

- the lack of clinical evidence on rheumatoid arthritis that has not responded to TNF-alpha inhibitors or has stopped responding
- the lack of evidence for tests other than Promonitor and the Sanquin tests for therapeutic monitoring of adalimumab

- the lack of data correlating test results and health states such as remission or active disease (which was out of scope for the EAG assessment).

The committee noted that the last limitation could be addressed by further secondary research. Without robust clinical outcomes data, the committee was not able to recommend ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis for routine use in the NHS.

Research considerations

5.20 The committee considered the ongoing NOR-DRUM trial in Norway, which will assess the efficacy of therapeutic monitoring of infliximab in a broad range of inflammatory diseases. The clinical experts advised that infliximab is rarely offered to people with rheumatoid arthritis in the UK. According to recent UK registry data, only about 5% of people with rheumatoid arthritis in the UK have infliximab. Therefore, the committee concluded that this study may be of limited relevance to the NHS but some findings could potentially be extrapolated to represent the likely value of therapeutic monitoring of TNF-alpha inhibitors as a class.

5.21 The committee expressed concern that because therapeutic monitoring of TNF-alpha inhibitors is already used in inflammatory bowel disease and may be provided free of charge by companies that make TNF-alpha inhibitors, the tests could be adopted inappropriately in rheumatoid arthritis, without proof of clinical and cost effectiveness. The committee concluded that if therapeutic monitoring of TNF-alpha inhibitors is currently done in rheumatoid arthritis, audit data should be collected.

5.22 The committee noted that further primary research comparing therapeutic monitoring of TNF-alpha inhibitors with current clinical

practice in the NHS in people with rheumatoid arthritis is needed. However, because of the high level of uncertainty about the potential value to the NHS, it was not clear whether this is a priority for NHS research funding.

5.23 Further research is also needed into the analytical and clinical validity of the ELISA tests, clinically meaningful thresholds for interpreting test results, the most appropriate test-based treatment algorithms, and which groups of people with rheumatoid arthritis are likely to benefit most from therapeutic monitoring of TNF-alpha inhibitors.

6 Recommendations for further research

6.1 Further secondary research is recommended to understand:

- the clinical validity of enzyme-linked immunosorbent assay (ELISA) tests, that is the correlation between ELISA test results and health outcomes or states, such as remission, response, low or high disease activity or flares in rheumatoid arthritis
- the comparative performance of different ELISA tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors in rheumatoid arthritis.

6.2 Further primary research is recommended on the clinical effectiveness of using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in people with rheumatoid arthritis.

7 Implementation

The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate.

8 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese
Chair, diagnostics advisory committee
March 2019

9 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Professor Anne Barton

Professor of rheumatology, University of Manchester / Manchester University Foundation Trust

Professor Frank McKenna

Consultant physician and rheumatologist, Department of Rheumatology, Trafford General Hospital, Manchester

Professor John Isaacs

Director, Therapeutics north East and professor of clinical rheumatology, Newcastle University

Dr Mandy Perry

Clinical scientist, Royal Devon and Exeter NHS Foundation Trust

Dr Martin Perry

Consultant physician and rheumatologist and lead clinician, Vale of Leven Hospital; Honorary Senior Clinical Lecturer, University of Glasgow

Mr Karl Nicholl

Biologics nurse specialist

Ms Stephanie Turner

Lay specialist committee member

Mrs Susan Moore

Lay specialist committee member

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Ewa Rupniewska

Topic lead

Frances Nixon

Technical adviser

Donna Barnes

Project manager

ISBN: