National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms can be found in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using ELISA tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack, and ELISA tests used by Sanquin Diagnostic Services) to measure circulating levels of drug and anti-drug antibodies during treatment with tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol and golimumab). The ELISA tests are intended for monitoring treatment response 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) or
- have disease that has stopped responding to TNF-alpha inhibitors (secondary non-response).

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 (580,000 people in England). Rheumatoid arthritis often results in substantial morbidity, impaired physical

activity, poor quality of life, and reduced life expectancy. When it does not respond to intensive conventional therapy (a combination of conventional disease-modifying antirheumatic drugs [DMARDs]), and is severe (disease activity score, DAS28 greater than 5.1), people may have biological therapy, including the TNF-alpha inhibitors adalimumab, etanercept, infliximab, certolizumab pegol and golimumab.

Although beneficial for many patients, there are some patients whose disease does not respond to TNF-alpha inhibitor treatment (primary non-response) or stops responding over time (loss of response; secondary non-response). This may be because antibodies to TNF-alpha inhibitors form and circulating TNF-alpha inhibitor levels fluctuate. So therapeutic drug monitoring that measures the levels of these antibodies and drugs in the body could help to understand the reasons for non-response (for example, it might exclude poor adherence) and help decide which treatment to offer next. Currently, treatment decisions are based on the judgement of the treating clinician.

Also, therapeutic drug monitoring could be beneficial in patients who have a sustained response to inform potential dose reductions. This could reduce the risk of unnecessary side effects and the cost of treatment. Dose reduction of TNF-alpha inhibitor is not currently routine management, and is based on clinical assessment and patient history only (see Exeter biologics clinic recommendations for biological dose reduction in appendix 5 of the diagnostics assessment report).

It has previously been reported that in people with rheumatoid arthritis, serum levels of TNF-alpha inhibitors or anti-drug antibodies or both correlate with clinical outcomes such as initial response, persistent remission or risk of flares (Bartelds et al. 2011; Incierte-Mundo et al. 2016; Chen et al. 2016).

Therapeutic drug monitoring of TNF-alpha inhibitors (circulating drug levels, anti-drug antibodies, or both) could help guide treatment decisions for people with rheumatoid arthritis when interpreted with other clinical signs and symptoms. This could lead to improved patient outcomes and reduced NHS costs. Table 1 shows an example of how therapeutic drug monitoring results

could help treatment decisions. The clinical and cost effectiveness of therapeutic drug monitoring could be affected by:

- concurrent compared with reflex testing (where testing for drug levels would be done first, and testing for anti-drug antibodies would be done only if drug levels were not detectable)
- measuring free, compared with total (both unbound [free] and bound to TNF-alpha inhibitor), levels of anti-drug antibodies
- timing of testing
- alternative algorithms to interpret test results.

Table 1 Algorithm for interpreting results of drug level and anti-drug antibody tests for people with rheumatoid arthritis taking biological DMARDs

Response	Drug levels	Free anti-drug antibody present?	Outcome
Good response – low disease activity or remission	Low	Yes	Consider early review of treatment [a]; consider stopping treatment [b]
		No	Continue monitoring; consider stopping treatment; check adherence to TNF-alpha inhibitor [b]
		Not measured[1]	Check adherence to TNF-alpha inhibitor; continue monitoring [b]
	High	Yes	Scenario unlikely to occur
		No	Consider dose reduction by increasing dosing interval [a]
		Not measured	
Loss of response or non-response – disease activity moderate or high	Low	Yes	Consider switching to less immunogenic drug [a, c]
		No	Assess adherence to TNF-alpha inhibitor and consider whether the dose is weight adjusted [c]
		Not measured[1]	Assess adherence to TNF-alpha inhibitor and consider switching to a different TNF-alpha inhibitor [b]
	High / normal	Yes	Scenario unlikely to occur
		No	Switch to a treatment with a different mechanism of action [a, c]
		Not measured[1]	Switch to a treatment with a different mechanism of action [b]

[a] Source: NHS Glasgow and Clyde guidance on rheumatology biological drug monitoring

[b] Informed by clinical expert advice during scoping

[c] Source: Greater Manchester medicines management group high cost drugs pathway for rheumatoid arthritis (advice on assays is for secondary non-response only)

[1] Etanercept only

Provisional recommendations on using these technologies will be formulated by the diagnostics advisory committee at the committee meeting on 13 February 2019.

1.2 Scope of the evaluation

Table 2 Scope of the evaluation

Decision question	What is the clinical and cost effectiveness of ELISA tests for monitoring TNF-alpha inhibitor drug serum levels and anti-drug antibodies in people with rheumatoid arthritis?
Populations	People with rheumatoid arthritis who are having treatment with a TNF-alpha inhibitor (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) and: • have reached treatment target (remission or low disease activity) • have disease that has not responded (primary non-response) or • have disease that has stopped responding (secondary non-response).
Interventions	• Promonitor ELISA kits (Grifols – Progenika)[a] • IDKmonitor ELISA kits (Immundiagnostik – BioHit Healthcare)[b] • LISA-TRACKER ELISA kits (Theradiag)[c] • RIDASCREEN ELISA kits (r-biopharm)[d] • MabTrack ELISA kits (Sanquin)[e] • Sanquin Diagnostic Services (testing service using validated ELISAs).[f] Evidence permitting, the use of both free and total anti-drug antibody assays will be assessed. The intervention tests will be used in addition to current clinical practice (clinical assessment and monitoring using a composite score such as DAS28).
Comparator	Treatment decisions made using clinical judgement and regular monitoring using a composite score such as DAS28
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • time to result • number of inconclusive results • impact on clinical management decisions.
	Clinical outcomes for consideration may include: • measures of disease activity • rates of response, relapse and remission • duration of response, relapse and remission

	• rates of hospitalisation • rates of surgical intervention • adverse effects of treatment, such as infections.
	Patient-reported outcomes for consideration may include health-related quality of life.
	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • costs of the testing, including sample transport when relevant • costs of staff and associated training • medical costs arising from testing including ongoing care, outpatient appointments, surgery and treatment • medical costs arising from adverse effects of treatment.
	The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

[a] 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

[b] 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

[c] 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 golimumab (LTG005), LISA-TRACKER infliximab (LTI002), LISA-TRACKER anti-infliximab (LTI003),LISA-TRACKER Duo infliximab (LTI005)

[d] RIDASCREEN ADM monitoring, RIDASCREEN anti-ADM antibodies, RIDASCREEN IFX monitoring, RIDASCREEN anti-IFX antibodies

[e] MabTrack level adalimumab M2910, MabTrack ADA adalimumab M2950, MabTrack level infliximab M2920, MabTrack ADA infliximab M2960

[f] Adalimumab drug levels, certolizumab drug levels, etanercept drug levels, etanercept anti-drug antibodies, golimumab drug levels, infliximab drug levels

Further details including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the clinical effectiveness of ELISA tests (Promonitor, IDKmonitor, LISA-TRACKER, RIDASCREEN, MabTrack kits and ELISA tests from Sanquin Diagnostic services) for monitoring response to tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) in people with rheumatoid arthritis who:

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

Full details of the inclusion and exclusion criteria start on page 76 of the diagnostics assessment report. The comparator was defined as current standard care, in which treatment decisions are based on clinical judgement and regular monitoring using a composite score such as DAS28, but without knowing drug levels and anti-drug antibodies of patients. The methodological quality of the included studies was assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies – of Interventions).

The EAG found 2 studies (reported in 4 sources) that met the inclusion criteria. Both studies were done in people with rheumatoid arthritis who had reached their treatment target (remission or low disease activity). One was a non-randomised controlled trial (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). The INGEBIO study used Promonitor ELISA kits to monitor adalimumab drug levels and anti-adalimumab antibodies. Pascual-Salcedo et al. (2013) used Sanquin ELISA (type not specified) to measure drug trough levels of adalimumab, infliximab and etanercept. Both studies were done in Spain. An overview of both studies is provided in tables 14 and 15, starting in section 2.3.2.1 of the diagnostics assessment report (page 83).

There were no studies found for people with rheumatoid arthritis who had primary or secondary non-response.

INGEBIO non-randomised controlled study

INGEBIO was a prospective, non-randomised, multicentre pragmatic trial. It assessed the efficacy and cost of implementing therapeutic drug monitoring to guide treatment decisions in people with different rheumatic diseases taking adalimumab, compared with standard care in which treatment decisions (including dose reductions) are based on clinical judgement only. Results were reported in 3 conference abstracts. Gorostiza et al. (2016) reported interim, 34-week outcomes, while Arango et al. (2017) and Ucar et al. (2017) both reported 18-month outcomes. Ucar et al. reported outcomes for all enrolled patients ('intention-to-treat' analysis), with a mean follow-up time of 499 and 505 days in the intervention and control groups, respectively. In comparison, Arango et al. reported outcomes only for patients who completed the follow-up (that is, it excluded 19 patients who were lost to follow-up), with a mean follow-up time of 530.8 days and 544.6 days in the intervention and control groups, respectively (see table 3).

The INGEBIO study recruited a mixed population of 169 patients with rheumatoid arthritis (n=63; 37%), psoriatic arthritis (n=54; 32%) and ankylosing spondylitis (n=52; 31%). Patients had treatment with adalimumab and had remained clinically stable for at least 6 months (Ucar et al. 2018). Median disease duration was 117.0, 98.5 and 101.5 months for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, respectively. At baseline, 10 (16.7%) and 29 (26.6%) patients had low disease activity, 50 (83.3%) and 80 (73.4%) patients were in remission, and median trough adalimumab levels were 5.5 mg/litre and 5.3 mg/litre in the control group and intervention group, respectively (Ucar et al. 2017).

In the study all patients had therapeutic drug 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 drug monitoring test results were not revealed to clinicians in the control arm, which reflected standard care in Spain where treatment decisions are based on clinical judgement only, without knowledge of drug levels and anti-drug antibodies of patients. The frequency of testing was once every 2–3 months. There were a total of 8 visits during the trial period (details were not provided). Patients were assessed for up to 18 months for change in disease response and health-related quality of life outcomes. Disease flare was defined as an increase in DAS28 greater than 1.2, or greater than 0.6 if DAS28 was 3.2 or higher.

In the intention-to-treat analysis, a total of 35.8% of patients 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-significant reduction in the risk of flare 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 (Ucar et al. 2017).

Table 3. Baseline characteristics and 18-month clinical outcomes reported in INGEBIO

	Ucar et al. 2017		**Arango et al. 2017**	
Outcome	Intervention arm (n=109)	Control arm (n=60)	Intervention arm (n=98)	Control arm (n=51)
Baseline characteristics				

	Ucar et al. 2017		Arango et al. 2017	
Outcome	Intervention arm (n=109)	Control arm (n=60)	Intervention arm (n=98)	Control arm (n=51)
Proportion of patients in remission (%)	73.4	83.3	71.4	82.7
Proportion of patients 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 patients with 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	NR	NR
Mean duration of remission or low disease activity (days)	NR	NR	460.2	475.2
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 number of patients 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 patients who were lost to follow-up (and thus had shorter follow-up time) rather than a longer data collection period. Abbreviations: NR, not reported				

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. At baseline, a total of 73.4% and 83.3% of patients were in remission at baseline in the intervention and control groups, respectively. The remaining patients, that is 26.6% in the intervention group and 16.7% in the control group, had low disease activity at baseline. There was a lack of adjustment for this baseline imbalance variable in the analysis of clinical outcomes.

In summary, the findings from the INGEBIO non-randomised controlled trial showed comparable treatment outcomes in both treatment groups. There was a non-statistically significant reduction in the risk of flare and significantly

improved health-related quality-of-life measures at visits 2 and 3 in the group having therapeutic drug monitoring compared with the control group (standard care). In the intention-to-treat analysis reported by Ucar et al. (2017), the mean duration of remission in the intervention group was slightly longer than in the control group, while in the analysis by Arango et al. (2017), which excluded 19 patients who were lost to follow-up, mean duration or remission or low disease activity was slightly shorter than in the control group. These results should be interpreted with caution given that they were reported in abstract format only, the study was non-randomised and at serious risk of bias as assessed by ROBINS-I (mostly linked to the baseline imbalance in disease activity between the groups). Also, the findings may not be generalisable to the UK rheumatoid arthritis population because the study was done in Spain with a mixed population of rheumatic diseases.

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

One observational study was found for people with rheumatoid arthritis who had reached treatment target (remission or low disease activity). The study was a single-centre observational study of daily clinical practice comparing clinical outcomes in 88 patients (43 rheumatoid arthritis and 45 spondyloarthritis) who had treatment with TNF-alpha inhibitors (31 infliximab, 29 adalimumab and 28 etanercept) before and after introducing therapeutic drug monitoring (capture ELISA by Sanquin; Pascual-Salcedo et al. 2013). All patients were in remission or had low disease activity (patients with rheumatoid arthritis had DAS28 less than 3.2) throughout the 7 years analysed (2006 to 2012; therapeutic drug monitoring introduced in 2010); the proportion of patients in remission compared with having low disease activity was not reported.

Following the introduction of therapeutic drug monitoring, the mean drug administration interval was significantly higher, and the mean weekly dose lower (approximately 20% reduction) than before the introduction of therapeutic drug monitoring for all 3 TNF-alpha inhibitors (see table 4). All patients had stable clinical activity in both periods. In patients with rheumatoid arthritis, the mean (± standard deviation, SD) DAS28 score was 2.31±0.52

after the introduction of therapeutic drug monitoring, compared with 2.51±0.85 in the first period (p=0.061). The authors concluded that therapeutic drug monitoring based on serum trough drug levels was a useful tool supporting therapeutic clinical practice and enabling cost-effective use of biological therapies (Pascual-Salcedo et al. 2013).

Table 4 Effects of therapeutic drug monitoring on dosing frequency, mean doses and clinical outcomes (DAS28) in Pascual-Salcedo et al. (2013)

Outcome	TNF-alpha inhibitor	Pre-TDM	Post-TDM	P value
Mean (SD) drug administration interval (n=88; mixed RA and SpA population)	IFX (weeks)	8.52 (1.43)	9.7 (1.44)	p<0.001
	ADL (weeks)	2.19 (0.58)	2.95 (1.58)	p=0.007
	ETN (weeks)	1.09 (0.27)	1.61 (0.91)	p=0.004
Mean (SD) weekly dose (n=88; mixed RA and SpA population)	IFX (mg/kg/week)	0.51 (0.14)	0.42 (0.12)	p<0.001
	ADL (mg/week)	19.19 (3.72)	15.52 (4.81)	p<0.001
	ETN (mg/week)	42.09 (13.25)	35.04 (13.37)	p=0.009
Mean (SD) DAS28 score (n=43; RA population)	Any	2.51 (0.85)	2.31 (0.52)	p=0.061

Abbreviations: ADL, adalimumab; ETN, etanercept; IFX, infliximab; post-TDM, period after the introduction of therapeutic drug monitoring; pre-TDM, period before introduction of therapeutic drug monitoring; RA, rheumatoid arthritis; SD, standard deviation; SpA, spondyloarthritis

Using ROBINS-I criteria, the study was judged to be at moderate risk of bias because of the use of a historical control. However, it should be noted that the same group of patients were assessed during the first period (that is, historical control, before therapeutic drug monitoring was introduced) and the second period (after therapeutic drug monitoring was introduced).

Additional studies

The EAG also considered a study by l'Ami et al. (2017), which did not meet the inclusion criteria of the systematic review, but reported data of interest. The study was an open-label, randomised, parallel-group, non-inferiority trial

done in the Netherlands. It assessed clinical outcomes in patients with rheumatoid arthritis with high serum adalimumab concentrations who had dose-interval prolongation, compared with patients who continued standard dosing. The trial considered consecutive patients 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 147 patients were screened and 55 patients who had adalimumab trough concentrations above 8 mg/litre were randomly (1:1) assigned to dose-interval prolongation (40 mg adalimumab once every 3 weeks) or continuation of standard dosing (40 mg adalimumab once every 2 weeks). Of 55 randomised patients, 54 were included for analyses and 53 completed the follow-up. The primary outcome was change in disease activity score in 28 joints (DAS28-erythrocyte sedimentation rate [ESR]) after 28 weeks. A clinically relevant change in DAS28-ESR was defined as 0.6 points or more.

The mean age of study participants was 60 years in the interval prolongation group and 58 years in the continuation group. The median disease duration was 11 years in both groups. Mean DAS28-ESR score was 2.0 (SD, 0.8) in the interval prolongation group and 1.6 (SD, 0.7) in the continuation group. 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. A total of 7 patients (26%) in the interval prolongation group and 10 patients (37%) in the continuation group had an increase in DAS28 of 0.6 points or more after 28 weeks (p=0.56). Of those 7 patients in the interval prolongation group who had increase in DAS28 activity, 2 preferred to return to the standard dose. In addition, 4 other patients also preferred to return to the standard dose after interval prolongation. On the contrary, 1 patient in the standard dosing group prolonged the dosing interval to every 3 weeks because of frequent infections. So the median dose of adalimumab at week 28 was not statistically significantly different between the 2 groups.

The authors concluded that the frequency of adalimumab dosing can be safely extended without the loss of disease control. However, considering a 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.

Ongoing studies

The EAG has found 1 ongoing Norwegian multicentre randomised controlled trial (NOR-DRUM) that evaluates the effect of therapeutic drug monitoring in people with rheumatoid arthritis in remission 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. This ongoing trial will provide further data on the effect of therapeutic drug monitoring in the target population. See pages 93–94 of the diagnostics assessment report for details.

2.2 Costs and cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of ELISA tests used to measure drug levels and anti-drug antibodies for monitoring response to TNF-alpha inhibitors. The EAG also constructed a de novo economic model to assess the cost effectiveness of ELISA tests in people with rheumatoid arthritis who have reached their treatment target. No economic model was constructed for people with rheumatoid arthritis who had primary or secondary non-response because of the lack of evidence to populate the model.

Systematic review of cost-effectiveness evidence

The systematic review identified 5 studies, reported in 11 sources, described in detail starting on page 119 of the diagnostics assessment report. 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).

Observational studies

The non-randomised comparative pragmatic trial (INGEBIO; Ucar et al. 2017, Arango et al. 2017) has been described in section 2.1 and on page 126 of the diagnostics assessment report. 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 drug monitoring). There was a gain of 0.069 QALYs with therapeutic drug monitoring; details of how the QALYs were calculated were not reported (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 in the abstract. Importantly, INGEBIO was done in a mixed population of patients with rheumatic diseases and the results were not reported separately for people with rheumatoid arthritis (37% of the mixed population). This affected the generalisability of the results to people with rheumatoid arthritis (Arango et al. 2017).

Pascual-Salcedo et al. (2013) did an observational study of routine clinical practice to compare the clinical and economic impact of the therapeutic drug monitoring, based on serum trough drug levels (Sanquin), in patients with rheumatic diseases in Spain (see section 2.1 and page 126 of the diagnostics assessment report). After the introduction of therapeutic drug monitoring, the monthly amount of spared drug was associated with a cost saving of €92 per patient on infliximab (assuming a mean patient weight of 70 kg), €324 per patient on adalimumab, and €257 per patient on etanercept, compared with the monthly costs of the drugs before monitoring.

Model-based studies

Krieckaert et al. (2015) considered the cost effectiveness of a personalised treatment algorithm, based on clinical response and drug levels (in-house ELISA tests, Sanquin) at 6 months of treatment, compared with standard care in people with rheumatoid arthritis taking adalimumab in the Netherlands (Figure 1; study population includes all patients who had treatment for 6 months, regardless of disease response). This test-based treatment strategy resulted in lower costs (because of reduced treatment costs) and greater

QALYs than standard care (see table 5). It was estimated that a test-based treatment strategy would save €646,266 per QALY from a societal perspective, and €666,541 per QALY gained from a healthcare provider perspective. In 72% of simulations a test-based treatment strategy dominated standard care (that is, testing was more clinically effective and cheaper than standard care), and in 28% it was cost saving with lower QALYs. Scenario analyses, for example, around the drug level cut-offs used, and the definitions of a good EULAR response, showed that ELISA testing of drug levels is generally cost saving, although some scenarios reported loss of QALYs.

Figure 1 Decision-making algorithm after 28 weeks of adalimumab treatment (Krieckaert 2015)

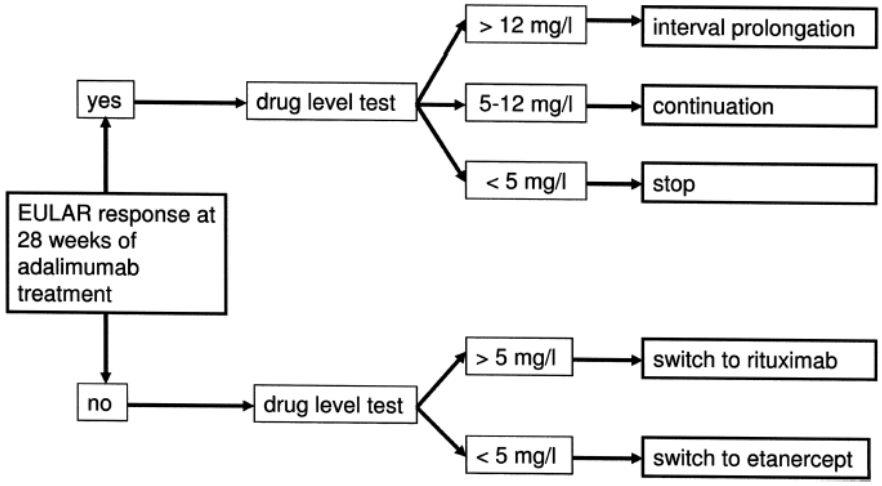


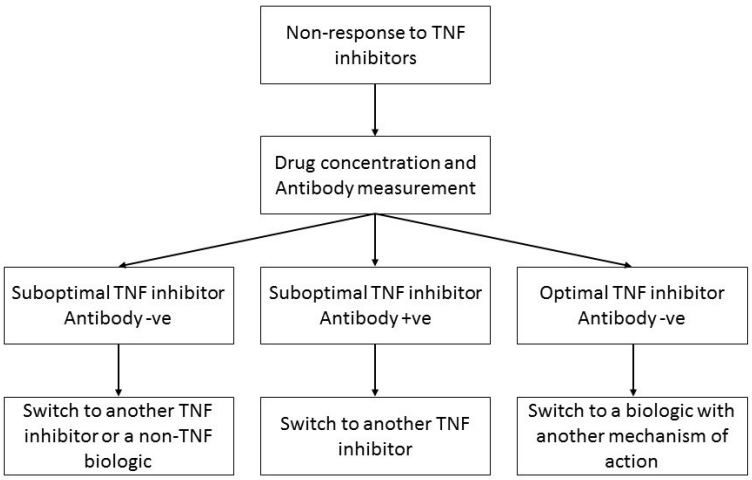
Table 5: Cost-effectiveness results reported in Krieckaert 2015

Perspective	Costs		QALYs		ICER
	Intervention	Control	Intervention	Control	
Societal	€15,466,869	€18,028,517	591.65	587.81	−€646,266
Healthcare provider	€13,607,067	€16,153,357	591.65	587.81	−€666,541
Note: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Laine et al. (2016) assessed the cost effectiveness of routine monitoring of serum drug concentrations and anti-drug antibodies in people with rheumatoid arthritis who had TNF-alpha inhibitors (adalimumab and infliximab), compared

with standard care in Finland. Treatment decisions were based on the algorithm in Figure 2. It was assumed that monitoring would allow for better decision making and would avoid costly periods of non-optimal treatment (typically lasting 3 to 6 months), with the estimated cost of 1-month non-optimal treatment being €1,471. Routine monitoring of both drug and antibody levels was estimated to be cost saving, assuming that it would affect treatment decisions for 2.5% to 5% of patients who would be otherwise have non-optimal treatment for 3 to 6 months in the standard care scenario. The authors also noted that in clinical practice, a higher proportion of patients could have non-optimal treatment.

Figure 2 Algorithm for treatment decisions after test results (Laine et al. 2016)



The PhD thesis by Gavan (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 (see Table 6) and 2 scenarios in which adalimumab doses were halved without prior testing (strategy 11 and 12). Current practice was defined as usual care for people with rheumatoid arthritis with no testing of drug level or anti-drug antibodies. Treatment decisions were based on the algorithm in Figure 3. Gavan (2017) concluded that routine adalimumab testing (either drug levels alone or drug levels plus anti-drug antibodies) was generally cost effective compared with current

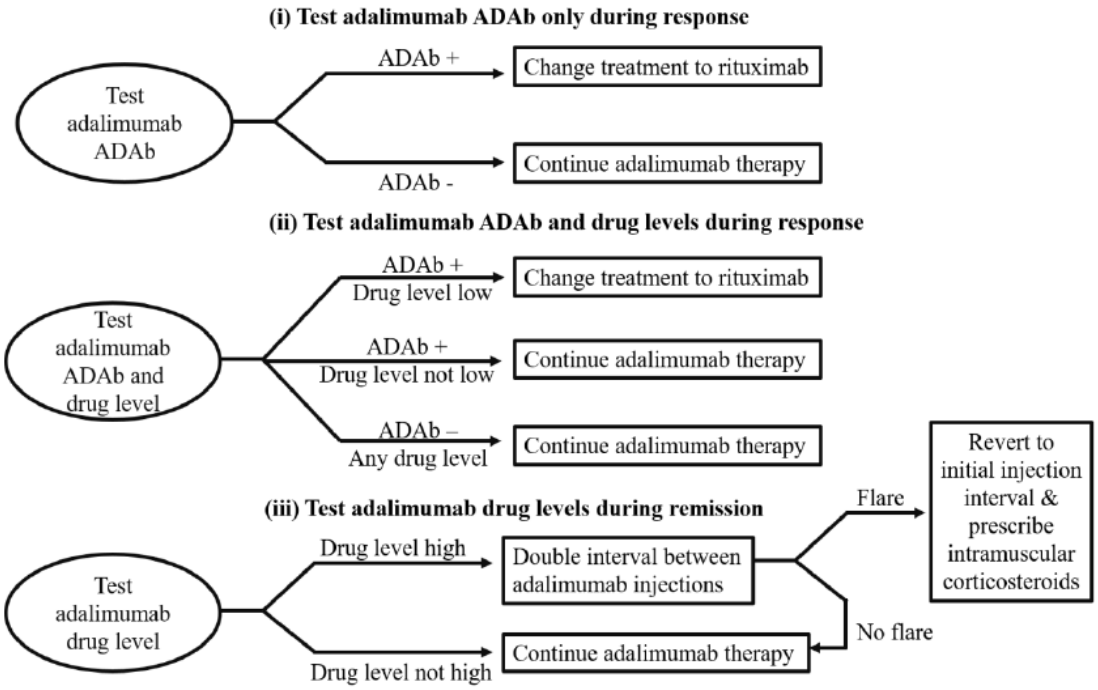
practice, but was unlikely to be cost effective relative to dose reduction (without testing) for people in remission. In particular:

- Strategies 3 and 4 dominated current practice (that is, testing was more clinically effective and cheaper than current practice).
- Strategies 1, 2 and 8 were cost effective at the maximum acceptable incremental cost-effectiveness ratio (ICER) of £20,000.
- Strategies 5 and 6 were associated with fewer costs and slightly fewer QALYs (<0.00001) and could potentially be considered cost saving.
- Strategies 9 and 10 were estimated to be less costly, but produced fewer QALYs compared with current practice (ICERs of £39,656 and £16,911, respectively).
- Strategy 7 was more costly and produced slightly fewer QALYs compared with current practice (incremental cost of £700 and incremental QALY of −0.01).
- Compared with strategy 11 (dose reduction not based on testing results), none of the testing strategies were cost effective at the maximum acceptable ICER of £30,000 per QALY gained.

Table 6 Strategies compared in Gavan (2017)

Strategy	Type of testing strategy	Description
Current practice	Not applicable	Usual care for people with RA with no testing of ADAb or drug level
1	Monitoring	ADAb and drug level testing every 3 months
2	Monitoring	ADAb and drug level testing every 6 months
3	Monitoring and dose reduction	ADAb and drug level testing every 3 months, drug level test in remission after 2 years
4	Monitoring and dose reduction	ADAb and drug level testing every 3 months, drug level test in remission after 3 years
5	Dose reduction	Drug level test in remission after 2 years
6	Dose reduction	Drug level test in remission after 3 years
7	Monitoring	ADAb testing only every 3 months
8	Monitoring	ADAb testing only every 6 months
9	Monitoring and dose reduction	ADAb testing only every 3 months, drug level test in remission after 2 years
10	Monitoring and dose reduction	ADAb testing only every 3 months, drug level test in remission after 3 years
11	Not applicable	No testing. Just half dose in remission after 2 years
12	Not applicable	No testing. Just half dose in remission after 3 years
Abbreviations: RA, Rheumatoid arthritis; ADAb, anti-adalimumab antibody. Note: Monitoring was done in participants whose disease responded, dose reduction was done in patients in remission		

Figure 3. Algorithm for test interpretation used in Gavan (2017)



Key: ADAb, anti-adalimumab antibodies.

Economic analysis

The EAG developed a de novo economic model designed to estimate the health and economic outcomes of adding TNF-alpha inhibitor testing to usual practice to guide treatment decisions in people with rheumatoid arthritis who had reached treatment target (remission or low disease activity). The primary analysis was based on the INGEBIO results (see section 2.1 of the overview and section 4.1.3.1 of the diagnostics assessment report for details), so it considered Promonitor kits for measuring adalimumab drug and antibody levels. Exploratory analyses were done to assess the health and economic outcomes of the Promonitor tests to measure drug levels and anti-drug antibodies for TNF-alpha inhibitors other than adalimumab, assuming 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.

The EAG did 2 separate types of economic analyses, which are described in detail starting on page 144 of the diagnostics assessment report:

- Threshold analysis, which estimated the cost of TNF-alpha testing in which the test-based treatment has no net monetary benefit at maximum acceptable ICERs of £20,000 and £30,000, taking into consideration the major components of differential costs and QALYs.
- ICER analysis.

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

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

Model structure

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.

Because of a short time horizon, a simple model was created. For the primary analysis (based on data reported by Ucar et al. 2017) it was assumed that patients could be in either of the 2 health states:

- remission
- low disease activity or active disease.

Patients could not move between health states in the model. The duration of time in each health state was based on INGEBIO results. Also, patients could have disutilities associated with flares and adverse events. In the primary analysis it was assumed that:

- A proportion of patients have their doses reduced in both intervention and control groups, as in INGEBIO, based either on the clinical assessment only (control group) or clinical assessment and therapeutic drug monitoring test results (intervention group).

- A proportion of patients in both intervention and control groups would have flares, as reported in INGEBIO. The average rates of flares in both arms were not stratified further according to dose of adalimumab taken (full or reduced). Therefore, within each arm, the EAG applied the same rate of flares to all patient, regardless of the dose taken.
- It was assumed that patients who had flares would be switched to the full dose. The estimates of the mean time to first flare were used to model the time when the dose in these patients was switched to the full dose (which affected the drug acquisition costs and wastage). The rates of flares were used to estimate the costs of flare management and reduction in QALYs caused by flares in the different arms. All patients who were switched back to the full dose would continue on the full dose for the rest of the model time horizon, while 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 analysis).
- Mortality associated with rheumatoid arthritis was not modelled and no discounting was applied to the costs and outcomes because of the short time horizon of about 18 months.

Model inputs

The model was populated with data from INGEBIO (see section 2.1 of the overview and section 4.1.3.1 of the diagnostics assessment report for details), and supplemented with information from secondary sources. The 18-month INGEBIO results were reported in 2 abstracts. Primary economic analysis was based on the intention-to-treat analysis in Ucar et al. (2017; Table 7). Additional analysis was based on results in Arango et al. (2017), which excluded 19 patients who were lost to follow-up. The EAG contacted the authors to clarify the differences between the 2 analyses but has had no response.

Table 7 Model inputs: health outcomes (INGEBIO and secondary sources)

Assumption	Estimate	Source	Relevant table or section in the DAR
Proportion of patients on reduced dose:			
Intervention	35.8%	INGEBIO (Ucar et al. 2017)	Table 40
Control	36.7%	INGEBIO (Ucar et al. 2017)	Table 40
Mean duration of remission (days)			
Intervention	344	INGEBIO (Ucar et al. 2017)	Table 40
Control	329	INGEBIO (Ucar et al. 2017)	Table 40
Mean follow-up (days)[1]	505	As in the control arm (Ucar et al. 2017)	Table 40
Flare rate[2]			
Intervention	0.463	INGEBIO (Ucar et al. 2017)	Section 4.1.8.1.1
Control	0.639	INGEBIO (Ucar et al. 2017)	Section 4.1.8.1.1
Mean time to first flare (days)[3]			
Intervention	208.07	Derived from Kaplan–Meier estimates of time to first flare (INGEBIO, Ucar et al. 2017)	Section 4.1.8.1.3
Control	189.32		Section 4.1.8.1.3
Flare duration (days)[3]	7	TA375	Section 4.1.8.1.2
Rate of AEs			
Patients on full dose	3/100 patient-years	Senabre Gallego et al. (2017)	Section 4.1.8.2.1
Patients on reduced dose	2/100 patient-years[4]	Singh et al. (2015)	Section 4.1.8.2.1
Duration of AE (days)	28	TA375, Oppong et al. (2013)	Section 4.1.8.2.2

Abbreviations: AE, adverse event; DAR, diagnostics assessment report; OR, odds ratio; RA, rheumatoid arthritis; RCTs, randomised controlled trials; TA, technology appraisal

Notes:

[1] The length of follow-up in the control arm (505 days) was used as the time horizon

in the economic analyses, which was slightly longer than follow-up in the intervention group (499 days). The estimates of the mean duration in remission in the intervention arm could not be adjusted to the 505 days horizon because the Kaplan–Meier curves for time in remission were not available to the EAG. However, because of small differences in the length of follow-up between the 2 groups (around 1%), the difference is expected to be small.

[2] 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 patients, regardless of their dose. The rates of flares were used to estimate the costs of flare management and reduction in QALYs because of flares in different arms.

[3] The estimates of the mean time to first flare were used to model the time when dose in these patients was switched to the full dose (which affected drug acquisition costs and wastage).

[4] This estimate was used for calculation of QALYs only since it was assumed that the adalimumab dose in people with flares is switched back to the full dose indefinitely.

[2] Based on OR=1.31 for standard-dose biologicals in people with RA reported by Singh et al. (2015). The OR estimate was obtained in a Bayesian network meta-analysis (using a binomial likelihood model) of 11 published RCTs (n=4,788) to assess the risk of serious infections in people with RA who have had anti-TNF-biologicals.

Costs

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

Costs were obtained from the British national formulary (BNF), NHS reference costs, from companies manufacturing the tests, and published and unpublished sources. Costs were converted to GBP and inflated to 2017-18 prices, as detailed on pages 159–60 of the diagnostics assessment report.

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 analysis, 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 is £8.75 per sample (seeTable 8). Potential price discounts, which depend on the uptake of testing, are explored in sensitivity analyses available in the Excel model.

The cost of the initial phlebotomy appointment, sample transport and other costs associated with testing are derived from Jani et al. (2016).

Table 8: Assay costs of Promonitor (exclude VAT)

	Single testing of patient samples			Duplicate testing of patient samples			Information source
Test	**N samples analysed per assay**	**Cost per assay**	**Cost per sample**	**N samples analysed per assay**	**Cost per assay**	**Cost per sample**	
Promonitor	80	£700	£8.75	40	£700	£17.50	Request for information submitted by Grifols

BNF list price of branded adalimumab (Humira) was considered in the primary analysis (£9,187; Table 9). However, the Humira patent expired on 16 October 2018, and biosimilar versions of adalimumab have been approved for use in the UK. As per NHS England guidance on biosimilar medicines (NHS England, 2017), rapid uptake of biosimilar adalimumab is expected in the UK. Because the true prices paid by the NHS are confidential and likely subject to large regional variations (regional tendering process), 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 adalimumab BNF list price on the ICER (see addendum 2 for details).

Other relevant costs considered in the model are listed in Table 9 and are explained in full in the diagnostics assessment report starting on page 163.

Table 9: Model inputs: costs

Assumption	Estimate	Source	Relevant table or section in the report
Acquisition costs (per patient-year): Adalimumab (Humira)			
Full dose[1]	£9,187	BNF	Section 4.1.9.1.3
Reduced dose	£6,125	BNF, Exeter biologics clinic recommendations	Appendix 5
Patients having flares[2]	£9,187	BNF, Exeter biologics clinic recommendations	Appendix 5
Treatment wastage on full dose (per patient-year)	£370	Clinical advice	Section 4.1.9.1.6
Administration cost for Humira (per patient-year)	£0	Clinical advice	Section 4.1.9.1.7
Cost of managing health states (per patient-year)[3]			
Remission	£11,409	Barbieri et al. (2005), Radner et al. (2014), National schedule of reference costs 2017-18	Section 4.1.9.1.16
LDA/active disease	£18,889		Section 4.1.9.1.16
Cost of flare management[4,5]	£423/per flare	Cost of diagnostic investigations (Maravic et al. 2005)	Section 4.1.9.1.19
	£68/month	Monthly cost of treatment (excluding DMARDs; Maravic et al. 2005)	Section 4.1.9.1.19
Cost of managing AEs (per infection)	£1,622[6]	TA375	Section 4.1.9.1.20

Abbreviations: AE, adverse event; BNF, British national formulary; HAQ, health assessment questionnaire; PPP, purchasing power parities; RA, rheumatoid arthritis; TA, technology appraisal

Notes:

[1] Assuming 40 mg every 2 weeks by subcutaneous injection using pre-filled pen, and NHS indicative price from the BNF.

[2] The mean time to first flare was estimated from additional evidence (Kaplan–Meier curves for time to first flare) from INGEBIO provided by Ucar et al. (2007; poster, personal communication).

[3] The costs of managing health states were included by HAQ-dependency, that is, by

assigning an annual cost to mutually exclusive HAQ intervals. Proportion of patients in different health states were derived from Radner et al. (2014).

[4] The estimates were derived from the costs of managing a flare in a hypothetical person with a 10-year history of RA in France. The costs were converted to GBP based on PPP and inflated to 2017-18 prices using the healthcare price index (section 4.1.9.1.1 in the diagnostics assessment report).

[5] The estimates from Maravic et al. (2005) do not include the cost of rheumatology appointments.

[6] The estimate of £1,479 per patient-year from the source was inflated to 2017-18 prices using the healthcare price index (section 4.1.9.1.11 in the diagnostics assessment report).

Health-related quality of life and QALY decrements

QALYs were estimated from the duration of remission, rates and duration of flares and adverse events in the intervention and control arms (Table 7), and corresponding utility values derived from published literature (Table 10 and section 4.1.9.2 in the diagnostics assessment report starting on page 182).

Utility estimates for remission and low disease activity or active disease health states were estimated from health assessment questionnaire (HAQ) scores for different HAQ bands (Radner et al. 2014) and mapped to EQ-5D values following Malottki et al. (2011). The estimate of the utility value for the low disease activity or active disease health state was computed from a weighted average HAQ score for low, medium and high disease activity, assuming distribution of patients across different health states as in Radner et al. (2014).

Disutility of flares were obtained from the Dutch multicentre, clinical study BeSt which involved 508 participants who had treatment-to-target for 10 years to reach disease activity score (DAS28) of at most 2.4 (Markusse et al. 2015). The disutility of serious adverse events was estimated as 0.156 over 4 weeks (equivalent to the loss of QALYs of 0.012).

Table 10: Model inputs: utilities

Assumption	Estimate	Source	Relevant sections in the DAR
Remission	0.718	Estimated from HAQ scores for different HAQ bands reported by Radner et al. (2014)	Section 4.1.9.2.1
LDA or active disease	0.568[1]		Section 4.1.9.2.1
Disutility of flare	0.140	Markusse et al. 2015	Section 4.1.9.2.2
Disutility of AEs	0.156	TA375, Oppong et al. (2013)	Section 4.1.9.2.3

Abbreviations: DAR, diagnostics assessment report; HAQ, health assessment questionnaire; HAD, high disease activity; LDA, low disease activity; MDA, moderate disease activity; TA, technology appraisal

Notes: [1] The estimate was computed from a weighted average HAQ score for the LDA, MDA and HDA health states reported by Radner et al. (2014) and mapped to EQ-5D values following Malottki et al. (2011).

Key assumptions

Major assumptions used in the primary analysis:

- Health outcomes are based on the INGEBIO results, as reported by Ucar et al. (2017; intention-to-treat analysis).
- The Promonitor test for adalimumab trough serum levels and anti-adalimumab antibodies is done concurrently, once per sample (singlicate testing), and once per year in a UK laboratory.
- Adalimumab acquisition costs are based on the Humira BNF list price.
- The dose is reduced in a proportion of people in each arm at the start of simulation.
- Adalimumab dose reduction is implemented by increasing the interval between doses from 2 to 3 weeks (that is, by spacing doses).
- A proportion of patients in each arm have flares (as reported in INGEBIO; Ucar et al. 2017).
- The full dose of adalimumab is restored in all people on reduced doses when their disease flares (based on mean time to first flare derived from INGEBIO; Ucar et al. 2017).

- Treatment wastage is £370 per patient-year in people on a full dose; it is reduced proportionally to the reduction in treatment dose.
- Adalimumab is self-administered (usually at home), and, therefore, the administration cost is zero.
- The costs associated with flare management are:
  - £423 per flare for diagnostic investigations
  - £68 per month for treatment (excluding the cost of DMARDs).
- The annual per-patient costs of managing remission and the low disease activity or active disease health states are £11,409 and £18,889 respectively.
- The cost of managing an adverse event is £1,622.
- The utilities for remission and low disease activity or active disease health states are 0.718 and 0.568, respectively.
- The disutility of flare is 0.140.
- The duration of flare is 7 days.
- The rates of adverse events in people on full and reduced doses are 3/100 and 2/100 patient-years, respectively.
- The duration of adverse event is 28 days.
- The disutility of adverse event is 0.156.
- The time horizon is defined by the follow-up in INGEBIO (18 months; no extrapolation of costs and health outcomes; no discounting applied).

Primary analysis results: ICER analysis

Results of primary economic analysis based on the INGEBIO intention-to-treat results (Ucar et al. 2017) are presented in Table 11. To highlight the uncertainty in the INGEBIO data, results of this primary analysis are presented alongside an additional economic analysis based on the INGEBIO results reported by Arango et al. (2017), which excluded 19 patients lost to follow-up (Table 12). Results of both analyses are presented in the diagnostics assessment report starting on page 195.

In the economic analysis based on data from Ucar et al. (2017), therapeutic drug monitoring 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. However, when the analysis was based on data from Arango et al. (2017), an 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 cost and loss of 0.007 QALYs. Therefore, the results of the economic analysis are inconclusive. The 2 analyses based on the 2 abstracts from INGEBIO not only produced opposite direction of effects but also were based on very small and uncertain differences in outcomes (QALY differences of less than 0.01).

Table 11: Primary cost-effectiveness results based on the INGEBIO data reported by Ucar et al. 2017

	Intervention arm	Control arm	Intervention vs. control
Costs			
Drug acquisition	£12,078	£12,120	−£42
Drug administration	£0	£0	£0
Drug wastage	£486	£488	−£2
Cost of managing health states	£19,071	£19,379	−£307
Cost of flare management	£281	£388	−£107
Cost of managing AEs	£64	£64	£0
Cost of testing			
Cost of phlebotomy appointment	£162	£0	£162
Costs of sample analysis[1]	£30	£0	£30
Cost of sample transport[2]	£6	£0	£6
Total costs (mean)	**£32,178**	**£32,438**	**−£260**
QALYs			
Remission	0.676	0.647	0.029
LDA/active disease	0.250	0.274	−0.023
Flares	-0.002	-0.002	0.001
AEs	0.000	0.000	0.000
Total QALYs (mean)	0.924	0.918	0.007
ICER (Cost / QALY gained)			**Intervention dominates standard care (ICER −£38,150)**

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Note:

[1] Includes cost per sample of: ELISA assay for drug level, ELISA assay for antibody level and other sample processing costs.

[2] The postage was £4 per parcel.

Table 12 Cost-effectiveness results based on INGEBIO data reported by Arango et al. 2017

	Intervention arm	Control arm	Intervention vs. control
Costs			
Drug acquisition	£13,075	£13,149	−£74
Drug administration	£0	£0	£0
Drug wastage	£527	£530	−£3
Cost of managing health states	£22,112	£21,757	£355

	Intervention arm	Control arm	Intervention vs. control
Cost of flare management	£303	£418	−£115
Cost of managing AEs	£69	£70	£0
Cost of testing			
Cost of phlebotomy appointment	£162	£0	£162
Costs of sample analysis[1]	£30	£0	£30
Cost of sample transport	£6	£0	£6
Total costs (mean)	**£36,284**	**£35,923**	**£361**
QALYs			
Remission or LDA	0.838	0.865	−0.027
Active disease	0.112	0.092	0.020
Flares	-0.002	-0.003	−0.001
AEs	-0.001	-0.001	−0.000
Total QALYs (mean)	**0.947**	**0.954**	**−0.007**
ICER (Cost / QALY gained)			**Standard care dominates Intervention (ICER −£53,375)**

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Note:

[1] Includes cost per sample of: ELISA assay for drug level, ELISA assay for antibody level and other sample processing costs.

[2] The postage was £4 per parcel.

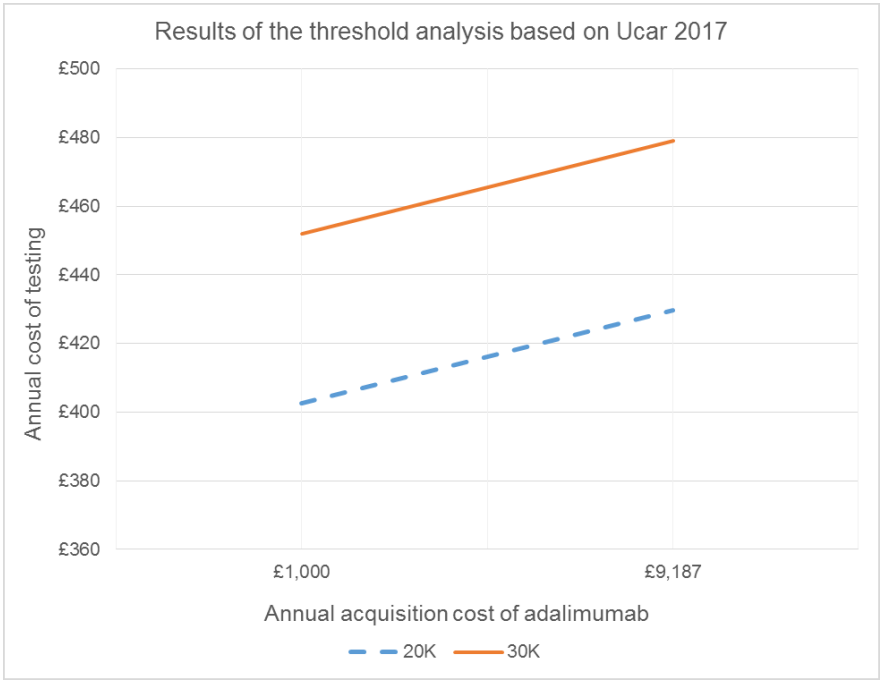
Primary analysis results: threshold analysis

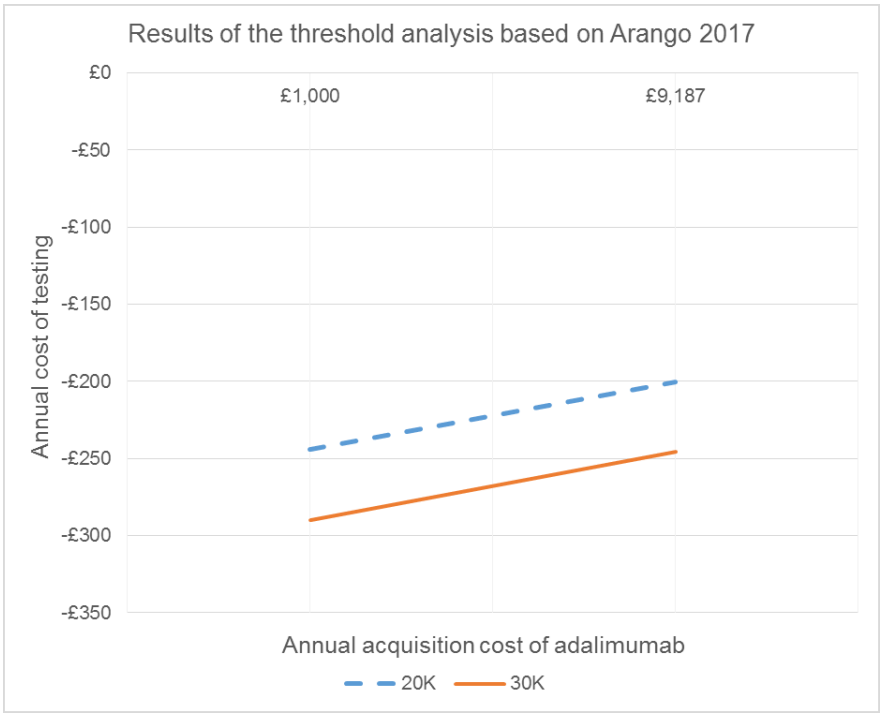
Figure 4 shows the annual cost of ELISA-based testing at which therapeutic drug monitoring would become cost effective at maximum acceptable ICERs of £20,000 and £30,000, based on the adalimumab (Humira) BNF list price of £9,187 as well as a hypothetical low cost of adalimumab biosimilars of £1,000. Based on data from Ucar et al. (2017) and the current list price of Humira, the overall cost of testing (assay cost, cost of the testing service and sample transport) would have to be lower than £430 or £479 per year to be considered cost effective at maximum acceptable ICERs of £20,000 and £30,000, respectively (an annual total cost of testing of £132 was assumed in the primary cost–utility analysis). At these ICERs and assuming an adalimumab acquisition cost of £1,000, testing would need to be cheaper than £200 and £246 to be considered cost effective, respectively. However, using

the results from Arango et al. (2017), there would be no cost of testing at which it could become cost effective (testing was estimated to be both more costly and less effective [dominated] than standard care).

Differences between the 2 models can be attributed to differences in the mean duration of time spent in different health states between the control and intervention arms. Ucar et al. (2017) reported a longer duration of remission in the intervention group (344 days compared with 329 days in the control group), whereas Arango et al. (2017) reported a shorter duration of remission or low disease activity in the intervention group (460.2 days compared with 475.2 days in the control group).

Figure 4 Results of the threshold analyses using INGEBIO results reported by Ucar et al. (2017) and Arango et al. (2017)





Analysis of alternative scenarios

A number of sensitivity analyses were done to explore the effect of parametric and structural uncertainty on the model outcomes (described in the diagnostics assessment report starting on page 197).

Results of the scenario sensitivity analyses are presented in Table 13. In all but 1 sensitivity 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), whereas in all but 1 sensitivity analysis based on data from Arango et al. (2017) the standard care dominated intervention (that is, standard care was more clinically effective and cheaper than testing). When the impact of flares only was modelled (that is, impact of health states and adverse effects were not considered), the ICERs in the analyses by Ucar et al. and Arango et al. were £72,645 and £8,804 per QALY, respectively.

Table 13 Sensitivity analyses (people in remission or low disease activity)

Sensitivity analysis	Assumptions	Ucar et al. 2017			Arango et al. 2017		
		Incr. Costs	Incr. QALYs	ICER Cost/QALY	Incr. Costs	Incr. QALYs	ICER
Impact of flares only (health states and AEs are not included)	Only flares contribute to differential costs and QALYs	£47	0.001	£72,645	£6	0.001	£8,804
Dose-reduction strategy	Spacing: reduction of ADA dose to 40mg every 4 weeks	−£282	0.007	−£41,355: intervention dominates standard care	£323	−0.007	−£47,720: standard care dominates intervention
Treatment wastage	No wastage	−£258	0.007	−£37,902: intervention dominates standard care	£364	−0.007	−£53,813: standard care dominates intervention
Flare duration, days	19	−£267	0.008	−£33,590: intervention dominates standard care	£354	−0.006	−£63,697: standard care dominates intervention
Proportion of flared patients in whom full dose is restored	55%	−£222	0.007	−£32,626: intervention dominates standard care	£372	−0.007	−£54,996 standard care dominates intervention
	0%	−£176	0.007	−£25,872: intervention dominates standard care	£386	−0.007	−£56,976 standard care dominates intervention
Utilities[1]							
Remission	0.496	−£260	0.009	−£30,154: intervention dominates standard care	£361	−0.007	−£53,375 standard care dominates intervention
LDA or active disease	0.302						
Disutility of flare	0.085	−£260	0.007	−£39,642 : intervention dominates standard care	£361	−0.007	−£51,279 standard care dominates intervention

	0.116	−£260	0.007	−£38,787: intervention dominates standard care	£361	−0.007	−£52,440 standard care dominates intervention
Frequency of testing (tests/year)	2	−£62	0.007	−£9,116: intervention dominates standard care	£559	−0.007	−£82,612 standard care dominates intervention
Cost of testing	A number of scenarios tested; see table 73 in the diagnostics assessment report for details	-	-	In all analyses intervention dominates standard care	-	-	In all analyses, standard care dominates intervention

Abbreviations: AE, adverse events; ICER, incremental cost-effectiveness ratio; Incr., incremental; LDA, low disease activity

Notes:

All costs are reported in 2017-18 prices.

[1] Utilities for the mixed disease population (as in INGEBIO) were assumed to be the same as those for people with rheumatoid arthritis.

Deterministic sensitivity analyses

A number of one-way deterministic sensitivity analyses were done and the results are presented in Table 14 and on page 202 of the DAR. The results show that changing any of the parameters had no effect on the findings; in the analysis based on data from Arango et al. (2017), standard care dominated the intervention in all analyses (that is standard care was more clinically effective and cheaper than testing).

The first 4 deterministic sensitivity analyses were not done for the analysis based on data from Ucar et al. (2017), because it was expected that results would be aligned with the primary analysis, that is, the intervention would dominate standard care. Sensitivity analyses on adalimumab cost (20% to 80% discount) also did not change the conclusions of the primary analysis; that the intervention dominated standard care regardless of adalimumab price.

Table 14 One-way deterministic sensitivity analyses based on data from Arango et al. (2017)

Parameter	Assumption	Intervention vs control		
		Incr. Costs	**Incr. QALYs**	**ICER**
Percentage of people in whom the dose of biological was reduced	+20% in the intervention arm and −20% in the control arm	£117	−0.007	−£17,367: standard care dominates intervention
Flare rate	−20% in the intervention arm, +20% in the control arm	£217	−0.006	−£36,880; standard care dominates intervention
Differential time in remission or low disease activity	+10% in the intervention arm, −10% in the control arm of the differential time in remission (+1.5 days and −1.5 days, respectively)[a]	£290	−0.005	−£55,027: standard care dominates intervention
Costs of managing health states	−20%	£290	−0.007	−£42,872: standard care dominates intervention
Adalimumab acquisition costs	−20%	£377	−0.007	−£55,637; standard care dominates intervention
	−40%	£392	−0.007	−£57,900; standard care dominates intervention
	−60%	£407	−0.007	−£60,162; Standard care dominates Intervention
	−80%	£422	−0.007	−£62,424; standard care dominates Intervention
Abbreviations: ICER, incremental cost-effectiveness ratio Time in remission or low disease activity: Intervention arm: 460.2 + 10%*(475.2-460.2) = 461.7 days Control arm: 475.2 – 10%*(475.2-460.2) = 473.7 days				

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was thought inappropriate because of the substantial variation in clinical practice with respect to disease management in people with rheumatoid arthritis in England.

Exploratory analyses for etanercept and infliximab

The cost effectiveness of therapeutic drug monitoring testing (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. The analyses 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. The analysis used all assumptions of the primary analysis, 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, and therefore the list prices of the biologicals were assumed (table 50 in the diagnostics assessment report; pages 161–162). Clinical effectiveness estimates were based on Ucar et al. (2017) and presented alongside analyses based on Arango et al. (2017).

The results are presented in Table 15. As in the case of primary analysis for adalimumab, the cost effectiveness of TNF-alpha inhibitors depended on the source of data for the clinical estimates. When data from Ucar et al. (2017) were used (intention-to-treat analysis), intervention dominated standard care (that is testing was more clinically effective and cheaper than standard care. But if data from Arango et al. (2017) were used, standard care dominated the intervention (that is standard care was more clinically effective and cheaper than testing).

Table 15 Cost-effectiveness results for Promonitor tests for other TNF-alpha inhibitors

Treatment	Biological's acquisition costs per year (£)	Cost-effectiveness results	
		Ucar et al. (2017)	Arango et al. (2017)
Etanercept			
Enbrel	9,327	Intervention dominates standard care (ICER: −£38,247; total costs: −£261; total QALYs: 0.007)	Standard care dominates intervention (ICER: £53,203; total costs: £360; total QALYs: −0.007)
Erelzi	8,394	Intervention dominates standard care (ICER: −£37,597;	Standard care dominates intervention (ICER: −£54,351; total

		total costs: −£256; total QALYs: 0.007)	costs: £368; total QALYs: −0.007)
Infliximab[1]			
Flixabi/ Renflexis	5,164	Intervention dominates standard care (ICER:−£36,580; total costs: −£249; total QALYs: 0.007)	Standard care dominates intervention (ICER: −£56,144; total costs: £380; total QALYs: −0.007)
Notes: [1] Infliximab administration cost was assumed to be £283 per injection; no vial wastage costs were assumed.			

3 Summary

Clinical effectiveness

The EAG identified 2 studies on the clinical utility of ELISA tests to inform treatment decisions in people with rheumatoid arthritis; 1 non-randomised controlled study (INGEBIO) and 1 observational study (Pascual-Salcedo et al. 2013).

The INGEBIO study was a prospective, non-randomised, multicentre pragmatic trial assessing the efficacy and cost of implementing therapeutic drug monitoring (Promonitor) to guide treatment decisions in people with different rheumatic diseases, as compared with standard care where treatment decisions are based on clinical judgement only (Ucar et al. 2017; Arango et al. 2017). It enrolled 169 patients who had treatment with adalimumab and who remained clinically stable for at least 6 months, and showed similar rates of adalimumab dose reduction (35.8% and 36.7%), mean duration of remission (344 and 329 days) and flares (0.463 and 0.639 per person-year) in the intervention and control groups, respectively, based on the intention-to-treat analysis reported by Ucar et al. 2017. The INGEBIO results were also reported in the abstract by Arango et al. 2017, which excluded 19 patients who were lost to follow-up. The EAG contacted the authors to clarify the differences between the 2 analyses but has not had any response.

Importantly, INGEBIO enrolled a mixed population of patients with rheumatic diseases (only 37% patients had rheumatoid arthritis), affecting the generalisability of the study to people with rheumatoid arthritis. Also, the study

was done in Spain, where dose reductions based on clinical assessment are part of standard care for people with rheumatoid arthritis in remission. Dose reductions based on clinical assessment are not yet part of standard care across the UK, but are done in some centres such as Exeter. In the INGEBIO study, clinicians were not obliged to follow any pre-defined treatment algorithm to interpret therapeutic drug monitoring test findings but could use tests to alter doses based on their judgement. Also, the study was reported only in abstract format, had a non-randomised design and was judged to be at serious risk of bias.

The observational study by Pascual-Salcedo et al. (2013) was identified in the review, but did not provide any data to inform the economic model.

An additional randomised controlled trial by l'Ami et al. (2017) was identified, which assessed clinical outcomes in patients with rheumatoid arthritis with high serum adalimumab concentrations who had dose-interval prolongation, compared with patients who continued standard dosing. However, considering its 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.

The EAG has identified 1 ongoing Norwegian multicentre randomised controlled trial (NOR-DRUM) that evaluates the effect of therapeutic drug monitoring in people with rheumatoid arthritis in remission compared with standard care. This ongoing trial will provide further data on the effect of therapeutic drug monitoring in the target population.

Cost effectiveness

The results of the economic analyses for therapeutic drug monitoring (Promonitor) of drug and antibody levels in people with rheumatoid arthritis who had reached treatment target (remission or low disease activity) with adalimumab were inconclusive and should be interpreted with caution. The primary analyses showed that therapeutic drug monitoring was either dominating, or dominated by standard care, depending on which source of INGEBIO data were used in the model: Ucar et al. 2017 (intention-to-treat

analysis; testing dominated standard care, that is, testing was more clinically effective and cheaper than standard care) or Arango et al. 2017 (analysis excluding 19 patients lost to follow-up; standard care dominated testing, that is, standard care was more clinically effective and cheaper than testing).

In all but 1 sensitivity analysis the intervention dominated standard care when data from Ucar et al. (2017) were used, and it was dominated by standard care if data were derived from Arango et al. (2017). When the impact of flares only was modelled (that is, impact of health states and adverse effects were not considered), the ICERs in the analyses by Ucar et al. and Arango et al. were £72,645 and £8,804 per QALY, respectively.

Results of exploratory analyses of Promonitor tests for tumour necrosis factor (TNF)-alpha inhibitors other than adalimumab (infliximab and etanercept; assuming 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), were aligned with the findings of the primary analyses. In analyses based on data from Ucar et al. 2017, therapeutic drug monitoring dominated standard care, whereas in analyses based on Arango et al. 2017, standard care dominated testing.

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

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

4 Issues for consideration

Clinical effectiveness

- Lack of evidence – there were no randomised controlled trials, only 1 non-randomised comparative study (INGEBIO; Promonitor for adalimumab testing; presented in 3 abstracts) and 1 observational study (Sanquin for adalimumab, infliximab and etanercept) assessing the effect of ELISA tests on decision making and patient outcomes. No studies were identified

assessing ELISA kits including IDKmonitor ELISA kits, LISA-TRACKER ELISA kits, RIDASCREEN ELISA kits and MabTrack ELISA kits.

- The INGEBIO study concluded that patients with rheumatic diseases have better quality of life, lower risk of flares (although not statistically significant), and lower treatment costs when standard care is complemented with data from therapeutic drug monitoring. However, the study has several limitations and generalisability issues.
- Generalisability issues with INGEBIO:
  - A mix of rheumatic diseases, only 37% of patients had rheumatoid arthritis.
  - Study done in Spain, where dose reductions based on clinical assessment are part of the standard care for people with rheumatoid arthritis in remission. Dose reductions based on clinical assessment are not yet part of standard care across the UK, but are done in some centres such as Exeter. Overall, a similar proportion of patients in the intervention (therapeutic drug monitoring) and control arms had dose reductions.
- Other limitations of INGEBIO:
  - Clinicians were not obliged to follow any pre-defined treatment algorithm to interpret therapeutic drug monitoring test findings but could use tests to alter doses based on their judgement.
  - Non-randomised design.
  - Judged to be at serious risk of bias.
  - Results reported in abstract format only.
  - Unclear differences between the 2 abstracts reporting 18-month data: Ucar et al. (2017; intention-to-treat analysis) and Arango et al. 2017 (analysis excluding 19 patients who were lost to follow-up).
  - Ucar et al. (2017) reported the duration of time in remission (consequently the other health state in the model was defined as low disease activity or active disease), while Arango et al. 2017 reported the duration of time in remission or low disease activity (consequently the other health state in the model was defined as active disease) – it was not clear if this was a true difference in reported outcomes.

  - Ucar et al. (2017) reported a longer duration of remission in the intervention group (344 days compared with 329 days in the control group), whereas Arango et al. (2017) reported a shorter duration of remission or low disease activity in the intervention group (460.2 days compared with 475.2 days in the control group). This difference had an effect on the results of the economic model.
- The study by l'Ami et al. (2017) concluded that in patients with rheumatoid arthritis who had high (above 8 mg/litre) serum trough concentrations of adalimumab, their dose can be safely reduced, by prolonging the dosing interval from 2 to 3 weeks, without negatively affecting patients' outcomes. However, the study was limited by its small sample size (55 patients only), short follow-up time (28 weeks) and the fact that the median adalimumab doses at week 28 were comparable in both groups. Consequently, the EAG did not include this study in the economic assessment.
  - The key differences between the study by l'Ami and INGEBIO were that l'Ami enrolled only patients with rheumatoid arthritis (compared with a mixed population in INGEBIO) who had high (above 8 mg/litre) serum trough concentrations of adalimumab (INGEBIO did not base inclusion criteria on therapeutic drug monitoring), and in the choice of the comparator. In l'Ami, patients in the comparator arm continued standard dosing of adalimumab (no dose reductions), whereas in INGEBIO, patients in the comparator arm had 'standard care', where therapeutic decisions, including dose reductions, were based on clinical judgement only.
- The ongoing Norwegian multicentre randomised controlled trial (NOR-DRUM) was set up to evaluate the effect of therapeutic drug monitoring in people with rheumatoid arthritis in remission compared with standard care. The study is expected to complete in March 2022.
- The assessment focused only on studies which investigated the clinical utility of therapeutic drug monitoring to inform treatment decisions and improve patient outcomes. Studies which only investigated correlation between serum levels of TNF-alpha inhibitors and/or anti-drug antibodies and patient outcomes were considered out of scope. However, such

correlations have previously been reported (Bartelds et al. 2011; Incierte-Mundo et al. 2016; Chen et al. 2016).

Cost effectiveness

- Simple model (no state transitions) based on poor quality data (small, non-randomised study judged to be at serious risk of bias and with poor generalisability to the NHS population of people with rheumatoid arthritis – see limitations described above in the clinical effectiveness section).
- The major challenge in this assessment was limited evidence on clinical effectiveness, health-related quality of life and costs associated with test-based treatment strategies.
- Depending on which INGEBIO study abstract was used, therapeutic drug monitoring either dominated or was dominated by standard care, which can likely be attributed to differences in the mean duration of time spent in different health states between the control and intervention arms. These inconclusive results suggest considerable uncertainty in the cost effectiveness of therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors in rheumatoid arthritis.
- Currently dose reductions are not part of the routine care in the UK, therefore it is not clear if the comparator arm in INGEBIO (in which 36.7% of patients had dose reduction based on clinical judgement alone) is applicable to the NHS. When dose reductions were explored in a sensitivity analysis, the direction of the results was not affected. However, this sensitivity analysis assumed that the rate of tapering would affect adalimumab acquisition costs and rates of adverse events only, with no effect on patient outcomes. This was because of the lack of evidence to inform this part of the model, because clinical outcomes in INGEBIO were not stratified by the dose of adalimumab taken.
- In the primary analysis, 100% of people with flare were assumed to return to the full adalimumab dose, and it is not clear if this would happen in clinical practice in the NHS.
- There is currently no agreement on the treatment algorithm based on results of therapeutic drug monitoring to be used in the NHS. INGEBIO did

not follow any treatment algorithm so it is unclear whether and to what extent the economic results based on this study are relevant to clinical practice in England.

- Since the rates of adverse events were not reported in INGEBIO, the effect of adverse events was modelled using evidence from another study, which is a limitation of this analysis. However, based on clinical advice and published literature on adverse events in people with rheumatoid arthritis who had TNF-alpha inhibitors, adverse events which carry a significant cost and disutility burden are relatively rare.
- Since the actual costs to the NHS of adalimumab (Humira), its biosimilars and other TNF-alpha treatments were not known to the EAG at the time of writing, the effect of variation in the annual acquisition costs of the biologicals was explored (hypothetical cost of £1,000 assumed in threshold analysis and up to 80% discount in the sensitivity analyses). This had no effect on the cost effectiveness of therapeutic drug monitoring.
- The time horizon of the threshold analysis done in this study was defined by the observational period in INGEBIO, which was 18 months. Costs and health outcomes were not extrapolated into the future. This was because the lack of long-term clinical studies meant external validation of extrapolated outcomes would not be feasible. Also, given the multifactorial nature of treatment decisions in people with rheumatoid arthritis, long-term extrapolation of cost and health outcomes would be prone to even greater uncertainties, which would not be possible to quantify given the substantial limitations in the evidence base.
- Because of limited reporting, it is not clear to what extent selection bias in INGEBIO (which was a non-randomised trial) could have influenced the results of the economic analysis.
- Economic analyses for ELISA tests other than Promonitor were not done because of the lack of evidence to inform the models.
- Economic assessment for the population with primary or secondary non-response was not possible because of the lack of evidence.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Rheumatoid arthritis can have a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities. Therefore, people with rheumatoid arthritis may be covered under the disability provision of the Equality Act (2010).

Therapeutic monitoring may also be helpful in people who have stopped treatment of rheumatoid arthritis because of pregnancy or comorbidities, and have restarted treatment with tumour necrosis factor (TNF)-alpha inhibitors.

6 Implementation

The key considerations for adoption highlighted through discussions with expert contributors are:

Clinical confidence

Clinical experts noted that more understanding and knowledge is needed about:

- What the test results mean for clinical practice and the treatment plan; clinicians will need training and education.
- Whether reflex or concurrent testing is the most cost-effective testing strategy, and if certain biological therapies only need anti-drug antibody testing.
- How the total and free anti-drug antibodies levels affect decisions to change the treatment plan.

Obtaining a sample

Patients who have biological therapies for rheumatoid arthritis have regular reviews and blood tests, therefore blood samples may be available for therapeutic drug monitoring tests without the need for additional

appointments. But sometimes an additional hospital or GP appointment may be needed to take a trough level (taken just before a drug dose is due). This would be an additional cost to the service.

Laboratory

Results vary with different tests, therefore the test kit that was used to do the test should be recorded alongside the result.

Equipment and staff training

Adopting the tests would need increased technician time and a senior laboratory scientist to review and sign off the results. However, they are reasonably easy tests to run and minimal training would be needed.

Frequency and centralisation

Centralised testing, either nationally or regionally, would mean that tests could be run frequently and at full capacity, giving timely availability of results and optimum use of resources.

Costs

Costs of testing could be a barrier to adoption, but savings on biological therapies could be made if drug doses are reduced without affecting clinical outcomes, and by guiding the most suitable and effective treatment for each patient. However, the costs of testing and the drug savings are likely to come from different budgets.

7 Authors

Ewa Rupniewska
Topic lead

Frances Nixon
Technical adviser

January 2019

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by:

Tikhonova I, Yang H, Salmon A et al. (2019) Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis. Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers of technologies included in the final scope:

- Grifols UK Limited
- Biohit HealthCare Ltd
- Theradiag
- R-Biopharm
- Sanqin Diagnostics Services B.V

Manufacturers of related technologies (not included in scope)

- Alpha Laboratories Ltd

Other commercial organisations:

- Cambridge Life Sciences Ltd
- Pfizer UK
- AbbVie
- Roche Products
- Amgen

Professional groups and patient/carer groups:

- Association for Clinical Biochemistry and Laboratory Medicine
- British Society for Rheumatology

- National Rheumatoid Arthritis Society (NRAS)
- Royal College of Physicians

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Adalimumab
A recombinant human anti-TNF-alpha IgG1 monoclonal antibody

Anti-drug antibodies
Antibodies produced by the body in an immune response against a therapeutic antigen, for example a monoclonal antibody, which may inactivate the drug and modify the pharmacokinetic characteristics of the drug

Immunosuppressants
A class of drugs used to supress of prevent an immune response

Infliximab
A chimeric (human-murine) anti-TNF-alpha IgG1 monoclonal antibody

Pharmacokinetics
The process by which a drug is absorbed, distributed, metabolised, and eliminated by the body

Primary non-response
A lack of improvement of clinical signs and symptoms during induction therapy

Secondary non-response
Loss of clinical response to therapy in patients whose disease had initially had a clinical response

TNF-alpha
An inflammatory cytokine which helps to regulate the immune system, but when present in high concentrations it is responsible for the destructive inflammatory processes that occur in inflammatory bowel disease

TNF-alpha inhibitors
Biological therapies which target the TNF-alpha protein with the aim of modifying the inflammatory disease process

Trough levels
In a medicine administered periodically the trough level is the lowest level of drug reached in the body before the next dose is administered.