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Clinical science

Cost-effectiveness of risk-stratified blood test monitoring strategies for adults with inflammatory conditions

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Abstract

Objectives: To assess the cost-effectiveness of extending the interval between monitoring blood tests beyond 3-monthly intervals during established treatment of adults prescribed low-dose weekly MTX (≤25 mg/week), LEF or SSZ.

Methods: Published prognostic models that estimated the risk of stopping treatment due to abnormal blood test results during 5 years of established treatment were incorporated into a cost-effectiveness model. The consequences of having an extended monitoring period and a delay in stopping treatment was estimated by clinicians as the probability of someone having 1 of the 11 adverse events (AEs) that could be avoided with monitoring. The clinicians erred towards overestimating the risks. The costs and quality-adjusted life year loss of the AEs were sourced from recent National Institute of Health and Care Excellence appraisals or from targeted searches. Incremental net monetary benefit (iNMB) of 6-, 12- and 24-monthly monitoring, compared with three monthly monitoring was calculated for each drug conditional on risk decile.

Results: Our analyses show that extending the duration between monitoring appointments is cost-effective in all scenarios, even in a pessimistic analysis, where the risks of all AEs were tripled, and the costs of some AEs were increased. In the base case, biennial monitoring was often most cost-effective although the iNMB between annual and biennial monitoring was often small.

Conclusion: Extending the interval between monitoring blood tests appears to be cost-effective with annual monitoring producing consistently good results regardless of assumptions related to risks of AEs, risk decile or treatment.

Keywords: cost-effectiveness, methotrexate, leflunomide, sulfasalazine, blood monitoring, immune-mediated inflammatory disease.

Rheumatology key messages

- It is cost-effective to extend the intervals between monitoring blood tests from 3-monthly.
- The largest relative gains were estimated when extending to 6-monthly or annual intervals.
- Findings need to be considered by health policy makers to influence clinical practice change.

Introduction

Inflammatory conditions such as RA and psoriasis (PsO) ± arthritis affect ∼3% of adults in the UK [1, 2]. MTX is the first-line conventional synthetic DMARD for these conditions with LEF and SSZ being subsequent second-line therapies for RA and PsA. These drugs can cause acute liver injury, acute kidney injury and cytopenia, especially early in the treatment course [3–7]. Fortnightly to monthly monitoring blood tests are recommended by specialist societies when initiating these treatments while 3-monthly monitoring blood tests are recommended during established therapy [8–11]. The British National Formulary (BNF) recommends that patients established on LEF, MTX and SSZ undergo 8-weekly, 2- to 3-monthly and 12-monthly monitoring blood tests, respectively.

The purpose of such testing is to facilitate the early detection of asymptomatic adverse drug reactions, thereby allowing for treatment to be stopped before clinically significant damage occurs. The recommendation to undertake 2- to 4-weekly blood tests during the first few months of treatment appears to have been grounded in clinical trials and observational studies in

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which there was a high rate of blood test abnormalities in this period [12, 13]. However, the practice of undertaking monitoring blood tests at 3-monthly intervals during established treatment for all patients does not appear to be justified as blood test abnormalities are uncommon during established treatment [14] and their risk varies from person to person with several predictors [15]. Monitoring blood tests undertaken at 3-monthly intervals using a one-size-fits-all approach burdens the patients and healthcare system. Organizing and attending their monitoring blood tests is time consuming and inconvenient for many patients because of work commitments, difficulties securing an appointment or having to chase results to receive their prescription [16]. Health professionals noted that monitoring was resource intensive, taking up a large proportion of their workload [16]. Capacity issues were highlighted within busy National Health Service (NHS) settings to provide and review tests at the current frequency [16].

Validated risk-prediction tools to aid personalized monitoring for adverse events (AEs) during established treatment were recently developed by our team for patients treated with MTX [17], LEF [18] and SSZ [19]. In the face of expanding demands on the NHS and finite human and financial resources, it is essential to evaluate whether it would be cost-effective to risk-stratify monitoring to minimize the use of low-value low-yield interventions. We explored the cost-effectiveness of extending the duration of monitoring periods to 6-monthly, annually or biennially for patients established on treatment, i.e. initiated and stabilized on either MTX, LEF or SSZ from a hospital clinic and then prescribed treatment by a general practitioner (GP) for at least 6 months. It was anticipated that extending the duration would result in cost savings through reduced healthcare utilization, although there is potential for additional AEs which would both cost money and cause patient harm.

Methods

Prognostic models

The probability of an abnormal blood test that required cessation of treatment that would be expected in each of the 20 quarters between the start of follow-up period for the prediction models and year 5 was taken from published prognostic models [17–19] conditional on treatment (i.e. MTX, LEF or SSZ) and on decile of risk. The development and validation of these models have been described in full previously [17–19].

In brief, these studies used primary care comorbidity, prescribing and monitoring data from the UK's Clinical Practice Research Datalink (CPRD). Adults aged 18 years or older diagnosed with an immune-mediated inflammatory disease (e.g. RA, axial SpA, psoriasis with or without arthritis) and prescribed a conventional synthetic DMARD by their GP were eligible for study inclusion. They were followed-up from 180 days after their first prescription for MTX in primary care to the earliest of outcome (drug discontinuation with a prespecified abnormal blood test results), drug discontinuation for any reason, leaving the practice, last data collection from the practice, death, 5 years or study end date. Predictors were selected by clinical members of the team. These included demographic and lifestyle factors, comorbidities, prior blood test results and prescriptions. Multiple imputation using chained equations handled missing predictor data. Cox regression was used to develop the model. Bootstrapping was used to correct for optimism. Royston's D statistic, a measure of discrimination, Royston's R^2, a measure of variation explained by the model, and Harrell's C statistic, a measure of the model's predictive accuracy was calculated. The final developed model equation was applied to the external validation dataset, and calibration and discrimination were analysed described previously. R^2 and C-statistic were calculated for the validation cohort. Separate model development and validation work was undertaken for each drug.

With standard 3-monthly monitoring the cessation of treatment due to an abnormal blood test would occur at the relevant quarterly appointment. However, for longer monitoring intervals, it was assumed that the patient may have to wait longer (until the next appointment, which could be nearly the full interval, thus almost 2 years in the biennial monitoring strategy) for treatment to be stopped. During this period, it is possible that clinically significant harm could occur, both impacting the patient and resulting in expenditure, which would not have occurred under 3-monthly monitoring. The risk of this happening is determined from the prognostic models.

Simulated patients

Data from patients representative of each decile were selected for each treatment by ranking the patients in terms of predicted risk in the model derivation cohort and selecting the patient at the 5th percentile, 15th percentile, and so on, until the 95th percentile. The predicted risk is a composite of various factors including demographic and lifestyle factors, comorbidities, concurrent prescriptions and prior blood test result. The patient profiles and predicted risks for LEF are provided in Supplementary Table S1, while those for MTX [17] and SSZ [19] have been published previously. In general, patients with more comorbidities and risk factors will lie in a higher decile. To aid interpretation, the patient representing decile 1 in the LEF cohort would have a cumulative probability of an abnormal blood result over a 5-year period of 10.26%; this probability increases to 32.22% for a patient in decile 10. Average results have been presented for the single patient representing each decile, and thus fractional number of monitoring appointments and delayed identification of abnormal blood results are possible.

Adverse events related to delayed identification of an abnormal blood test

The potential AEs and the rates of each occurring due to increased duration between monitoring appointments were chosen, and estimated, by six highly experienced professorial clinical experts [M.W.T. (renal), G.P.A. (liver), C.P.F. (haematology), H.C.W. (dermatology), T.C. (gastroenterology/medicine), A.A. (rheumatology/medicine)] via a videoconference followed by asynchronous e-mail discussion. This approach was driven by lack of data on the rates of these AEs during established treatment. The AEs that the clinicians thought could occur were: acute kidney injury; acute liver failure; anaemia; chronic kidney disease; cirrhosis; drug-induced liver injury; early liver fibrosis; mildly reduced neutrophil count with sepsis (i.e. infection in people with mildly low neutrophil count and not sufficient to be diagnosed as neutropenic sepsis); neutropenic sepsis; thrombocytopenia requiring hospitalization; and thrombocytopenia with superficial bleeding. The clinicians erred towards overestimating the risks rather than underestimating them. The AEs to be

Table 1. Estimated incidence of adverse events at different monitoring intervals associated with LEF, MTX and SSZ during established treatment

	LEF	MTX	SSZ
Six monthly monitoring			
Acute kidney injury	1 in 10 000	1 in 10 000	1 in 10 000
Acute liver failure			1 in 1000
Anaemia		1 in 10 000	
Chronic kidney disease	1 in 10 000	1 in 10 000	1 in 1000
Cirrhosis		1 in 10 000	
Drug-induced liver injury	1 in 1000	1 in 1000	1 in 1000
Early fibrosis		1 in 1000	
Mildly low neutrophil count with sepsis	1 in 1000	1 in 1000	1 in 10 000
Neutropenic sepsis	1 in 1000	1 in 10 000	1 in 10 000
Thrombocytopenia requiring hospitalization		1 in 10 000	
Thrombocytopenia with superficial bleeding		1 in 10 000	
Annual monitoring			
Acute kidney injury	1 in 10 000	1 in 10 000	1 in 10 000
Acute liver failure			1 in 1000
Anaemia		1 in 5000	
Chronic kidney disease	1 in 10 000	1 in 10 000	1 in 1000
Cirrhosis		1 in 10 000	
Drug-induced liver injury	1 in 1000	1 in 1000	1 in 1000
Early fibrosis		1 in 1000	
Mildly low neutrophil count with infection	1 in 500	1 in 500	1 in 5000
Neutropenic sepsis	1 in 500	1 in 5000	1 in 5000
Thrombocytopenia requiring hospitalization		1 in 5000	
Thrombocytopenia with superficial bleeding		1 in 5000	
Biennial monitoring			
Acute kidney injury	1 in 10 000	1 in 10 000	1 in 10 000
Acute liver failure			1 in 1000
Anaemia		1 in 2500	
Chronic kidney disease	1 in 2500	1 in 2500	1 in 125
Cirrhosis		1 in 10 000	
Drug-induced liver injury	1 in 1000	1 in 1000	1 in 1000
Early fibrosis		1 in 1000	
Mildly low neutrophil count with infection	1 in 250	1 in 250	1 in 2500
Neutropenic sepsis	1 in 250	1 in 2500	1 in 2500
Thrombocytopenia requiring hospitalization		1 in 2500	
Thrombocytopenia with superficial bleeding		1 in 2500	–

included in the model, and the incidence of each, conditional on monitoring interval and drug are shown in Table 1.

The costs and quality adjusted life year (QALY) losses associated with each AE were sourced from reviews of National Institute For Health and Care Excellence (NICE) technology appraisals, where available, and from targeted searches where not. All costs were inflated where required using the latest inflation indices in Jones and Burns [20] and Jones *et al.* to be in 2023/24 prices [21]. Discounting of future costs and future health was undertaken assuming a rate of 3.5% for each as recommended by NICE [22]. Discounted costs and discounted QALY losses associated with each AE are presented in Table 2. Details on the derivation of these values are provided in Supplementary Data S1. An additional monitoring appointment after cessation of treatment due to an abnormal blood test was assumed.

Monitoring strategies modelled

Monitoring appointment intervals of 3 months, 6 months, 1 year and 2 years were modelled along with a 'staged' strategy that assumed four 6-monthly intervals followed by three annual intervals which may be of interest to clinicians who wish to incrementally increase the duration between monitoring appointments.

Time horizon of the model

A time horizon of 5 years was chosen for the period to model monitoring appointments although the potential health impacts of AEs was modelled over a patient lifetime. Patients were monitored according to each strategy for a period of 5 years (4 years in the biennial strategy although the impact of missed abnormal blood tests spanned the 5-year period).

Costs and disutility associated with monitoring

The cost estimated for a monitoring appointment and blood test in primary care was assumed to be £34.09. This was calculated based on 10 min of phlebotomist time (costed as band 4) costing £6.50 [23], 5 min of GP time costing £22.50 including qualification and direct care staff costs [23], £2.61 for a full blood count, £1.24 for a liver function test [24] and £1.24 for a creatinine test (which was assumed to have the same price as a liver function test). No disutility was assumed for attending a monitoring appointment.

Calculation of cost-effectiveness

For each strategy, the costs associated with both monitoring and AEs were estimated, as were the loss in QALYs due to the AEs. Results are presented in terms of incremental net monetary benefit (iNMB), compared with monitoring every 3 months, assuming a cost per QALY threshold of £20 000, as recommended by NICE [22]. iNMB is defined as the incremental QALYs gained multiplied by the assumed cost per

Table 2. Costs and quality adjusted life year (QALY) losses associated with adverse events in the model

Adverse event	Discounted costs (£)	Discounted QALY loss
Acute kidney injury	2601	0.014
Acute liver failure	4369	0.651
Anaemia	522	0.001
Chronic kidney disease	29 952	1.308
Cirrhosis	24 698	3.042
Drug-induced liver injury	4369	0.651
Early fibrosis	0	0.075[a]
Mildly low neutrophil count with sepsis	3127	2.490
Neutropenic sepsis	10 808	2.490
Thrombocytopenia requiring hospitalization	1584	0.016
Thrombocytopenia with superficial bleeding	230	0.001

[a] Per 6 months unidentified.

QALY threshold (£20 000 in our analysis) minus the incremental costs. Working in iNMB has the advantage that strategies can be simultaneously compared with a higher iNMB value indicating that the strategy is more cost-effective. The strategy with the greatest iNMB value is estimated to be the most cost-effective treatment. In our results, as the strategies are compared with 3-monthly monitoring, any iNMB value greater than zero means that the strategy would be seen as cost-effective compared with standard practice. Both probabilistic and deterministic analyses were performed. A pessimistic sensitivity analysis was conducted that tripled the risks of AEs estimated by the clinicians, assumed that the costs of neutropenic sepsis and low neutrophil count plus sepsis was double the base case values, and assumed that the cost of acute liver failure was equal to the cost of increased cost of neutropenic sepsis.

As this research is secondary research, no ethical approval or informed consent was required.

Results

Results are presented individually for MTX, LEF and SSZ. As the deterministic and probabilistic results were similar only the deterministic have been presented. Supplementary tables provide detail on the number of monitoring appointments and abnormal blood results that were identified later than would be the case with 3-monthly monitoring for each strategy. The net savings associated with each strategy and the net QALY losses are contained in the Supplementary tables.

Methotrexate

All extended monitoring periods were more cost-effective than 3-monthly monitoring as the iNMB for each strategy is greater than zero, as shown in Fig. 1. For all deciles, monitoring every 2 years was estimated to be most cost-effective, but at higher risks the difference between annual and biennial monitoring was small (estimated to be an iNMB of less than £50 per patient in the highest-risk decile).

Supplementary Table S2 provides disaggregated results detailing the number of monitoring appointments, and the number of abnormal blood results that would be identified after a delay, For example, for a patient in decile 2 with an annual interval between monitoring appointments, there were 4.83 monitoring appointments and 0.055 abnormal blood results identified late over a 5-year period, which compares with 19.26 and 0, respectively, with a 3-month interval. Aggregated results, reporting the average net cost saving and average net QALY loss (for example, £458.04 and 0.0003, respectively, for a patient in decile 2 under an annual interval) are provided in Supplementary Table S3.

Supplementary Fig. S1 shows the results when the pessimistic scenario was run. In this sensitivity analysis, biennial monitoring was estimated to be most cost-effective up to decile 9, with annual monitoring most cost-effective at decile 10; all extended monitoring periods remained more cost-effective than 3-monthly monitoring.

Leflunomide

All extended monitoring periods were more cost-effective than 3-monthly monitoring, as shown in Fig. 2. Up to decile 10, monitoring every 2 years was estimated to be most cost-effective, with annual monitoring more cost-effective at the highest risk decile, but at any decile the difference between annual and biennial monitoring was small (estimated to be an iNMB of less than £60 per patient in the lowest risk decile). Further results for the base case are shown in Supplementary Tables S4 and S5; these should be interpreted as for Supplementary Tables S2 and S3.

Supplementary Fig. S2 shows the results when the pessimistic scenario was run. In this sensitivity analysis, annual monitoring was estimated to be the most cost-effective at all deciles bar the highest decile where the staged approach was most cost-effective. Extended monitoring periods remained more cost-effective than 3-monthly monitoring at all deciles, but notably biennial monitoring was less cost-effective than 6-monthly from decile 8 onwards.

Sulfasalazine

Extended monitoring periods were more cost-effective than 3-monthly monitoring (Fig. 3). For all deciles, monitoring every 2 years was estimated to be most cost-effective, but at higher risks the difference between annual and biennial monitoring was small (estimated to be an iNMB of less than £50 per patient in deciles 9 and 10). Further results for the base case are shown in Supplementary Tables S6 and S7; these should be interpreted as for Supplementary Tables S2 and S3.

Supplementary Fig. S3 shows the results when the pessimistic scenario was run. In this sensitivity analysis, biennial monitoring was estimated to be most cost-effective up to decile 6, with annual monitoring most cost-effective for higher-risk deciles.

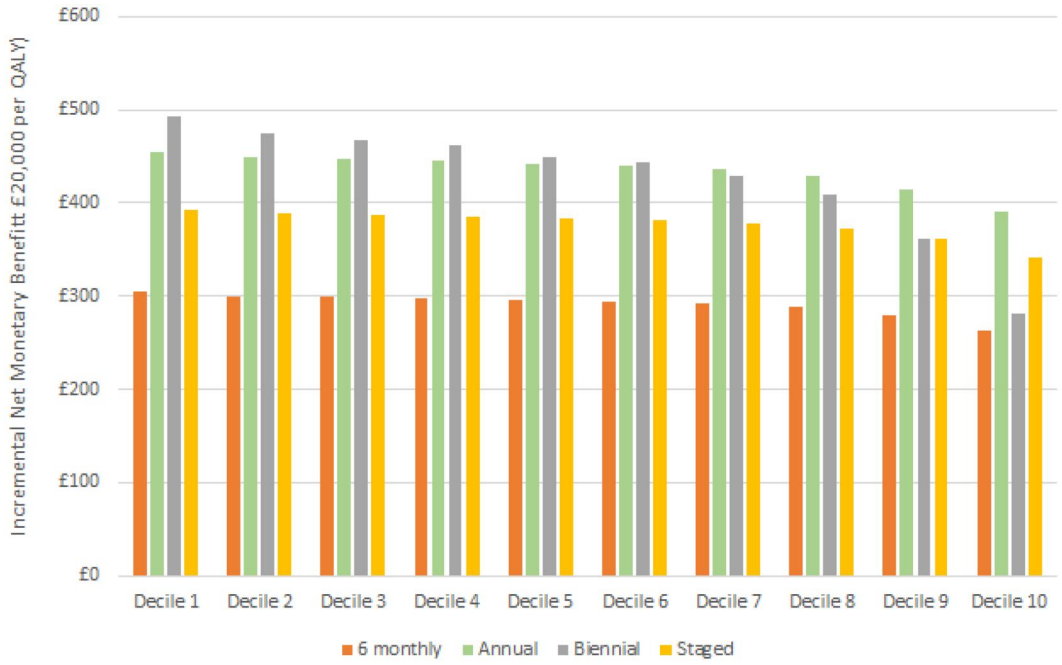

Figure 1. The incremental net monetary benefit associated with extended monitoring periods compared with 3-monthly monitoring across deciles of predicted risk for MTX

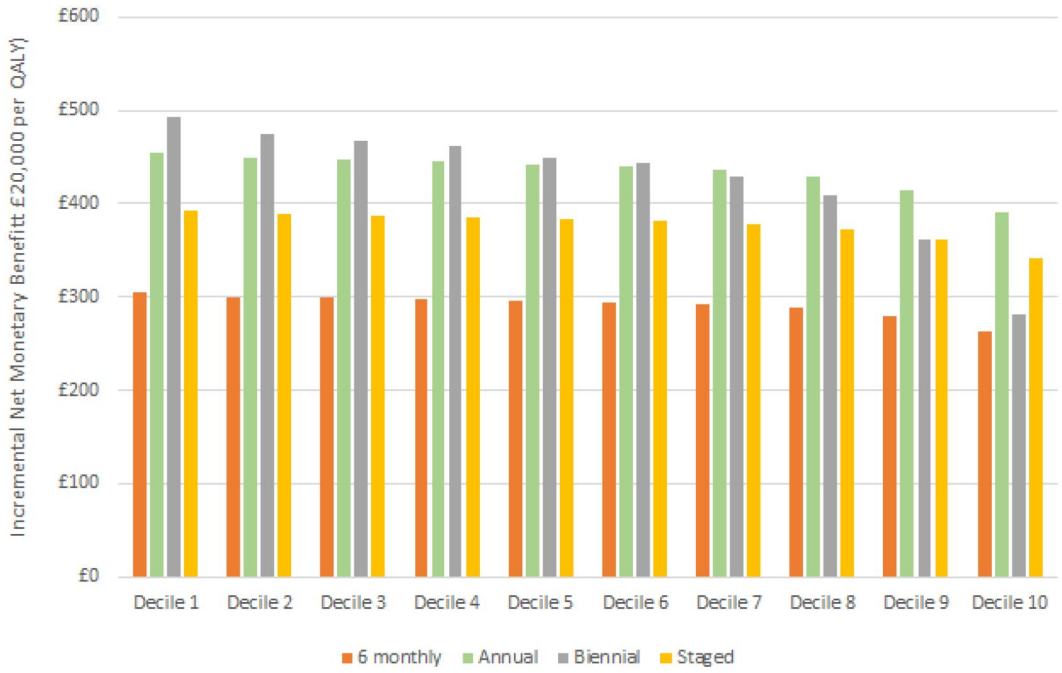

Figure 2. The incremental net monetary benefit associated with extended monitoring periods compared with 3-monthly monitoring across deciles of predicted risk for LEF

Discussion

The health economic analyses show that undertaking monitoring blood tests in primary care once every 6 months, annually or biennially were all more cost-effective in most deciles of risk than undertaking these tests at 3-monthly intervals for patients stabilized on MTX, LEF and SSZ treatment, even when pessimistic scenarios were assumed. It is worth noting that most of the savings in costs originated from increasing the interval between monitoring blood tests from every 3 months to every 6 months and every 12 months, respectively, with less gain upon extending to biennial monitoring. We previously found similar results for monitoring of patients established on thiopurines and anti-TNF-α biologics [25, 26]. The incremental net monetary benefit was similar between the first decile to up to the seventh decile for an index change in interval between monitoring blood tests for each of the three drugs. This occurred as there was only a

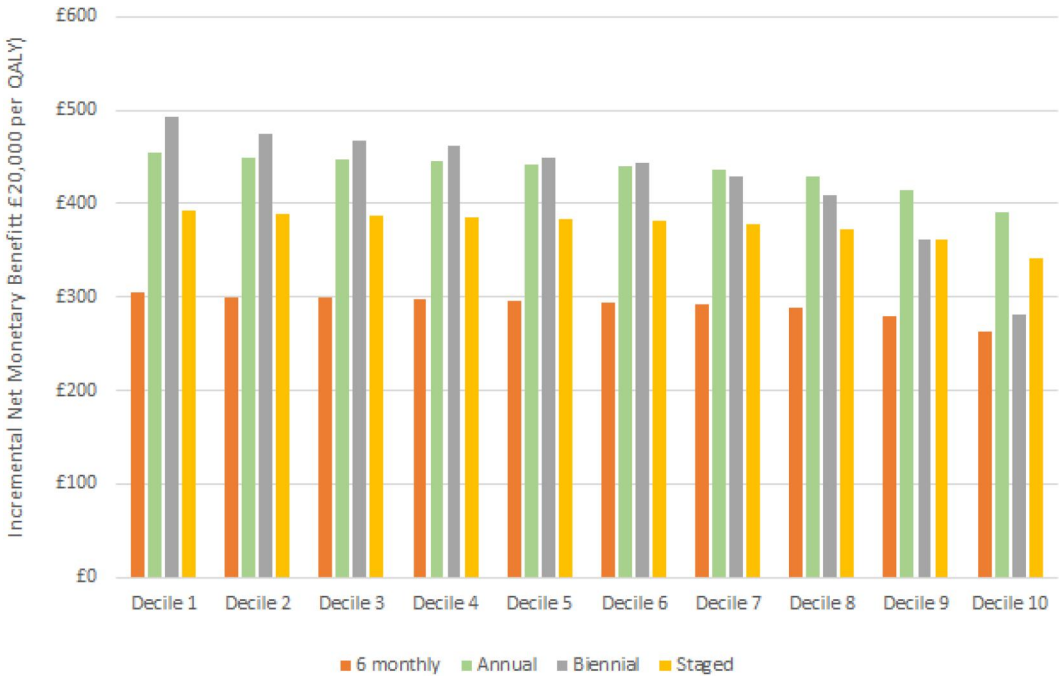

Figure 3. The incremental net monetary benefit associated with extended monitoring periods compared with 3-monthly monitoring across deciles of predicted risk for SSZ

marginal increase in the risk of adverse events (i.e. stopping treatment with abnormal monitoring blood tests) from the first decile to the seventh decile of risk [17–19].

Whilst our analyses appear to indicate strong support for increasing the duration between monitoring appointments, this finding would be difficult to implement if patients were not comfortable with it. Patients accept drug monitoring and view it as important but are adversely affected by the frequency of testing, lack of flexibility with appointments, travel requirements and parking, difficulty in getting blood test results and difficulty managing work commitments for those in employment [27]. Nevertheless, in a recent study both patients and clinicians found it acceptable to increase the interval between blood tests from 3 months to either 6 months or 12 months depending on the individual risk profile of the patient [16] provided that there was clinician and patient autonomy in determining the monitoring schedule, that this could change if a patient's risk profile changes, and there was endorsement from healthcare providers and specialist societies [16]. These are important considerations to support a safe and acceptable implementation of appropriate monitoring. To acknowledge this, the staged strategy was explored, which could substantially allay the fears of clinicians and patients about missing a potential adverse event. This strategy was markedly more cost-effective than the current 3-monthly intervals, and in the higher risk patients assuming a pessimistic scenario produced similar results to those produced by immediately adopting an annual interval.

Extending the interval between monitoring blood tests would also have several practical benefits including saving patient and clinician time, minimizing discomfort from unnecessary venepunctures, and conserving healthcare resources. These are not trivial considerations. People with long-term conditions often find the requirement to have repeated blood tests time-consuming and burdensome. This adds to the 'work' that they are required to do to manage their condition and increases the perception of treatment burden defined as the impact of the 'work of being a patient' on functioning and well-being, and the actions and resources they devote to their healthcare [28]. From a provider perspective, there is a high demand on phlebotomy services and clinicians in primary care face a growing burden arising from the need to check and respond to blood test results. Thus, in addition to being cost saving, decreasing the frequency of testing will reduce treatment burden for patients and alleviate pressure on over-stretched primary care services. Furthermore, from an environmental perspective, unnecessary blood tests also contribute a significant carbon footprint. Each monitoring blood test comprised of a full blood count, urea electrolytes and creatinine, and liver function test results in 215 g of carbon being emitted, excluding patient travel [29].

Whilst our health economic analyses provide some support to extending the interval between monitoring blood tests to once every 2 years, such a long gap between monitoring blood tests was not acceptable to patients in our previous interview study [16]. Both patients and health professionals view monitoring as necessary to prevent adverse events [16, 27]. Thus, a dramatic change in clinical practice from 3-monthly monitoring blood tests to biennial monitoring in those stabilized on treatment is unlikely to be welcome. Perhaps an initial change to 6-monthly monitoring would be an appropriate first step, but such as decision rests with those responsible for developing national and international guidelines, that incorporate wider views of patients, clinicians and other stakeholders. This study suggests that there is little health economic benefit from using risk stratification on the frequency of monitoring for those stabilized on treatment, and that it would be cost effective to move everyone to a longer interval between monitoring blood tests, e.g. from 3-monthly to 6-monthly regardless of their own risk. However, this finding is limited by assumptions on the rates of adverse events based on expert opinion due to lack of published data. In our previous research, we found a large variation in the cumulative risk of

discontinuing DMARDs during established treatment, ranging from <2% to >25% within 5 years [17–19].

The possibility of increased chance of harm in those at high risk should therefore be considered alongside the health economic findings when changing clinical practice recommendations. We would recommend further research to ascertain the risk thresholds at which 3-monthly, 6-monthly or annual monitoring blood tests could be undertaken. Further work needs to be done with primary care stakeholders to assess the feasibility of extending blood test monitoring for those stabilized on treatment. Such a change might be gradual (i.e. a move from 3-monthly monitoring to 6-monthly monitoring in those at low risk initially, for a few years, and then moving onto annual monitoring) at an individual patient level or at a national level. Change may also be slow given that blood test monitoring has become a ritualized practice in managing many long-term conditions, despite lack of evidence that such a practice is useful—such as for monitoring blood tests to detect adverse events in patients prescribed isotretinoin [30].

There are several strengths of this study. First, the health economic analyses used real patient characteristics across the entire risk profile of potentially eligible patients in the UK, thus increasing generalizability of the findings. Second, the monitoring strategies that were most cost-effective were robust to pessimistic changes in assumptions, e.g. related to 3-fold higher probability of AEs following delayed abnormal blood test. Third, the model did not include any disutility to a patient of attending for a blood test and monitoring appointment; if a disutility was included it would make the results more favourable to extended durations of monitoring blood tests.

Limitations included the lack of published data on the relationship between abnormal blood test results and clinically significant illnesses, necessitating that the rates of AEs were estimated by a multidisciplinary team of clinicians. This could potentially be either an overestimate or an underestimate. While an overestimation of rates will not be an issue for the conclusions from a health economic analysis, to minimize any risk of overoptimistic health economic modelling from underestimation of rates, the clinicians were advised to overestimate the rates of AEs based on their clinical experience, and these estimates were tripled in a sensitivity analysis which also increased the costs of some AEs. Another limitation is the fact that the clinicians selected were from within the research team and we did not undertake a survey of the wider research community. The prediction model used in this study was developed and validated using a UK dataset, and the costs were taken from a UK perspective. These findings are therefore not directly applicable to healthcare systems from other countries. We did not undertake health economic analyses for scenarios where monitoring was undertaken in secondary care. Monitoring in secondary care is either undertaken by consultants or by specialist nurses (that are mostly band 6 or higher) with consultant oversight and would be more expensive. As such, the cost-effectiveness estimates would be favourable to extended monitoring periods, were monitoring undertaken in secondary care.

In conclusion, 6-monthly to biennial monitoring was more cost-effective than 3-monthly monitoring across all ranges of risk considered. These findings call for the recommended interval between monitoring blood tests to be revised to include these new research findings. Further research ought to consider the systems and support needed to implement risk-stratified monitoring in the NHS with the safety of such an approach potentially evaluated in a clinical trial or observational study if thought appropriate. Our findings should be considered by national and international specialist societies' guideline writing groups to decide upon the recommended frequency of monitoring blood tests during long-term treatment with MTX, LEF or SSZ.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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