Dr Frances Sutcliffe
National Institute for Health and Care Excellence
Level 1A City Tower
Piccadilly Plaza
Manchester
M1 4BD

BY EMAIL

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RE: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis [ID537]

Dear Frances,

Thank you for giving us the opportunity to comment on the ScHARR Assessment Report for the above appraisal. Due to the substantial size of the assessment report, we believe the standard consultation period was insufficient for consultees to have adequate time to review the contents of the report in sufficient detail. In addition, due to the considerable amount of information that has been redacted within the report, we would again stress that the release of the Assessment Group (AG) economic model is of significant importance to us to ensure a fair appraisal.

Our response has focused on the following key areas within the assessment report which are bulleted below:

- Long term HAQ progression when treated with cDMARDs
- The assumed treatment sequences modeled within the cost-effectiveness analyses.
- Excluded biologic therapies in the monotherapy subgroup analysis
- Inclusion criteria within the network meta-analyses sensitivity analysis

Yours Sincerely,

[redacted]

[redacted]

HAQ Progression on cDMARDs

We are concerned that the cohort of patients modelled in the ERAS cohort may not accurately reflect RA patients today. Norton et al used evidence from patients enrolled as early as 1986, and we strongly believe that further validation is needed with more recent cohort data before conclusions can be drawn. Clinical experts have confirmed that over the last 20-25 years, the treatment pathway and clinical management for RA patients has changed immensely, with significant improvements in how cDMARDs are used. We know that cDMARDs are now used much earlier and more aggressively in the treatment pathway for RA patients, therefore the effect of modifying a patient's disease (or indeed changes in HAQ) may not be fully captured in the Norton study.

Patients in the ERAS database had early rheumatoid arthritis (ERA), RA literature suggests that there is a difference in HAQ response between patients with ERA and those with established RA [Aletaha et al, 2006]. The AG's methodology for modeling HAQ progression from the ERAS database is difficult to interpret, in particular how the ERAS database and NOAR dataset were combined to capture patients with more established RA matching the target population of the economic analysis. We would request that the AG provides further details on how the analysis was undertaken as we were unable to conclude the methodology from the assessment report.

Treatment Pathway

In section 6.3.2, the AG outlined the chosen treatment sequence within the three populations modeled. Roche has noted that the sequences are based on current NICE guidance and not on the licensed indications of the biologics assessed. While we agree broadly with most of the sequences modeled we do have concerns with particular scenarios relating to the population who cannot receive methotrexate (MTX). The AG omits an explanation for the chosen treatment sequences for patients who cannot receive MTX.

The AG has assumed patients treated with tocilizumab (TCZ) in the first line would only receive one further biologic therapy. However, when either adalimumab (ADA) or etanercept (ETN) are given as first line therapy, the assumption is that at least 3 biologics (including TCZ) can be administered. In the absence of NICE guidance for the use of TCZ in patients who cannot receive MTX, we are unsure of the rationale behind the chosen treatment sequence in the TCZ arm.

Furthermore, the anti-TNF (aTNF) therapy chosen following TCZ is assumed to be ADA, this appears to be in contrast with the results of the network meta-analysis which shows that ETN is superior to ADA when administered without MTX. If only one aTNF therapy was assumed to be administered following TCZ, it would be more appropriate to assume that the next most effective agent would be used, therefore we consider ETN should follow TCZ in strategy 4 outlined in the below table.

Table 1: The treatment sequences for those patients who cannot receive MTX

	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment	Fifth-line treatment
Strategy 1	SSZ	NBT			
Strategy 2	ADA	ETN	TCZ	SSZ	NBT
Strategy 3	ETN	ADA	TCZ	SSZ	NBT
Strategy 4	**TCZ**	**ADA**	**SSZ**	**NBT**	

Subgroup Analysis

We support the conclusion of the AG that there is an important subgroup of patients who cannot receive MTX. Current NICE guidance has focused very little on this population which represents approximately 30% of all RA patients; therefore we fully endorse the MTA reviewing the monotherapy indication separately. The AG's network meta-analysis demonstrates that TCZ is as effective with and without MTX.

Due to the different treatment sequences employed by the AG, the results for TCZ monotherapy and in combination with MTX are significantly different. Without access to the economic model, we assume that the difference in the ICER is largely based on the omission of rituximab within the monotherapy sequence. While the AG are correct that rituximab is not licensed for use in monotherapy, it is commonly used within the UK and therefore should be considered a comparator within the analysis. We note that there is strong precedent by NICE to consider the use of off label treatments as a comparator within technology appraisals [systemic lupus erythematosus ID416].

Inclusion Criteria in Network Meta-Analysis

Based on the information provided within the AG report, we consider the network meta-analysis (NMA) base case a reasonable reflection of the comparative efficacy between the relevant biologic therapies. Our own NMA produced very similar results to the base case analysis of the Assessment Groups.

The AG has undertaken a sensitivity analysis which included studies where prior bDMARDs was not an exclusion criterion. As the scope of the appraisal is restricted to early RA and DMARD-IR, patients, we would question the appropriateness of including studies where patients had received bDMARDs. While we accept the main analysis has excluded trials where patients had received bDMARDs, we would challenge the relevance of presenting results for a subgroup which is outside the scope of the appraisal.

Minor Inaccuracies

We have identified a number of minor errors within the assessment report. This is not a complete list, as due to the time constraints we were unable to capture all inaccuracies within the report.

Reference	Description
Table 179:	In the population 2 and 3 box, tocilizumab is meant to have '+ MTX' following.
Page 363	The following sentence is repeated on the same page: 'The Assessment Group assume that the relationship between EULAR response and HAQ improvement is independent of bDMARD'
Page 364	In the final sentence influence is spelt 'onfluence'
Page 365	The following sentence has several errors 'For goor responders there is a degree of loss of initial 6month HAQ improvement in subsequent periods'
Page 370	Importantly is spelt 'Importanlty'
Page 371	In is spelt 'int'
Page 372	The text refers to Figure 93 and 94, but these are the wrong graphs
Page 384	Figure 101 is incorrectly labeled QALYs instead of 'costs'

References

Aletaha D, Ward M. Duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. Ann Rheum Dis 2006;65:227-333

Norton S, Sacker A, Dixey J, Done J, Williams P, Young A. Trajectories of functional limiteation in early rheumatoid arthritis and their association with mortality. *Rheumatology* 2013; Epub Ahead of Publication

Systemic lupus erythematosus ID416: http://guidance.nice.org.uk/TAG/273