National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537]

Limitations of this assessment

Assessment of these models would be greatly assisted by information typically provided in an accompanying paper or handbook. This is addressed in part in Issues 1 – 5 shown overleaf. A number of other issues raised might also be addressed by improving the clarity and transparency of the models. The complexity of the models greatly increases run time which together with the large number of variables precludes thorough testing of the models. In our hands, probabilistic analysis was prone to crashing.

References

Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology 2010 Jun 1;49(6):1197-9

Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, et al. Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. Rheumatology 2012 Jan 1;51(1):169-75.

Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess 2011 Mar;15(14):1-278.

Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology 2013 Jan 1;52(1):91-8.

Morgan CL, Emery P, Porter D, Reynolds A, Young A, Boyd H, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. Rheumatology (Oxford) 2014 Jan;53(1):186-94.

Tanaka Y, Hirata S, Saleem B, Emery P. Discontinuation of biologics in patients with rheumatoid arthritis. Clin Exp Rheumatol 2013 Jul;31(4 Suppl 78):S22-S27.

Tosh J, Brennan A, Wailoo A, Bansback N. The Sheffield rheumatoid arthritis health economic model. Rheumatology 2011 Sep 1;50(suppl 4):iv26-iv31.

Issue 1 Overview of Model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
No overview of model presented as text or diagram	Present overview of model in text and diagrams	Clarity and transparency support reliability

Issue 2 Rationale for replacing previous models

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Rationale for replacing previous models with additional complexity not presented	Present rationale and justification for each parameter adding to the complexity of these new models	Clarity and transparency support reliability

Issue 3 Rationale for two versions of the new model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Rationale for two versions of the new model not presented	Present rationale and justification for the two versions of the new model	Clarity and transparency support reliability

Issue 4 Sources of data used and their limitations

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sources of data used and their limitations not presented	Reference all sources of data used and highlight their potential limitations	Clarity and transparency support reliability

Issue 5 Assumptions underlying new models

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Assumptions underlying new models not presented	Justify assumptions by clinical and analytical relevance. Present key assumptions underlying models to consider when interpreting the results.	Clarity and transparency support reliability

Issue 6 Confidence Intervals for Incremental Cost Effectiveness Ratios (ICERs)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Confidence intervals for ICERs not found	Present 95% confidence intervals for ICERs	Clarity and transparency support reliability

Issue 7 Probabilistic Sensitivity Analysis (PSA)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Method used for PSA not presented	Describe method for PSA and present results in text and graphical format	Highlights areas of uncertainty

Issue 8 Minimal Informative Parameter Set

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Minimal informative parameter set not presented	Present minimal informative parameter set to highlight how much value each parameter adds to the new model	Simplicity, clarity and transparency support reliability

Issue 9 Minimal Comparison Analysis

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Minimal comparison analysis of two or three treatment pathways not enabled	Enable minimal comparison analysis of say two – three treatment sequences of say four – five treatment	Quickly highlight comparisons for further consideration

Issue 10 Lifetime approach: Justification

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Does the lifetime approach go beyond the datasets available?	Describe the limitations which currently available datasets impose on the lifetime approach Contrast this approach with a 20 year time frame	Clarity and transparency support reliability

Issue 11 Lifetime approach: Long term effects and Improved Survival

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Long term effects of treatment on risk of lymphoproliferative disease, cardiac events and mortality not included in model	Test impact of these parameters on the lifetime analysis, see Morgan 2014, Mercer 2013	To be determined by the authors

Issue 12 Lifetime approach: Remission of Disease Treated as Early Arthritis

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sustained remission of disease treated as early arthritis described both for conventional and biological DMARDs	Test impact of these parameters on the lifetime analysis of ICERs, see Jayakumar 2012, Tanaka 2013	To be determined by the authors

Issue 13 Lifetime approach: Low Dose Treatment Maintains Stable Low Disease Activity in Established Disease

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Low disease activity after remission induction in established disease may be maintained by low doses of biological DMARDs	Test impact of reduced dose of biological DMARDs in maintaining low disease activity on cost-effectiveness in the lifetime analysis, see Tanaka 2013	To be determined by the authors

Issue 14 Lifetime approach: Rebound

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Assumption that disease activity rebounds on withdrawal of treatment by 1. The same amount as the improvement in HAQ resulting from that treatment 2. Plus any progression of the disease during that treatment.	Test impact of partial rebound on the lifetime analysis of ICERs	To be determined by the authors

Issue 15 Lifetime approach: Adverse events

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Utility and cost impact of adverse events due to conventional DMARDs not included	Test impact of these parameters on the lifetime analysis	To be determined by the authors

Issue 16 Disease Activity Thresholds

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Intervention threshold set at **severe** disease but a **moderate** disease threshold shows equal or greater treatment efficacy, versus radiological progression, functional decline and loss of work similar to severe disease when not treated	Test impact of a **moderate disease threshold** on the ICERs, see Deighton 2010	To be determined by the authors