National Institute for Health and Clinical Excellence

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

Comment 1: The draft scope

Section	Consultees	Comments	Action
Background information	Abbott Laboratories	Accurate. However, Abbott considers it might be worth including the excess mortality seen in RA patients compared to the general population as it is a serious consideration of the disease.	Comments noted. The scope has been amended to include increased mortality associated with rheumatoid arthritis.
	British Health Professionals in Rheumatology	Fatigue prevalence 40%-80% in RA Depressive symptoms 13% - 20% Impact on relationships is also important. Now we have effective treatments the aim is to induce and maintain remission in RA	Comments noted. The scope has been amended to include mention of fatigue and depressive symptoms. Comments noted. The scope has been amended to include induction and maintenance of remission in the description of treatment aims.
	Bristol-Myers Squibb	No comments	Noted.

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	British Society for Rheumatology	***Paragraph 5…'*****People with rheumatoid arthritis are usually treated in an out-patient setting and then in primary care.'** This is incorrect, patients are usually treated in an outpatient setting and then move on to shared care between the primary and second care sectors. ***Paragraph 5…*** **'Treatment for rheumatoid arthritis usually includes: non-steroidal anti-inflammatory agents (NSAIDs), which reduce pain, fever and joint swelling / inflammation; disease modifying anti-rheumatic drugs (DMARDs), which slow the disease process and reduce joint damage; and corticosteroids, which also control inflammation.'** Should read '… (DMARDS) for example methotrexate or salazophrane'. ***Paragraph 6…*** **In 2002, NICE guidance (TA36) recommended the first-use of TNF inhibitors etanercept and infliximab after the failure of two conventional DMARDs, including methotrexate.** Should read '…including methotrexate, provided the patient also has a DAS score of 5.1'. ***Paragraph 6…*** **This guidance (TA130) does not address the use of these agents in sequential use, except where a TNF inhibitor is discontinued owing to an adverse event.** Should read 'adverse event. This has caused difficulty/ problems with patients who having failed conventional immunosuppressives.' Rheumatoid arthritis also exerts a significant impact on mortality, with the risk of cardiovascular disease approximately doubled when compared with the rest of the population. The peak age of incidence is in the early seventies, but it can develop at any age. Corticosteroids both modify the course of the disease and also control inflammation, but are recommended for short term use whenever possible (see NICE RA Guidelines). Background is reasonable – but I would suggest that there is the addition to the document of the current goal in treating rheumatoid arthritis namely, *induction and maintenance of remission*.	Comments noted. The scope has been amended to reflect these comments. No changes have been made to paragraph 6. The purpose of the scope is limited to providing a framework for the appraisal. The scope defines the issues of interest (for example, population and comparators) as clearly as possible and sets the boundaries for the work undertaken by those producing reports for the Appraisal Committee. Please refer to section 2 of the methods guide.

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	National Rheumatoid Arthritis Society	You state that RA is usually treated in an outpatient setting and then in primary care. It is important to note that at present there is insufficient expertise in the primary care community to treat and manage RA which is generally currently managed by specialist teams based usually in a secondary care setting but there are now more specialists treating in a community setting.	Comments noted. The scope has been amended to reflect this correction.
	Roche Products Ltd	Roche suggests that the definition of seropositive autoantibody is expanded to include those patients who test positive for anti-cyclic citrullinated peptides (aCCPs). This is because the rheumatoid factor (RF) currently described in the scope is not the only autoantibody that is important in determining response to treatment with a biologic. Another important autoantibody is anti-CCP and the measurement of aCCP positivity is encouraged in NICE Clinical Guideline 79. Rituximab is presently the only biologic that NICE guidance specifically recommends after the failure of an anti TNF inhibitor (TA 126) and neither etanercept, adalimumab nor infliximab are specifically recommended for use after the failure of a TNF inhibitor. In fact etanercept, infliximab and adalimumab are not specifically licensed for use after anti-TNF failure, that is to say, in sequential use.	The scope has been amended to reflect that there are multiple auto-antibodies which contribute to the disease process. Noted. No changes required to the scope.
	Schering-Plough	Complete.	Noted.
The technology/ intervention	Abbott Laboratories	Accurate for adalimumab. However, the licence for etanercept (in combination with methotrexate) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.	The scope has been amended to include “moderate to severe” in the description of the licence for etanercept.
	British Health Professionals in Rheumatology	yes	Noted.
	Bristol-Myers Squibb	No comment.	Noted.

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	British Society for Rheumatology	Yes – but why not add tocilizumab as this now has an EEC licence?	Tocilizumab is subject to an ongoing appraisal. Tocilizumab is therefore included in the list of comparators. No changes made to the scope.
	National Rheumatoid Arthritis Society	I believe so	Noted.
	Schering-Plough	Yes.	Noted.
Licensing Issues	Abbott Laboratories	There are no licensing issues. Adalimumab is available in the UK for the treatment of patients with moderate to severe rheumatoid arthritis.	Noted.
	Bristol-Myers Squibb	There are no RCT assessing the efficacy of anti-TNF agents in the target patient population of patients with moderate to severe RA and an insufficient response to TNF therapies. Hence, anti-TNF therapies are not specifically indicated in this patient population. Although they may be prescribed in these patients, anti-TNF therapies have therefore not been studied nor proven effective or cost-effective in this patient population. Specific consideration should be given to rituximab being indicated in patients with SEVERE RA and an insufficient response to at least 1 anti-TNF agent.	Noted. Noted.
	Wyeth Pharmaceuticals	There are no pending licences for etanercept with respect to other indications.	Noted.
Population	Abbott Laboratories	Accurate.	Noted.
	British Health Professionals in Rheumatology	Those with erosive changes on xray but whose disease activity score may not reach the threshold eg 5.1 as in current guidelines	Noted. The technologies will be appraised in accordance with their marketing authorisations including any definitions of disease activity.

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	Bristol-Myers Squibb	Specific consideration should be given to EMEA approved labels.	Noted. The technologies will be appraised in accordance with their marketing authorisations.
	British Society for Rheumatology	Yes	Noted.
	National Rheumatoid Arthritis Society	Sero negative groups should be considered separately as Rituximab may not be an appropriate treatment following failure of one Anti-TNF	The 'Other Considerations' section of scope makes allowance for the consideration of subgroups based on autoantibody status.
	Royal College of Nursing	Yes	Noted.
	Schering-Plough	Population has been defined appropriately.	Noted.
	Wyeth Pharmaceuticals	It is important to analyse subgroups of patients failing a first anti-TNF, according to whether they received no clinical effect (primary failures), or gradually lose the effect over time (secondary failures).	The 'Other Considerations' section of scope makes allowance for the consideration of subgroups based on failure of response to a first TNF inhibitor.

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Comparators	Abbott Laboratories	No. The conventional DMARDs listed in the scope and the following biologics: adalimumab, etanercept, infliximab and rituximab are currently used in the NHS as treatment options for rheumatoid arthritis patients who have failed a TNF inhibitor. Abatacept is not currently used in England and Wales because it is not recommended for use by NICE in this patient population, but as it is being reviewed in this MTA, it seems logical to include it as a comparator. However, the biologic agents tocilizumab, golimumab and certolizumab pegol are not standard treatments currently used in the NHS. Both golimumab and certolizumab do not have marketing authorisations in the UK and tocilizumab has yet to be launched. Therefore, these drugs should not be included. Furthermore, fundamental data such as price are not known for these drugs, which prevent an accurate cost-effective analysis being performed.	Comments noted. The list of potential comparator interventions includes drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.
	British Health Professionals in Rheumatology	The listed biological agents are not yet routinely available. The only realistic options are returning to standard DMARDs (and by definition these have failed) or steroids.	Comments noted. The list of potential comparator interventions includes drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.
	Bristol-Myers Squibb	It is unclear why the 3 biologic therapies have been included as comparators as they are not currently standards of care in the UK for the patient population in this appraisal. Instead these 3 therapies should be included as interventions and appraised alongside. Consideration should be given to therapeutic options available to moderate to severe RA patients who are resistant, intolerant of presenting contra-indications to some specific biologic therapies.	Comments noted. The list of potential comparator interventions include drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.

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	British Society for Rheumatology	Long term high dose steroid therapy	The scope has been amended to include supportive care as a comparator, which allows for the inclusion of steroid therapy.
	National Rheumatoid Arthritis Society	Yes, however the biologic agents which have not yet been passed by NICE can only be compared by RCT as they are not yet in routine clinical use	Comments noted. The list of potential comparator interventions include drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.
	Roche Products Ltd	Since rituximab is the only biologic that NICE guidance presently recommends after the failure of a TNF inhibitor (TA 126) and there is no clear treatment pathway recommendation after a rituximab failure, Roche suggests that to enhance the usefulness of the appraisal, the scope of the appraisal should cover the identification of treatment pathways of all interventions and comparators identified, including potential treatments after rituximab failure.	Noted. The consideration of the whole treatment pathway more appropriately reflects the decision problem of a clinical guideline and is beyond the scope of a technology appraisal. No changes made to the scope.
	Royal College of Nursing	Yes.	Noted.
	Schering-Plough	The listed comparators (tocilizumab, golimumab and certolizumab) are not routinely used in the UK. The comparators are appropriate conditional on market authorisation and availability to the NHS.	Comments noted. The list of potential comparator interventions include drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.

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	Wyeth Pharmaceuticals	Tocilizumab, golimumab and certolizumab are not standard treatments currently used in the NHS.	Comments noted. The list of potential comparator interventions include drugs that are likely to receive their marketing authorisation during the timelines for this appraisal, as well as drugs that may not have a marketing authorisation but are used in clinical practice.
Outcomes	Abbott Laboratories	Yes.	Noted.
	British Health Professionals in Rheumatology	Work disability should be included. Productivity. Days lost.	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Bristol-Myers Squibb	It should be clarified that low disease activity and remission are important patient outcomes of “Disease activity” especially given that they represent the goal of RA treatment and are central within the NICE clinical guidelines on Rheumatoid Arthritis. Achieving and maintaining a low level of disease activity was also shown to have a significant prognostic value for joint damage progression, disability and costs.	The scope includes disease activity as an outcome measure. No changes required to the scope.

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	British Society for Rheumatology	Yes, but should also include 1. the decrease in co-morbidities such as cardiovascular disease and osteoporosis 2. iatrogenesis, particularly from drugs such as steroids where other strategies could have minimised their use.	Such outcomes are captured by the general outcome measure of “extra-articular manifestations of the disease” and are included in the scope. The scope includes “adverse events”, which may include those associated with comparator treatment strategies.
	National Rheumatoid Arthritis Society	The only others I would add are ability to remain working or ability to return to work	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Royal College of Nursing	Yes if time allows, full review of evidence and costs /including social costs related to healthcare needs	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Schering-Plough	Yes.	Noted.

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Economic analysis	Abbott Laboratories	Given that rheumatoid arthritis is a chronic condition usually affecting people in their 40's, a life-time horizon is an appropriate time horizon for this appraisal.	Comment noted. The reference case stipulates that 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.
	British Health Professionals in Rheumatology	Work disability should be included. Productivity. Days lost. Benefits claimed.	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Bristol-Myers Squibb	Consistent with the OMERACT guidelines, the time horizon should be aligned with the scope of the economic analysis undertaken.	Comment noted. The reference case stipulates that 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.
	British Society for Rheumatology	This is a long-term condition	Comment noted. The reference case stipulates that 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.

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	National Rheumatoid Arthritis Society	Can only re-iterate our call for NICE's remit to be widened to include work related disability and wider societal costs but appreciate that these currently are not within their remit.	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Royal College of Nursing	Would like to be able to scope longest benefits seen so far in class of drugs particularly when considering aspects of changes in healthcare utilisations e.g. joint replacement surgery, inpatient care etc.	Comment noted. The reference case stipulates that 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.
Other considerations	Bristol-Myers Squibb	No comments.	Noted.
	British Society for Rheumatology	If the evidence allows, the appraisal will include other co-morbidity sub-groups such as hypogammaglobulinaemia, and other diseases where some drugs would be relatively contraindicated. Include Tocilizumab.	The scope has been amended to allow for consideration of sub-groups related to co-morbidities. Tocilizumab in included in the list of comparators
	Roche Products Ltd	Regarding subgroups of patients identified as sero-negatives or sero-positives. Since RF is not the only autoantibody that is important in determining response to treatment with a biologic, the scope should include other important autoantibodies such as anti-CCP status.	The 'Other Considerations' section of scope has been amended to make allowance for the consideration of subgroups of patients defined by auto-antibody status, which can include such auto-antibodies as aCCP.

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	Royal College of Nursing	Wider healthcare costs including costs of adaptations to the home, carer's loss of income, work related issues regarding support and occupational health support if evidence is available. Costs related to orthoptics, podiatry support. Reduction in use of other medications including NSAIDs, Steroids, PPIs	The appraisal will be completed in accordance with the published guide to the methods of technology appraisal. The reference case includes only those costs which relate to resources under the control of the NHS or PSS.
	Schering-Plough	The scope should specify an analysis of a wider range of doses of infliximab as stipulated by NICE's Appeal Panel and subsequently explored by NICE's Decision Support Unit. This additional consideration should include an assessment of optimal dosing with infliximab.	All included technologies will be appraised as per their respective licensed indications, which will include the alternative dosing schedules for infliximab. No changes made to the scope.
	Wyeth Pharmaceuticals	Given the available data, Wyeth welcomes the proposed subgroup analysis. An economic evaluation in the field of rheumatology should by definition include relevant cost offsets, such as joint replacements and hospital admissions.	Noted. The 'Other Considerations' section of scope makes allowance for inclusion of the costs of joint replacement therapy and hospital admissions.
Additional comments on the draft scope.	British Society for Rheumatology	No	Noted.
	Royal College of Nursing	This wide scope addressing the treatment options available is welcomed.	Noted.
	Schering-Plough	Review of TA 126 and TA 141 in this appraisal is appropriate to eliminate concurrent RA guidance and resulting contradictions.	Noted.
	Wyeth Pharmaceuticals	Wyeth regards it to be appropriate to include reviews of the current guidance for rituximab and abatacept (TA 126 and TA 141) in this appraisal. The subgroups included in the 'Other Considerations' section are appropriate.	Noted. Noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Pain Society
NHS Quality Improvement Scotland
Royal College of Pathologists
RICE – The Research Institute for the Care of Older People
Sanofi-Aventis

No consultees/commentators commented on the provisional matrix.