A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

POST-PEER REVIEW VERSION, FINAL CIC REVISED VERSION SENT TO NICE

Commissioned by: NHS R&D HTA Programme

On behalf of: The National Institute for Health and Clinical Excellence

Produced by: West Midlands HTA Collaboration, The University of Birmingham

Authors: Yen-Fu Chen, Systematic Reviewer
Paresh Jobanputra, Consultant Rheumatologist
Pelham Barton, Lecturer in Mathematical Modelling
Sue Jowett, Health Economist
Stirling Bryan, Professor in Health Economics
Wendy Clark, Information Pharmacist
Anne Fry-Smith, Information Specialist
Amanda Burls, Senior Clinical Lecturer in Public Health and Epidemiology

Correspondence to: Dr Amanda Burls
Department of Public Health and Epidemiology
The University of Birmingham
Edgbaston
Birmingham B15 2TT
Telephone +44 121 41 47508
Email: A.J.Burls@bham.ac.uk

Date completed: 3 October 2005

Expiry Date: 2008
CONTRIBUTIONS OF AUTHORS

Dr Pelham Barton constructed and analysed the new version of the Birmingham Rheumatoid Arthritis Model (BRAM), drafted the section of the report relating to the BRAM, responded to peer review and read and edited the draft report.

Professor Stirling Bryan selected studies from the searches for published economic analyses, contributed to economics review, review of submissions from industry, development of model structure and unit cost data collection, and edited the report.

Dr Amanda Burls was the senior reviewer on this report and provided project management and advice on all aspects of the report, participated in data extraction and analyses, drafted the results section, summary and discussion, compiled and edited the draft report and takes final responsibility for the whole report.

Dr Yen-Fu Chen was the main reviewer on this report and maintained day-to-day running of the review. He compiled the study protocol, carried out study selection, data extraction (mainly for etanercept and infliximab), and did meta-analyses. He also drafted the following sections: methods, narratives for included trials, and part of the results and discussion, and edited the report.

Wendy Clark applied the inclusion and exclusion criteria, was involved in data extraction principally for adalimumab, and commented on the draft report.

Anne Fry-Smith devised and implemented search strategies for bibliographic databases, drafted the searching methods section and commented on the draft report.
Dr Paresh Jobanputra drafted the introduction, assisted with study selection, data extracted some studies, contributed to the development of the economic model, identified data sources for parameters for the model, edited the report and responded to peer review comments.

Sue Jowett wrote the review of existing economic evaluations.

CONFLICTS OF INTEREST

None.

SOURCE OF FUNDING

This report was commissioned by the NHS R&D HTA programme.

RELATIONSHIP OF REVIEWERS WITH SPONSOR

Dr Paresh Jobanputra is a Consultant Rheumatologist and a member of the British Society for Rheumatology. He has received funding for educational purposes from Abbott and has been entertained by manufacturers of all three TNF inhibitors. He has been involved in research studies of adalimumab and etanercept for rheumatoid arthritis and his department has received funding from Wyeth and Abbott for these studies.

None of the other authors have any competing interests.

ACKNOWLEDGEMENTS

The contents remain the responsibility of the authors and Dr Amanda Burls is guarantor. They are grateful to the following individuals for their help or advice during the writing of this report:
Linda Briscoe, Department of Public Health and Epidemiology, University of Birmingham
Becky Taylor, Health Economics Facility, University of Birmingham
David Fisher, Dr Nigel Arden, Dr Chris Edwards and Dr Tjeerd van Staa, MRC
Epidemiology Resource Centre, University of Southampton, for providing GPRD data on
DMARD use in the UK
Peter Conway and Alan Reynolds, Wyeth Laboratories UK, for providing additional data from
etanercept trials
Alan Kane, Schering-Plough UK, for providing additional data from infliximab trials
Abbott Laboratories, for providing additional data from adalimumab trials

MATERIAL AND IS HIGHLIGHTED IN THIS REPORT WITH UNDERLINE
CONTENTS

1 AIMS OF THE REVIEW ........................................................................................................... 22

2 BACKGROUND .................................................................................................................... 23
2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM ....................................................... 24
2.1.1 Clinical features of rheumatoid arthritis ....................................................................... 24
2.1.2 Diagnosis of rheumatoid arthritis ................................................................................. 24
2.1.3 Radiographic features of rheumatoid arthritis ............................................................... 25
2.1.4 Epidemiology ................................................................................................................. 25
2.1.5 Aetiology ........................................................................................................................ 26
2.1.6 Pathology ......................................................................................................................... 26
2.1.7 Role of tumour necrosis factor ....................................................................................... 27
2.1.8 Goals of management .................................................................................................... 28
2.1.9 Current drug therapy for rheumatoid arthritis ............................................................... 28
2.1.9.1 Non-drug treatments ................................................................................................. 29
2.1.9.2 Assessment of response to DMARDs ....................................................................... 31
2.1.10 Prognosis ....................................................................................................................... 32
2.1.11 Burden of illness .......................................................................................................... 32
2.2 CURRENT SERVICE PROVISION ................................................................................ 33
2.3 DESCRIPTION OF THE TECHNOLOGY ............................................................................. 34
2.3.1 Adalimumab (Humira®) ................................................................................................. 34
2.3.2 Etanercept (Enbrel®) ..................................................................................................... 34
2.3.3 Infliximab (Remicade®) ................................................................................................ 35
2.3.4 Special precautions for use of TNF inhibitors ............................................................... 35
2.3.5 Choosing between TNF inhibitors and patient preferences ......................................... 36
2.4 CURRENT NICE GUIDANCE FOR USE OF TNF INHIBITORS ........................................ 37
2.5 DEGREE OF DIFFUSION & ANTICIPATED COSTS ............................................................. 40

3 EFFECTIVENESS ............................................................................................................ 41
3.1 METHODS FOR REVIEWING EFFECTIVENESS ................................................................ 42
3.1.1 Search strategy ............................................................................................................ 42
3.1.2 Inclusion and exclusion criteria .................................................................................... 43
3.1.3 Data extraction strategy ............................................................................................... 44
3.1.4 Quality assessment strategy ....................................................................................... 44
3.1.5 Data analysis ................................................................................................................. 44
3.1.5.1 Outcomes of interest ............................................................................................... 44
3.1.5.2 Approach for meta-analysis .................................................................................... 46
3.1.5.3 Handling of data and presentation of results .......................................................... 48
3.2 RESULTS FOR EFFECTIVENESS REVIEW ......................................................................... 49
3.2.1 Number and type of studies included .......................................................................... 49
3.2.2 Adalimumab ................................................................................................................. 52
3.2.2.1 Descriptions of individual adalimumab trials .......................................................... 52
3.2.2.2 Meta-analyses of adalimumab trials ....................................................................... 61
3.2.3 Etanercept .................................................................................................................... 73
3.2.3.1 Description of included etanercept trials .............................................................. 73
3.2.3.2 Meta-analyses of etanercept trials ....................................................................... 85
3.2.4 Infliximab ..................................................................................................................... 106
3.2.4.1 Description of included infliximab trials .............................................................. 106

Last amended: 11 October 2005
3.2.4.2 Meta-analysis of infliximab results .............................................................. 126

3.3 SUMMARY OF EFFECTIVENESS REVIEW AND ADDITIONAL EVIDENCE ................ 138
3.3.1 TNF inhibitors versus DMARDs ................................................................. 138
3.3.2 TNF inhibitors versus placebo ................................................................. 141
3.3.3 Combination of TNF inhibitor + MTX versus MTX................................. 141
3.3.4 Additional information on effectiveness and safety ..................................... 142

4 HEALTH ECONOMICS ............................................................................................... 144
4.1 SYSTEMATIC REVIEW OF ECONOMIC EVALUATIONS ........................................ 145
4.1.1 Method ............................................................................................................. 145
4.1.2 Results of systematic review of economic evaluations ................................. 147
4.1.3 Summary of review of existing economic evaluations ..................................... 156
4.1.4 Review of industry cost-effectiveness submissions ....................................... 158
4.1.5 Abbott submission (adalimumab) ............................................................... 159
4.1.6 Wyeth submission (etanercept) ................................................................. 162
4.1.7 Schering-Plough submission (infliximab) ..................................................... 167
4.2 ECONOMIC ANALYSIS USED IN THIS REPORT ...................................................... 171
4.2.1 Strategies compared using the BRAM ......................................................... 174
4.2.2 Data used in the BRAM ................................................................................. 183
4.2.3 Results ............................................................................................................. 199

5 IMPLICATIONS FOR OTHER PARTIES ................................................................ 215
6 FACTORS RELEVANT TO NHS ............................................................................. 215
7 DISCUSSION .............................................................................................................. 217
7.1 PRINCIPAL FINDINGS ....................................................................................... 218
7.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES ............................... 223
7.3 IMPLICATIONS FOR RESEARCH ........................................................................ 226
8 CONCLUSIONS ....................................................................................................... 226
9 APPENDICES ......................................................................................................... 229
10 REFERENCES ......................................................................................................... 373
LIST OF FIGURES

Figure 1 Flow chart for study selection ...................................................................................... 51
Figure 2 ACR20 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 65
Figure 3 ACR20 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 65
Figure 4 ACR50 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 66
Figure 5 ACR50 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 66
Figure 6 ACR70 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 67
Figure 7 ACR70 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 67
Figure 8 HAQ change – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 68
Figure 9 Serious adverse events RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 68
Figure 10 Serious adverse events RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 69
Figure 11 Malignancy RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 69
Figure 12 Malignancy RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX) ............................................................................................................................ 70
Figure 13 ACR20 RR – Etanercept licensed dose vs. other active treatment .................................. 90
Figure 14 ACR20 RD – Etanercept licensed dose vs. other active treatment .................................. 90
Figure 15 ACR50 RR – Etanercept licensed dose vs. other active treatment .................................. 91
Figure 16 ACR50 RD – Etanercept licensed dose vs. other active treatment .................................. 91
Figure 17 ACR70 RR – Etanercept licensed dose vs. other active treatment .................................. 91
Figure 18 ACR70 RD – Etanercept licensed dose vs. other active treatment .................................. 92
Figure 19 HAQ change – Etanercept licensed dose vs. other active treatment .................................. 92
Figure 20 Serious adverse events RR – Etanercept licensed dose vs. other active treatment ................. 92
Figure 21 Serious adverse events RD – Etanercept licensed dose vs. other active treatment ................. 93
Figure 22 Malignancy RR – Etanercept licensed dose vs. other active treatment ................................. 93
Figure 23 Malignancy RD – Etanercept licensed dose vs. other active treatment ................................. 94
Figure 24 ACR20 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ............................................................................................................................ 98
Figure 25 ACR20 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ............................................................................................................................ 98
Figure 26 ACR50 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ............................................................................................................................ 99
Figure 27 ACR50 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ............................................................................................................................ 99
Figure 28 ACR70 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ................................................................................................................................ 100
Figure 29 ACR70 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX) ................................................................................................................................ 100
Figure 30 HAQ change – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX) ................................................................................................................ 101
Figure 31 Serious adverse events RR – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX) ........................................................................................... 101
Figure 32 Serious adverse events RD – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX) ........................................................................................... 102
Figure 33 Malignancy RR – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX) ................................................................................................................ 102
Figure 34 Malignancy RD – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX) ................................................................................................................ 103
Figure 35 ACR20 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)........ 130
Figure 36 ACR20 RD – Infliximab licensed dose vs. placebo (with concurrent MTX) ....... 130
Figure 37 ACR50 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)....... 131
Figure 38 ACR50 RD – Infliximab licensed dose vs. placebo (with concurrent MTX) ...... 131
Figure 39 ACR70 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)...... 132
Figure 40 ACR70 RD – Infliximab licensed dose vs. placebo (with concurrent MTX) ....... 132
Figure 41 HAQ change – Infliximab licensed dose only vs. placebo (with concurrent MTX)133
Figure 42 Serious adverse events RR - Infliximab licensed dose vs. placebo (with concurrent MTX).................................................................................................................. 133
Figure 43 Serious adverse events RD - Infliximab licensed dose vs. placebo (with concurrent MTX).................................................................................................................. 133
Figure 44 Malignancy RR – Infliximab licensed dose vs. placebo (with concurrent MTX).... 134
Figure 45 Malignancy RD – Infliximab licensed dose vs. placebo (with concurrent MTX) .... 134
Figure 46 Basic structure of the model .................................................................................... 173
Figure 47 Modelled distribution of HAQ change on starting leflunomide ....................... 186
Figure 48 Illustrative curve for survival time on a treatment (based on leflunomide data).... 188
Figure 49 Early cessation of treatment ................................................................................. 193

Last amended: 11 October 2005
LIST OF TABLES

Table 1 Description of included randomised controlled trials and baseline patient characteristics – adalimumab .......................................................... 53
Table 2 Quality of included randomised controlled trials - adalimumab.......................................................... 57
Table 3 Summary of 2-year results from PREMIER study - Adalimumab alone (licensed dose only) vs. MTX alone in MTX naïve patients .......................................................... 62
Table 4 Meta-analyses – Adalimumab s.c. licensed dose only vs. placebo (with or without ongoing conventional DMARDs), end of trial .......................................................... 64
Table 5 Summary of 2-year results from PREMIER study – Combination of adalimumab (licensed dose only) + MTX vs. MTX alone in MTX naïve patients .......................................................... 72
Table 6 Included studies for etanercept and baseline patient characteristics .......................................................... 74
Table 7 Quality of included studies - etanercept .......................................................... 79
Table 8 Summary of 2-year results from ERA study – Etanercept alone vs. MTX alone in MTX naïve patients .......................................................................................... 87
Table 9 Summary of 2-year results from TEMPO study – Etanercept alone vs. MTX alone in MTX naïve patients/responders .......................................................................................... 89
Table 10 Meta-analyses – Etanercept s.c. licensed dose only vs. placebo (with or without ongoing conventional DMARDs), end of trial .......................................................... 97
Table 11 Summary of 2-year results from TEMPO study – Combination of etanercept + MTX vs. MTX alone in MTX naïve patients/responders .......................................................... 104
Table 12 Description of included randomised controlled trials and baseline patient characteristics – infliximab .......................................................... 107
Table 13 Quality of included randomised controlled trials – infliximab .......................................................... 115
Table 14 Key outcomes for the BeSt study .......................................................................................... 125
Table 15 Meta-analyses – Infliximab i.v. licensed dose only vs. placebo with ongoing MTX in MTX partial responders/non-responders, end of trial .......................................................... 128
Table 16 Meta-analyses – Combination of infliximab (i.v. licensed dose only) + MTX vs. MTX alone in MTX naïve patients, end of trial .......................................................... 137
Table 17 Summary of the results of primary analyses for key outcomes included in this review (CIC) .......................................................................................... 139
Table 18 Inclusion criteria for the review on cost-effectiveness .......................................................................................... 146
Table 19 Summary of published economic analyses .......................................................................................... 147
Table 20 Summary of published ICERS for TNF inhibitors* .......................................................................................... 148
Table 21 Published etanercept economic analyses .......................................................................................... 151
Table 22 Published infliximab economic analyses .......................................................................................... 153
Table 23 Published economic analyses for more than one TNF inhibitor therapy .......................................................................................... 155
Table 24: Summary of methods used in industry economic analyses .......................................................................................... 158
Table 25 HAQ changes by response type .......................................................................................... 161
Table 26: HAQ Change Parameters .......................................................................................... 165
Table 27 Serious adverse events parameters .......................................................................................... 166
Table 28 Base case CE results (Schering-Plough) .......................................................................................... 169
Table 29 Basic structure of the model .......................................................................................... 175
Table 30 Strategy set with TNF inhibitors at the start .......................................................................................... 177
Table 31 Strategy set with TNF inhibitors in third place .......................................................... 179
Table 32 Strategy set with TNF inhibitors as last active therapy .............................................. 180
Table 33 Strategy set with adalimumab followed by another TNF inhibitor ............................ 181
Table 34 Strategy set: adalimumab and etanercept possibly followed by infliximab .............. 183
Table 35 Initial age and sex distribution.................................................................................. 183
Table 36 Starting distribution of HAQ scores......................................................................... 183
Table 37 Fitting beta distribution to HAQ change data for leflunomide ................................. 185
Table 38 Beta distributions for HAQ multipliers ..................................................................... 187
Table 39 Early cessation of DMARDs: data, sources and comments...................................... 190
Table 40 Times to quitting DMARD ..................................................................................... 194
Table 41 Unit costs for tests and visits.................................................................................... 196
Table 42 Unit costs for drugs (sources: British National Formulary, BNF No. 49 (March 2005), accessed on line at www.bnf.org) ........................................................................ 196
Table 43 Monitoring assumptions.......................................................................................... 197
Table 44 Treatment costs ....................................................................................................... 198
Table 45 Summary of base-case ICERs for each TNF inhibitor (alone and with MTX) ......... 201
Table 46 TNF inhibitors in third place (200,000 patients) (late RA values) ......................... 202
Table 47 TNF inhibitors in third place (100,000 patients) (early RA values) ......................... 203
Table 48 TNF inhibitors at the start (400,000 patients) ......................................................... 204
Table 49 TNF inhibitors in last place (20,000 patients) .......................................................... 205
Table 50 Summary ICERs for sequential use of two TNF inhibitors .................................... 206
Table 51 Second TNF inhibitor following adalimumab (20,000 patients) ............................. 207
Table 52 Second TNF inhibitor following etanercept (20,000 patients) ................................. 207
Table 53 Second TNF inhibitor following infliximab (40,000 patients) ................................. 208
Table 54 Third TNF inhibitor following Adal and Etan (10,000 patients) .............................. 208
Table 55 Third TNF inhibitor following Adal and Infl (20,000 patients) ............................... 209
Table 56 Third TNF inhibitor following Etan and Adal (10,000 patients) ............................. 209
Table 57 Third TNF inhibitor following Etan and Infl (10,000 patients) ............................... 209
Table 58 Third TNF inhibitor following Infl and Adal (20,000 patients) ............................... 210
Table 59 Third TNF inhibitor following Infl and Etan (20,000 patients) ............................... 210
Table 60 Sensitivity analyses - TNF inhibitors at the start ..................................................... 211
Table 61 Sensitivity analyses - TNF inhibitors in third place – early RA values .................... 212
Table 62 Sensitivity analyses - TNF inhibitors in third place – late RA values ....................... 213
Table 63 Meta-analyses - Adalimumab licensed dose and above vs placebo (with or without ongoing conventional DMARDs), end of trial ......................................................... 238
Table 64 Meta-analyses - Adalimumab (s.c. or i.v. all doses) vs placebo (with or without ongoing conventional DMARDs), end of trial ......................................................... 239
Table 65 Summary of 24-week results from Codreanu 2003 - Etanercept vs sulfasalazine in sulfasalazine partial responders/non-responders ................................................. 240
Table 66 Meta-analyses – Etanercept s.c. all doses vs placebo (with or without ongoing conventional DMARDs), end of trial ................................................................. 242
Table 67 Meta-analyses - Infliximab i.v. (all doses) without MTX vs control (placebo or MTX) in MTX partial responders/non-responders, end of trial ......................................................... 244
Table 68 Meta-analyses – Infliximab i.v. licensed dose and above vs placebo with ongoing MTX in MTX partial responders/non-responders, end of trial ........................................ 245
Table 69 Meta-analyses – Infliximab i.v. all doses vs placebo with ongoing MTX in MTX partial responders/non-responders, end of trial ......................................................... 247

Last amended: 11 October 2005
Table 70 Meta-analyses – Combination of infliximab (i.v. all doses) + MTX vs MTX alone in MTX naïve patients, end of trial ................................................................. 249
Table 71 Strategy set with etanercept followed by another TNF inhibitor................................. 260
Table 72 Strategy set with infliximab followed by another TNF inhibitor................................. 261
Table 73 Strategy set: adalimumab and infliximab possibly followed by etanercept.................. 262
Table 74 Strategy set: etanercept and adalimumab possibly followed by infliximab.................... 263
Table 75 Strategy set: etanercept and infliximab possibly followed by adalimumab................. 264
Table 76 Strategy set: infliximab and adalimumab possibly followed by etanercept ................. 265
Table 77 Strategy set: infliximab and etanercept possibly followed by adalimumab............... 266
Table 78 TNF inhibitors at the start (40,000 patients)............................................................ 292
Table 79 TNF inhibitors in third place – early RA values (10,000 patients)............................. 294
Table 80 TNF inhibitors in third place – late RA values (40,000 patients)............................. 295
Table 81 TNF inhibitors at the start (1,000,000 patients)...................................................... 297
Table 82 TNF inhibitors in third place (early RA data) (40,000 patients)............................... 298
Table 83 TNF inhibitors in third place (late RA data) (200,000 patients)............................... 300
Table 84 TNF inhibitors at the start (100,000 patients).......................................................... 301
Table 85 TNF inhibitors in third place (early RA values) (40,000 patients)............................ 303
Table 86 TNF inhibitors in third place (late RA values) (1,000,000 patients*)....................... 304
Table 87 TNF inhibitors at the start (100,000 patients).......................................................... 306
Table 88 TNF inhibitors in third place (early RA values) (40,000 patients)............................ 307
Table 89 TNF inhibitors in third place (late RA values) (100,000 patients)............................ 309
Table 90 TNF inhibitors at the start (40,000 patients)............................................................ 310
Table 91 TNF inhibitors in third place (early RA values) (40,000 patients)............................ 312
Table 92 TNF inhibitors in third place (late RA values) (40,000 patients)............................... 314
Table 93 TNF inhibitors at the start (20,000 patients)............................................................. 315
Table 94 TNF inhibitors in third place (early RA values) (40,000 patients)............................ 317
Table 95 TNF inhibitors in third place (late RA values) (200,000 patients)............................ 318
Table 96 TNF inhibitors at the start (200,000 patients).......................................................... 320
Table 97 TNF inhibitors in third place (early RA values) (100,000 patients)............................ 321
Table 98 TNF inhibitors in third place (late RA values) (200,000 patients)............................ 323
Table 99 TNF inhibitors at the start (40,000 patients)............................................................ 324
Table 100 TNF inhibitors in third place (early RA values) (100,000 patients)......................... 326
Table 101 TNF inhibitors in third place (late RA values) (40,000 patients)............................... 328
Table 102 TNF inhibitors at the start (100,000 patients).......................................................... 330
Table 103 TNF inhibitors in third place (early RA values) (200,000 patients)......................... 332
Table 104 TNF inhibitors in third place (late RA values) (1,000,000 patients)....................... 334
Table 105 TNF inhibitors at the start (40,000 patients)............................................................ 336
Table 106 TNF inhibitors in third place (early RA values) (40,000 patients)............................ 338
Table 107 TNF inhibitors in third place (late RA values) (40,000 patients)............................ 340
Table 108 TNF inhibitors at the start (40,000 patients)............................................................ 342
Table 109 TNF inhibitors in third place (early RA values) (100,000 patients)......................... 344
Table 110 TNF inhibitors in third place (late RA values) (200,000 patients)......................... 347
Table 111 TNF inhibitors at the start (40,000 patients)............................................................ 348
Table 112 TNF inhibitors in third place (early RA values) (100,000 patients)......................... 350
Table 113 TNF inhibitors in third place (late RA values) (200,000 patients)......................... 352
Table 114 TNF inhibitors at the start (20,000 patients)............................................................ 354
Table 115 TNF inhibitors in third place (early RA values) (100,000 patients)......................... 356
Table 116 TNF inhibitors in third place (late RA values) (200,000 patients)......................... 358
Table 117 TNF inhibitors at the start (40,000 patients) ........................................ 360
Table 118 TNF inhibitors in third place (early RA values) (40,000 patients) ........... 362
Table 119 TNF inhibitors in third place (late RA values) (100,000 patients) .......... 364
Table 120 TNF inhibitors at the start (40,000 patients) ........................................ 366
Table 121 TNF inhibitors in third place (early RA values) (100,000 patients) ....... 368
Table 122 TNF inhibitors in third place (late RA values) (1,000,000 patients) ....... 370

LIST OF APPENDICES

Appendix 1 Details of key outcomes used in RA trials ..................................... 229
Appendix 2 Searches - clinical Effectiveness ..................................................... 233
Appendix 3 Additional tables and figures for clinical effectiveness review .......... 237
Appendix 4 Searches – economic evaluations .................................................... 250
Appendix 5 Searches – decision analytic models .............................................. 253
Appendix 6 Searches – systematic reviews of DMARDs ................................. 255
Appendix 7 List of excluded studies for clinical effectiveness review ................. 257
Appendix 8 Details of strategy sets used in BRAM ........................................... 260
Appendix 9 Existing economic evaluations: appraisal and data extraction .......... 267
Appendix 10 Sensitivity Analysis ...................................................................... 292
Appendix 11 Ongoing research ......................................................................... 372
ABBREVIATIONS

ACR                American College for Rheumatology
ADORÉ              Add Enbrel or Replace Methotrexate study
AZA                azathioprine
ARAMIS             Arthritis, Rheumatism and Aging Medical Information System
ARMADA             Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis
ASPIRE             Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
ATTRACT            Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy
AUC                area under the curve
BeSt               Behandel-Strategieën study
BCP                biochemical profile
BP                 blood pressure
BRAM               Birmingham Rheumatoid Arthritis Model
BSR                British Society for Rheumatology
BSRBR              British Society for Rheumatology Biologics Register
CRP                C-reactive protein
CyA                ciclosporin
DAS                Disease Activity Score
DMARD              disease modifying anti-rheumatic drug
DPen               penicillamine
EMEA               European Medicines Agency
ESR                erythrocyte sedimentation rate
EULAR              European League Against Rheumatism
FBC                full blood count
FDA                Food and Drug Administration
GP                 general practitioner
GPRD               General Practice Research Database
GST                injectable gold
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
</tr>
<tr>
<td>HCQ</td>
<td>hydroxychloroquine</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HTA</td>
<td>health technology assessment</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>IgG1</td>
<td>immunoglobulin G (class I)</td>
</tr>
<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
</tr>
<tr>
<td>IL-1</td>
<td>interleukin-1</td>
</tr>
<tr>
<td>IL-2</td>
<td>interleukin-2</td>
</tr>
<tr>
<td>IL-6</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
</tr>
<tr>
<td>i.m.</td>
<td>intramuscularly</td>
</tr>
<tr>
<td>LEF</td>
<td>leflunomide</td>
</tr>
<tr>
<td>MCP</td>
<td>metacarpophalangeal joint</td>
</tr>
<tr>
<td>MeSH</td>
<td>medical subject heading</td>
</tr>
<tr>
<td>MHAQ</td>
<td>modified HAQ</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MTX</td>
<td>methotrexate</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Services</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NNH</td>
<td>number needed to harm</td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>PSS</td>
<td>personal and social services</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RD</td>
<td>risk difference</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
</tbody>
</table>
s.c. subcutaneous
SD standard deviation
SDD smallest detectable difference
SEER Surveillance Epidemiology and End Results (National Cancer Institute, USA)
SEM standard error of mean
SF-36 Short Form with 36 items
SLE systemic lupus erythematosus
SJC swollen joint count
SMD standardised mean difference
SSZ sulfasalazine
STAR Safety Trial of Adalimumab in Rheumatoid Arthritis
START Safety Trial for Rheumatoid Arthritis with REMICADE Therapy
sTNFR soluble tumour necrosis factor receptor
TACE tumour necrosis factor alpha converting enzyme
TAR technology assessment report
TB tuberculosis
TEMPO Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes
TJC tender joint count
TNF tumour necrosis factor
TNFα tumour necrosis factor alpha
VAS visual analogue scale
WMD weighted mean difference

DEFINITIONS OF TERMS

ACR20 Defined as a twenty percent improvement in the counts of the number of tender and swollen joints and at least 3 items from the following: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability; and improvements in blood acute phase responses.

ACR50 Defined as a fifty percent improvement in the parameters described above.

ACR70 Defined as a seventy percent improvement in the parameters described above.
| **ACR-N** | ACR-N is a single number that describes the percentage of improvement from baseline a patient experiences, and is derived from the same clinical parameters as the ACR response. Details are provided in Appendix 1. |
| **Anti-TNFs** | Biological agents that block tumour necrosis factor activity. |
| **Cytokines** | Small peptides that mediate signals between cells primarily in a localised environment. |
| **HAQ** | The Health Assessment Questionnaire is designed to assess the physical function of patients. Scores range from 0 (no functional impairment) to 3 (most impaired). Details are provided in Appendix 1. |
| **DAS** | Disease Activity Score. The DAS is calculated using a formula which includes counts for tender (53 joints) and swollen joints (44 joints), an evaluation by the patient of general health, and blood acute phase response. Scale 0 (best) to 10 (most active disease). |
| **DAS28** | Disease Activity Score 28, similar to DAS above but using only 28 joints for assessment only. Scale 0 (best) to 10 (most active disease). |
EXECUTIVE SUMMARY

Description of technology
This report reviews the evidence for the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab, agents that inhibit tumour necrosis factor alpha (TNFα), when used in the treatment of rheumatoid arthritis (RA) in adults. RA is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Drugs that inhibit joint destruction are known as Disease Modifying Anti-Rheumatic Drugs or DMARDs. There are around eight DMARDs, that are not biologics, that are in common use in the UK. These drugs are not always effective, may lose effectiveness with time or cause adverse effects. Alternative DMARDs are therefore needed and TNF inhibitors are one class of new agents that have been developed.

TNFα is a cytokine that plays an important role in mediating joint inflammation. These new drugs, known as anti-TNFs or TNF inhibitors, have been designed to inhibit its actions. Three TNF inhibitors are currently licensed for use in the U.K.:

- **Adalimumab** - given by subcutaneous injections every other week, but the dose may be increased to weekly if the disease is poorly controlled.
- **Etanercept** - usually given by twice weekly subcutaneous injection, but it may also be given weekly
- **Infliximab** - given by intravenous infusion at 0, 2 and 6 weeks and at 8-weekly intervals thereafter. It is only licensed for use concomitantly with methotrexate in RA.

Current recommendations and service provision
NICE guidance for the use of TNF inhibitors, produced in 2002, recommended

- that etanercept and infliximab be used only in patients who have tried and failed conventional agents
• that details of patients and their treatment should be recorded in a registry.

There is variable implementation of the guidance with limited access to these agents in some areas. Where these drugs are used they have tended to be used after people have failed two or more DMARDs (as recommended) but they are also being used sequentially, after patients fail on a previous TNF inhibitor (not recommended). There are currently around 10,000 patients (~2% of the RA population) on these drugs in the UK with an estimated annual cost to the NHS of ~£100 million. These figures are rising.

Since the 2002 NICE guidance more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. Additionally, all three TNF inhibitors have been licensed for use in early disease.

Methods
Systematic reviews of the literature on effectiveness and one on cost effectiveness, were undertaken. A wide range of databases were searched and further information sought from leading researchers and industry. Industry submissions, including economic models, to NICE were reviewed. Meta-analyses of clinical effectiveness data were undertaken for each of the agents.

The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model, was further developed and used to produce an incremental cost-effectiveness analysis.

Number and quality of studies
Twenty-nine RCTs, mostly of high quality, were included in the effectiveness review: adalimumab 9; etanercept 11; infliximab 9. There were 14 economic evaluations identified: 3 from industry submissions; 1 in the report from the British Society for Rheumatology (BSR); 10 from the published literature.

Direction of evidence and size of treatment effect
Direct comparison with standard treatments
The only head-to-head comparisons with alternative DMARDs were against methotrexate. For patients with short disease duration (≤ 3 years) who were naïve to methotrexate:

- adalimumab was marginally less effective than methotrexate except for radiographic joint damage
- etanercept was marginally more effective and was better tolerated than methotrexate

Etanercept was also marginally more effective and was better tolerated in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate.

**TNF inhibitors versus placebo**

All the three TNF inhibitors, either alone (where so licensed) or in combination with ongoing DMARDs, were effective in reducing the symptoms and signs of RA in patients with established disease. At the licensed dose the NNTs (95% CI) required to produce an improvement in ACR response in comparison with placebo were:

- ACR20: adalimumab 3.6 (3.1, 4.2), etanercept 2.1 (1.9, 2.4), infliximab
- ACR50: adalimumab 4.2 (3.7, 5.0), etanercept, infliximab
- ACR70: adalimumab 7.1 (5.9, 11.1), etanercept, infliximab

**Combination (TNF inhibitor + methotrexate) versus methotrexate**

In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, combination of a TNF inhibitor plus methotrexate was significantly more effective than methotrexate alone. The combination of infliximab and methotrexate was associated with an increased risk of serious infections (RR=2.74, 95% CI 1.12 to 6.70; NNH =25, 16.7 to 100).

**Existing economic evaluations**

Ten published economic evaluations were reviewed. All met standard criteria for quality but the incremental cost-effectiveness ratios (ICERs) ranged from being within established limits for cost-effectiveness to being very high because of varying assumptions and parameters. All three industry sponsors submitted their own economic models. All made assumptions that were
favourable to their product (e.g. assuming that “responders” can be separated from “non-responders” and choosing the most favourable trial data for effectiveness estimates).

Cost effectiveness

An incremental economic analysis was undertaken using a simulation model to estimate the additional costs and QALY gains associated with the use of adalimumab, etanercept or infliximab at various points in a sequence of DMARDs. This model considers improvements in quality of life and mortality but does not assume that TNF inhibitors reduce the need for joint replacement in the base case. When used in accordance with current NICE guidance, as the third DMARD in a sequence of DMARDs, the base-case ICER produced by the model depended on whether the effectiveness data was taken from early RA or late RA patients. This is shown in the table below. In clinical practice there will be a mixture of both sorts of patients. Sensitivity analyses showed that the results were most sensitive to figures for HAQ progression on TNF inhibitors and the effectiveness of DMARDs, but not particularly sensitive to changes in mortality ratios used per unit HAQ.

<table>
<thead>
<tr>
<th>TNF Inhibitor</th>
<th>Comparator</th>
<th>Cost/QALY</th>
<th>Sensitivity analyses - late RA data (early RA data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (no MTX)</td>
<td>Dominated</td>
<td>£55K</td>
<td>£56K (£27K) Dominated (£101K)</td>
</tr>
<tr>
<td>Etanercept (no MTX)</td>
<td>£93K</td>
<td>£45K</td>
<td>£30K (£23K) £505K (£79K)</td>
</tr>
<tr>
<td>Adalimumab (with MTX)</td>
<td>£169K</td>
<td>£45K</td>
<td>£40K (£25K) Dominated (£70K)</td>
</tr>
<tr>
<td>Etanercept (with MTX)</td>
<td>£94K</td>
<td>£42K</td>
<td>£30K (£22K) £608K (£69K)</td>
</tr>
<tr>
<td>Infliximab (with MTX)</td>
<td>Dominated</td>
<td>£49K</td>
<td>£61K (£26K) Dominated (£75K)</td>
</tr>
</tbody>
</table>

TNF inhibitors are most cost-effective when used last in a sequence of DMARDs which gives an ICER for etanercept of £32k/QALY. This is substantially lower than the ICERs for adalimumab (£67k/QALY) or infliximab (£69k/QALY). Suggesting that, in agreement with the effectiveness data, etanercept should be the TNF inhibitor of choice, other things being equal.

First-line use in early RA gave ICERs over £100k/QALY for etanercept and adalimumab and infliximab was dominated by the base strategy.
For sequential use of TNF inhibitors, only etanercept was clinically worth using as a second or third TNF inhibitor. It produced an ICER of £88k/QALY or higher. Adalimumab and infliximab were dominated by base strategy when used as the second or third TNF inhibitors.

**Recommendations for research**

Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs are needed, as are RCTs of different TNF inhibitors in patients who have failed a previous TNF inhibitor.

Longer term studies of the quality of life (QoL) in patients with RA and the impact of DMARDs and other interventions on QoL are needed. Longer term studies or follow up, directly assessing the impact of DMARDs on joint replacement, other disease and drug-related morbidity, and mortality, are also required.
1 AIMS OF THE REVIEW

- To provide a background on rheumatoid arthritis including epidemiology, current therapeutic options, and impact of disease on individuals and health services.
- To update and undertake a systematic review and meta-analysis of the clinical benefits and harms of adalimumab, etanercept and infliximab for rheumatoid arthritis.
- To review published cost-effective and cost-utility studies of these agents and economic evaluations included in manufacturer submissions;
- To adapt the Birmingham Rheumatoid Arthritis Model (BRAM) to evaluate the cost effectiveness of these agents compared with other treatment options.
2 BACKGROUND

Summary

RA is a common, chronic, inflammatory condition causing systemic illness and pain, swelling and destruction of the joints. The cause is not known. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Although there are a number of disease-modifying drugs for this condition these are of limited efficacy and are often withdrawn because of toxicity or loss of effectiveness. New treatments are needed. TNF inhibitors are new biological agents that have been designed to interrupt the inflammatory pathway. Three are licensed for use in the UK: adalimumab, etanercept and infliximab.

NICE guidance for the use of TNF inhibitors was produced in 2002. Guidance recommends that etanercept and infliximab should only be used in patients who have tried and failed conventional agents and that details of patients and their treatment should be recorded in a registry. There is variable implementation of the guidance with limited access to these agents in some areas. Where the drugs are used they tend to be used after people have failed two or more DMARDs (as recommended) but they are also used sequentially when patients fail on a previous TNF inhibitor (not recommended). There are currently around 10,000 patients on these drugs in the UK with an annual cost to the NHS of £100 million. These figures are rising.

Since this guidance more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. Additionally, all three agents have now been licensed for use early in the disease.

This report reviews evidence about the effectiveness and cost-effectiveness of all three agents when used both early and later in the disease.
2.1 Description of underlying health problem

2.1.1 Clinical features of rheumatoid arthritis
Rheumatoid arthritis (RA) is a systemic inflammatory disorder that most often begins between the ages of 40 and 70. It is commoner in women than men and is characterised, pathologically, by an inflammatory reaction and increased cellularity of the lining layer of synovial joints. RA causes pain, swelling and stiffness of affected joints: these symptoms are often worse in the morning and after periods of inactivity. Other organ systems, occasionally with potentially life threatening complications, may also be affected. Patients commonly experience fatigue and blood abnormalities such as anaemia and a raised platelet count. Weight loss, lymph node enlargement, lung diseases (such as pleurisy, pleural fluid, and alveolitis), pericarditis, vascular inflammation (vasculitis), skin nodules, and eye diseases (reduced tear production or inflammation) may also occur.

The severity of disease, its clinical course and individual responses to treatment vary greatly. For example, in a community cohort nearly one in five patients were in ‘remission off treatment’ after 3 years follow-up. By contrast, one half of the patients attending hospital clinics were at least moderately disabled (rated by a Health Assessment Questionnaire (HAQ) of greater than 1.0; see Appendix 1, page 229). Symptoms of RA may develop within days or evolve over many weeks and months. Several distinct patterns of joint disease are recognised including: predominantly small or medium joint disease; predominantly large joint disease; flitting or transient attacks of joint pain (palindromic rheumatism); pain and stiffness of the shoulder and pelvic girdles (polymyalgic disease); and disease associated with weight loss and fever (systemic onset); or any combination of these. Pain and disability, in early RA, is linked to disease severity and to measures of psychological distress. Disease progression can be relentless, or punctuated by partial or complete remissions, of variable and unpredictable intervals.

2.1.2 Diagnosis of rheumatoid arthritis
RA is diagnosed from a constellation of clinical, laboratory and radiographic abnormalities. Diagnosis may be obvious or may need specialist assessment or a period of clinical observation.
Internationally agreed classification criteria for RA are used widely in contemporary research studies. The most recent criteria require patients to fulfill four of the following: morning stiffness in joints exceeding 1 hour, physician observed arthritis of 3 or more areas with soft tissue swelling, arthritis involving hand joints, symmetrical arthritis, rheumatoid skin nodules, a positive blood test for rheumatoid factor and radiographic changes typical of rheumatoid disease. Such criteria have limited utility in routine practice and most clinicians diagnose RA without reference to them. Indeed many patients do not meet formal disease classification criteria, at least early in their disease.

2.1.3 Radiographic features of rheumatoid arthritis

Conventional radiographs may be normal or may show soft tissue swelling and reduced bone density around affected joints, in early RA. Later, there may be diffuse joint damage, indicated by narrowing of the joint space, or focal loss of bone and cartilage at the joint margin, called erosions. Joint damage is assessed in clinical trials using scores of both joint space narrowing and joint erosions. Joint deformity or instability may occur as damage progresses and in advanced disease bony fusion occurs. More sensitive imaging, for example with magnetic resonance imaging (MRI), shows detailed anatomic and pathological change. Some studies indicate that erosions are seen on MRI up to two years before they become visible on radiographs; however, only a quarter of erosions seen on MRI are eventually also seen on X-rays. The clinical importance of some MRI changes is debated but MRI remains, potentially, an important and sensitive outcome measure.

2.1.4 Epidemiology

RA affects around 0.5% to 1% of the population, three times as many women as men, and has a peak age of onset between the ages of 40 and 70. Prevalence of disease at age 65 is six times that at age 25. Recent estimates from England and Wales show an annual incidence of 31 per 100,000 women and 13 per 100,000 men, suggesting a decline in recent decades and a prevalence of 1.2% in women and 0.4% in men. There are approximately 426,800 patients with RA in England & Wales (population 52,793,000). A Primary Care Trust, with a population of one half of a million, for example, has around 4,000 patients with RA.
2.1.5 Aetiology

A specific cause for RA has not been identified; it appears to have many contributing factors including genetic and environmental influences. Genetic influence is estimated at 50 to 60\%. The occurrence of RA in both of a pair of monozygotic twins is 12\% to 15\% and a family history of RA gives an individual a risk ratio of 1.6, compared with the expected population rate. The human leukocyte antigen HLA-DRB1 of chromosome 6 has been most clearly linked to RA although this accounts for less than half of the overall genetic susceptibility of RA. HLA plays a key role in immune function and regulation. The only known function of DR is in presentation of peptides to T cells for mounting an immune response to particular antigens. Rheumatoid factor, an auto-antibody produced by B lymphocytes and directed against immunoglobulin G, is also an important feature of a proportion of patients with RA and is implicated in disease.

Infectious agents have been suspected but no consistent relationship with an infective agent has been shown. Sex hormones have also been suspected because of the higher prevalence of RA in women and a tendency for disease to improve in pregnancy. However, a precise relationship has not been identified. A causal link with lifestyle factors such as diet, occupation, or smoking has not been shown.

2.1.6 Pathology

Synovial joints occur where the ends of two bones, covered with hyaline cartilage, meet in a region where free movement is desirable. This joint space is encapsulated by a fibrous capsule lined, on the inside, by a synovial membrane; which functions to secrete fluid to lubricate and nourish hyaline cartilage. The synovial layer of affected joints becomes enlarged due to increased cellularity, or hyperplasia, infiltration by white blood cells and formation of new blood vessels. This is accompanied by increased fluid in the joint cavity which contains white blood cells and a high level of protein (an exudate) contributing to the joint swelling. Bony erosions of cartilage and bone occur where synovial tissue meets cartilage and bone. This occurs through the combined actions of synovial tissue (pannus) and resident cartilage and bone cells. Erosions, and loss of cartilage, are rarely reversible. Such damage therefore compromises the structure and function of a normal joint.
2.1.7 Role of tumour necrosis factor

TNFα and other cytokines such as interferon-γ, interferon-β, interleukin-1 (IL-1), interleukin-2 (IL-2), and interleukin-6 (IL-6), produced by macrophages and activated lymphocytes promote inflammation. In early RA TNFα is expressed in abundance in synovial tissues and, locally, promotes growth of new blood vessels, orchestrates inflammation and other cytokine production, and induces migration of white blood cells into the joint which release potentially harmful enzymes. Systemically, TNFα is an important mediator of cachexia, fever, bone resorption and cardiovascular collapse (as in septic or endotoxic shock).

TNFα has a half-life of a few minutes and its production can comprise as much as 1-2% of protein released by activated macrophages. Newly produced TNFα spans the cell membrane and may be active in this membrane bound form, especially in T lymphocytes. More usually TNFα is released as a soluble molecule by cleavage of the intra-cellular tail by an enzyme known as TNFα converting enzyme (TACE). Three soluble molecules combine together, forming a trimer, and signal to cells by binding to one of two possible cell receptors: a 55-kd (TNF-R1) or a 75-kd TNF (TNF-R2) receptor. Receptor binding induces a pair of receptors to combine and triggers biological activity. TNFα has a greater affinity for TNF-R1 than for TNF-R2; the latter appears to capture TNFα and pass it on to TNF-R1. Mice lacking TNF-R1 have poorly developed lymphoid organs, are highly susceptible to infection by *Mycobacteria* and *Listeria monocytogenes*, are particularly prone to chronic inflammation and to endotoxic shock induced by TNFα. Expression of TNF-R2 is restricted to endothelial cells (lining cells in blood vessels), and white blood cells. TNF-R1 is expressed by virtually all cell types.

The extracellular sections of TNF receptors on cells are shed by proteolysis and these soluble TNF receptors (sTNFR) are natural inhibitors of TNF and a means of regulating TNFα activity, although, it has also been suggested that sTNFR stabilise circulating TNFα and function as TNF agonists. Levels of sTNFR are raised in RA and other conditions causing inflammation. Defective shedding of the TNF-R1 can be caused by rare autosomal recessive gene defects; known as familial periodic syndromes or TNF-receptor-associated periodic syndromes (TRAPs). People with these conditions experience episodic fever, inflammation and
deposition of amyloid but may also have a survival advantage in terms of a more effective host defence against certain bacterial infections.\textsuperscript{20,21}

2.1.8 Goals of management
Physicians treating RA aim to control symptoms of joint pain and stiffness and to minimise loss of function and improve the quality of life of their patients. Reducing the risk of disability associated with joint damage and deformity and treating any extra-articular manifestations are also key objectives. Since RA is a heterogeneous disease, which may vary over time, a long-term plan with regular clinical evaluation to assess disease status, comorbidity, patient preferences and psychosocial factors is essential and is aided by well informed and satisfied patients and carers.\textsuperscript{22,23}

2.1.9 Current drug therapy for rheumatoid arthritis
Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are commonly used for symptom relief in RA. These drugs do not modify the disease process and, in severe disease, are often insufficiently effective for symptom control. Corticosteroids may produce dramatic and rapid improvements in RA symptoms, including systemic features such as fatigue and weight loss, and may be given by mouth, as intra-muscular injections, intravenously, or as joint injections. Steroid injections provide only short-term benefits but oral steroids may provide prolonged benefits. In clinical practice a significant proportion of patients take steroids for years and experience difficulty when therapy is withdrawn.

A proportion of RA patients are managed solely with oral steroids, NSAIDs and analgesics; in varying combinations. Corticosteroids are also commonly used for short-term management of acute symptoms, or as bridge therapy, to allow rapid control of disease whilst awaiting the effects of slower acting drugs such as disease modifying anti-rheumatic drugs (DMARDs), which reduce the risk of joint damage. Drugs used commonly in the UK and regarded as DMARDs include: azathioprine, etanercept, ciclosporin A, hydroxychloroquine, infliximab, leflunomide, sulfasalazine, methotrexate, and injectable gold.\textsuperscript{24-26}

Glucocorticoids may be regarded as DMARDs, as their use appears to reduce the risk of joint damage\textsuperscript{27} We have not included steroids in the baseline clinical pathway of the economic
model for the following reasons. Firstly, glucocorticoids are used widely as an adjunct to other anti-rheumatic therapy whether that therapy includes conventional DMARDs or TNF inhibitors. For example, in clinical trials in established RA 50% or more of adalimumab or placebo treated patients were on glucocorticoids. Secondly, practice with regard to steroid use varies greatly such that some physicians prefer high dose oral therapy whilst initiating a DMARD, others prefer intramuscular or even intravenous steroids, others low oral prednisolone given for prolonged periods (with or without DMARDs) and yet others may rely on intra-articular therapy wherever possible. Thirdly, patients with established RA also differ in their preferences for how glucocorticoids are used and many, particularly those experiencing adverse effects such weight gain or osteoporosis, prefer to avoid them altogether.

DMARDs rarely induce complete disease remission though effective disease control can be achieved and may also lead to other benefits such as reduced cardiovascular mortality. The mode of action of most DMARDs is incompletely understood. It is recommended that patients with active RA should be treated soon after diagnosis with DMARDs, since delayed use appears to lead to worse clinical outcomes. This has led to the concept of ‘window of opportunity’ in the treatment of RA; that is, delayed use of DMARDs reduces the prospect of benefits in the future. Appropriate concerns have been expressed about data supporting this idea. Indeed the ‘window of opportunity’ concept risks creating a therapeutic imperative for DMARD use when clinicians and patients face newly diagnosed inflammatory polyarthritis: this may be misplaced since early inflammatory polyarthritis commonly remits. Thus careful evaluation and appropriate clinical judgements are needed in choosing therapies.

Effective disease control with DMARDs commonly leads to successful withdrawal of NSAIDs, analgesics and corticosteroids. Some DMARDs such as azathioprine and hydroxychloroquine are probably less effective than other agents such as methotrexate, sulfasalazine and leflunomide. Toxicity of DMARDs also differs and each drug has a specific dosing and monitoring schedule. Unfortunately discontinuation of therapy is common with these agents; for example, the proportion of people still taking gold after 5 years is 20%, sulfasalazine 35%, and methotrexate 57%. Such data highlight the limitations of the available agents; that is, relatively short-term drug ‘survival’ for a disease with a life-long course.
DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preferences, complicating comorbidity or a combination of these. Toxicity varies from relatively minor reactions to life-threatening events such as bone marrow suppression. Hydroxychloroquine and methotrexate appear to have the most favourable risk-benefit profile. Methotrexate is widely regarded as the standard against which other drugs should be judged, especially because treatment is more likely to be sustained with this drug.

DMARDs are used in a variety of ways: several agents, often with corticosteroids added, may be combined early in disease (combination therapy) which may then be continued or some drugs gradually withdrawn (step-down treatment); DMARDs may be used singly and agents added (step-up); or withdrawn and replaced (sequential monotherapy), if disease control is judged to be inadequate. In the UK monotherapy with sulfasalazine or methotrexate, in newly diagnosed patients, is currently the preferred initial strategy. Preferred DMARD combinations include methotrexate and sulfasalazine given together, or ciclosporin A or hydroxychloroquine given with methotrexate. It appears that as successive DMARDs are tried to control disease the likelihood of sustained drug use declines, regardless of the choice of initial DMARD; that is, the second DMARD tried is likely to be used for a shorter time than the first and the third shorter than the second, and so on. Patients achieving good disease control, or remission, with a DMARD are at risk of relapse if treatment is discontinued and current guidelines advocate sustained long-term therapy. Nearly a quarter of patients on long-term therapy, however, are consistently non-compliant with DMARDs.

2.1.9.1 Non-drug treatments

With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. Long-term observations show that around a quarter of patients with RA undergo a total joint arthroplasty. It cannot, of course, be assumed that all such surgery is directly attributable to RA, especially as osteoarthritis is the most prevalent form of arthritis. Other surgical interventions such as removal of synovial tissues and rheumatoid nodules, peripheral nerve decompression (such as in carpal tunnel syndrome), or soft tissue procedures such as tendon release or repair may be necessary at any stage of disease. Patients often also need advice and support from a multi-disciplinary team including specialist
nurses, podiatrists, physiotherapists and occupational therapists in contemporary rheumatology practice.

2.1.9.2 Assessment of response to DMARDs

Remission is not usually achieved in RA but very effective disease control is often possible. Modern clinical trials rely on composite endpoints such as the American College for Rheumatology (ACR) definition of improvement, preferred in US trials, and the disease activity score (DAS), preferred in European studies. The ACR response, for example, requires an improvement in counts of the number of tender and swollen joints (using designated joints) and at least 3 items from the following: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability; and improvements in blood acute phase responses (e.g. ESR or CRP). Response is defined as ACR20, ACR50 or ACR70 where figures refer to percentage improvement of these clinical measures. This creates a dichotomous outcome of responders and non-responders. Achieving an ACR20 response has been regarded as a low hurdle but in clinical practice patients who achieve this hurdle often gain a worthwhile clinical response, especially in early RA.

The DAS is calculated using a formula that includes counts for tender and swollen joints, an evaluation by the patient of general health (on a scale of 0 to 100), and blood acute phase (usually ESR, but more recently using CRP). Originally the DAS was based on an assessment of 53 joints for tenderness and 44 joints for swelling. More recently DAS28, based on an evaluation of 28 joints, has been developed and proposed for use in routine clinical practice. DAS28, like DAS, is a continuous scale with a theoretical range from 0 to 10. Thresholds have been suggested for the scale such that a score greater than 5.1 is regarded as indicating high disease activity, a score of less than 3.2 low disease activity and a score of less than 2.6 remission (for DAS28). The thresholds were originally derived from actual decisions by physicians in practice and are now being proposed as instruments for decision making in practice. Details of both scoring systems are provided in Appendix 1, page 229.

Radiographic outcomes are believed by many to be the most important outcome measure in RA. It is acknowledged, however, that variation in joint inflammation has a more profound and
immediate impact on disability compared with the slow and cumulative effect of radiographic damage on disability. The most commonly used tools for assessing joint damage are the Sharp and Larsen methods and their modifications, which rely on evaluations of plain radiographs (Appendix 1, page 229). As indicated above plain radiographs are rather insensitive to change but are cheap and widely available. A majority of patients show only mild or no progression on plain radiographs over periods of 1 to 2 years, highlighting one of their limitations in modern clinical trials.

2.1.10 Prognosis
The impact of RA on an individual can be viewed from a variety of perspectives including employment status, economic costs to the individual or society, quality of life, physical disability, life expectancy, and medical complications such as extra-articular disease and joint deformity, radiographic damage or the need for surgery. In general, persistent disease activity is associated with poorer outcomes, although in the first five years of disease physical function is especially labile. Greater physical disability at presentation is associated with greater disability later in disease. Other factors linked with poorer function include older age at presentation, the presence of rheumatoid nodules, female sex, psychological distress, and degree of joint tenderness.

Continued employment is related to type of work and other aspects of the workplace such as pace of work, physical environment, physical function, education and psychological status: work disability is not necessarily linked to measures of disease activity. Radiographic damage in RA joints is also influenced by rheumatoid factor status, age, disease duration and extent of disease and perhaps genetic factors. Life expectancy in RA is reduced and is related to age, disability, disease severity, comorbidity and rheumatoid factor status, in particular. For example, a 50-year old woman with RA is expected to live for 4 years less than one without RA. This appears to be due, principally, to increased cardiovascular disease particularly in those who are rheumatoid factor positive.

2.1.11 Burden of illness
Early in disease indirect costs exceed costs due to health care utilisation and medication (direct costs), by two-fold. It is also clear that informal caregivers shoulder a considerable burden in terms of foregone paid employment, leisure activity and personal health. Inevitably, in a
disease characterised by lifelong pain, discomfort and physical impairment, the burden on individuals and families is increased. Recent studies show that medication costs, especially in those treated with biologic agents such as TNF inhibitors, account for a majority of the direct costs of RA. Some drug intervention studies have shown reduced work absence with aggressive treatment strategies although only a third of employed patients cease because of disease and, unsurprisingly, manual workers are much more likely to stop work.

2.2 Current service provision
Most patients with RA are referred to hospital services for assessment but up to a quarter of those with early inflammatory arthritis (not necessarily RA) are managed in primary care. Most district general hospitals now have a department of rheumatology with varied support from clinical nurse specialists and other professionals allied to medicine. The majority of patients followed up in a hospital rheumatology department have RA or another type of inflammatory arthritis or connective tissue disease. A proportion of such patients may also require in-patient treatment though there are considerable variations in in-patient facilities and hospitalisation rates for RA. The Arthritis and Musculoskeletal Alliance (ARMA) has recently proposed standards of care for patients with inflammatory arthritis. The principle motive for these standards is to improve service provision and delivery and to reduce regional variations in access to services. For example, access to TNF inhibitors varies depending on local funding arrangements such that some districts operate waiting lists for patients to begin treatment despite wide drug availability. A recent survey, commissioned by ARMA and the BSR with support from Schering-Plough, indicated that around a third of 148 rheumatologists mainly from England and Wales were unable to prescribe TNF inhibitors. Principle barriers to prescribing were identified as difficulties with local funding arrangements or problems of infrastructure such as availability of day-case facilities or nursing support. Variable implementation of guidance on the use of TNF inhibitors was also confirmed by a survey of 196 hospitals and PCTs undertaken by the Audit Commission which found that "the biggest perceived barrier to implementation among NHS bodies, for both clinical guidelines and technology appraisals, was lack of money. We found that 85 per cent of respondents identified that the funds available to implement technology appraisals were insufficient, particularly in relation to high-cost appraisals, such as ... etanercept and infliximab for rheumatoid
arthritis. Access to adalimumab has caused particular difficulties in some areas because this drug has not yet been evaluated by NICE.

However, some services have managed to secure additional funding for drugs and junior medical and nursing staff to enable NICE guidance to be implemented.

2.3 Description of the technology

2.3.1 Adalimumab (Humira®)
Adalimumab is a recombinant monoclonal antibody, made from human peptide sequences, which binds specifically to TNF and neutralizes its biological functions by blocking interactions with the p55 and p75 cell surface TNF receptors. Treatment is currently recommended for use in people with moderate or severe RA who have not responded to one or more DMARDs, including methotrexate. An application to extend the licence of adalimumab for use in early RA was submitted by Abbott Laboratories in December 2004 and approved in June 2005. Concomitant treatment with methotrexate is recommended for optimum efficacy, but adalimumab may be used alone where methotrexate is not tolerated or contra-indicated. Clearance of adalimumab from the body is decreased with age and by concomitant methotrexate administration; whereas adalimumab increases methotrexate clearance. Patients normally self-administer adalimumab by subcutaneous injections, after training, at a standard dose of 40 mg every other week; but the dose may be increased to 40 mg weekly if disease is poorly controlled.

2.3.2 Etanercept (Enbrel®)
Etanercept is a combination protein consisting of the extra-cellular portion of two of the 75kd-TNF receptors (TNF-R2) for TNF combined with a human Fc portion of human IgG1. Etanercept binds soluble and cell-bound TNFα with high affinity and does this by competing with TNF receptors. Etanercept is administered as a twice-weekly subcutaneous injection of 25 mg in RA. Recently a once weekly injection of 50 mg was approved by the European Medicines Agency (EMEA). Patients or caregivers normally administer etanercept, after suitable training. No dose changes are necessary for patients with renal or hepatic failure or in elderly subjects. Etanercept may be used in combination with methotrexate or alone, including...
treatment in those not previously treated with methotrexate. Etanercept is also licensed for use in juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and severe psoriasis.

2.3.3 **Infliximab (Remicade®)**

Infliximab is a recombinant chimeric human-murine monoclonal antibody that binds soluble and membrane bound TNFα. Stable complexes are formed, binding of TNFα prevented and TNFα already bound to TNF receptors may be dissociated. The TNFα binding region is of mouse origin and comprises 30% of the amino acid sequence of infliximab. The remainder is a human IgG1 heavy chain and kappa chain constant region.

Infliximab is licensed for use in RA with methotrexate though in clinical practice it is used without methotrexate or with other DMARDs if patients are intolerant of methotrexate.70 The recommended dose of infliximab for RA is 3 mg/kg body weight given as an intravenous infusion followed by further infusion, at the same dose, 2 and 6 weeks later. Thereafter infusions are given at 8-week intervals. An interval between infusions of greater than 16 weeks is not recommended because of an increased risk of hypersensitivity reactions, although infusions after longer gaps have been administered safely62,71,72 Freshly reconstituted infliximab is diluted to a volume of 250ml using 0.9% sodium chloride and the infusion is administered intravenously over at least 2 hours using a low-protein-binding filter. Treated patients should be observed for 1 to 2 hours post infusion. Recent studies indicate that patients who tolerate infusions well and are established on therapy may receive infusions over 1 hour or less.73

Infliximab is also licensed for use in severe Crohn’s disease (5 mg/kg), including disease complicated by fistulae, ankylosing spondylitis (5 mg/kg), and psoriatic arthritis (5 mg/kg). Use of higher doses of infliximab in trials has encouraged use of higher doses or a shorter interval between infusions in RA.74

2.3.4 **Special precautions for use of TNF inhibitors**

TNF inhibitors may cause a variety of adverse effects.1 Reactivation of *Mycobacteria tuberculosis* organisms lying dormant in walled granuloma, in individuals previously infected with tuberculosis, is a particular concern. Such ‘latent’ tuberculosis, thought to be highly prevalent in the world’s population, rarely causes disease. TNFα is a key component of host
defence against *M tuberculosis*, especially in the formation of granulomas.\textsuperscript{75} Inhibition of TNF\textsubscript{α} appears to increase the risk of *M tuberculosis* and other granulomatous diseases such as *Listeria monocytogenes* (a bacterium associated with food borne diseases) and *Histoplasma capsulatum* (a fungus which, in endemic areas, causes lung disease in people with a compromised immune system). The risk appears to be significantly greater with infliximab (53 patients per 100,000 treated cases) compared with etanercept (28 per 100,000).\textsuperscript{76} Data for adalimumab are limited but an increased risk has also been shown. Official summary of product characteristics (SPC) and guidance, including proposed guidance from the BSR, British Thoracic Society and the British Society for Gastroenterology recommends screening patients before treatment.\textsuperscript{77} In RA this is currently done by taking a personal and family history of tuberculosis (TB) and a pre-treatment chest X-ray; but, the addition of skin tests using tuberculin have been proposed. Skin testing prior to use of TNF inhibitors poses problems in the UK because of the use of Bacillus Calmette-Guerin (BCG) vaccination for TB prevention in childhood. In addition, many patients with RA are poorly responsive to tuberculin, perhaps as a result of previous or current immunosuppressive therapy but also due to the disease.\textsuperscript{78} Preventive anti-tuberculous drug treatment in latent TB is also associated with a risk of drug-induced hepatitis which needs to be considered in deciding about prophylactic therapy.

Routine blood monitoring is not necessary for patients taking TNF inhibitors but may be needed for concomitantly used DMARDs such as methotrexate. TNF inhibitors can induce anti-nuclear and anti double-stranded DNA antibodies in the blood of some patients treated with TNF inhibitors. These antibodies are associated with systemic lupus erythematositis (SLE), a potentially serious rheumatic disease. Cases of drug-induced SLE have been reported with TNF inhibitors, but are rare.\textsuperscript{79}

### 2.3.5 Choosing between TNF inhibitors and patient preferences

Physicians may prefer one TNF inhibitor to another for clinical reasons; for example, etanercept or adalimumab may be preferred to infliximab if a patient has had an adverse effect to methotrexate, since the licence for infliximab stipulates combined therapy with methotrexate. Physicians also favour drugs with which they are familiar – etanercept and infliximab have been around longer than adalimumab - and also based on their personal preferences.
experiences, or perceived efficacy, in individual circumstances. Often a choice is made for practical reasons such as convenience of self-administered injections against a need to attend hospital for intravenous infusions\textsuperscript{80}, or the availability of resources to deliver timely infusions. Indeed preliminary data for infliximab administered as subcutaneous injections compared with intravenous infusions have recently been presented.\textsuperscript{81}

Patients starting DMARDs are most concerned about drug toxicity\textsuperscript{82} and commonly have a fear of giving their own injections; but clinical experience shows that a majority, even those with markedly impaired hand dexterity, cope very well. Patients may prefer adalimumab to etanercept, as fewer injections are needed, and also because adalimumab is available as a pre-filled syringe whereas etanercept needs to be prepared from a powdered formulation. However a pre-filled syringe of etanercept was approved in the US late in 2004 but at the time of writing is not available in Europe. Personal experience also suggests that some elderly patients prefer to receive intravenous infusions rather than contemplate administrating their own injections.

2.4 Current NICE guidance for use of TNF inhibitors

Treatment of RA with etanercept and infliximab were considered in a previous NICE appraisal and the guidance published in 2002\textsuperscript{83} mirrors that proposed earlier by a committee of the British Society for Rheumatology.\textsuperscript{84} A brief commentary on aspects of this guidance is given below.

- A key feature of the guidance is a requirement to register treated patients, with their consent, in a national register (the BSR biologics register – BSRBR). The BSRBR is a prospective cohort study designed to compare the risk, over 5 years, of developing malignancy, lymphoproliferative malignancy, infection requiring hospitalisation, serious comorbidity and death. There are two cohorts: a group of patients with rheumatic disorders newly exposed to biologic agents, mainly TNF inhibitors; and, a comparison group with similar disease characteristics being treated with other non-biologic DMARDs. It is proposed that patients are monitored for 5 years or more.\textsuperscript{85} The target for recruiting patients treated with etanercept was met recently and clinicians are no longer required to register patients being treated with this drug. Clinicians have described their difficulties finding funding for TNF inhibitors and also meeting the demands of current guidance in terms of BSRBR registration and patient evaluations.\textsuperscript{63}
• It is recommended that neither etanercept nor infliximab are used unless a patient has failed to respond to two DMARDs including methotrexate. Other eligibility criteria, dose ranges and desired duration of previously tried therapies were as proposed by the BSR. Since 2002 evidence of the use of TNF inhibitors before other DMARDs has accumulated and this is considered in our review. The BSR, in their updated guidance, state that circumstances leading to first-line use of TNF inhibitors would be rare.86 Data from the BSRBR show that the median number of previous DMARDs used by registered patients was four, indicating conservative use of these new drugs.87

• The BSR, endorsed by NICE in 2002, recommended that patients should only be eligible for TNF inhibitors if they fulfil the 1987 American Rheumatism Association criteria for the classification of rheumatoid arthritis.88 We indicated earlier that clinicians rarely apply criteria for diagnosis in practice. Around 10% of patients in the BSRBR with a clinical diagnosis of RA appeared not to meet disease classification criteria.85 The criteria, especially the list version, have important limitations.89 Moreover, patients may take several years after disease onset to fulfil these criteria7, and it is possible that, as TNF inhibitors are used earlier in disease, some patients suitable for TNF inhibitors do not meet formal classification criteria.

• Current guidance stipulates that patients should have active disease determined by a DAS28 score of greater than 5.1 and that disease activity should be assessed at two time points one month apart, prior to therapy. Funding agreements between some hospital trusts and primary care trusts require that these thresholds must be met before funding is agreed. Inevitably, this influences the DAS scores recorded in busy clinics. Some argue that it is unreasonable for patients to have to continue with active disease for a month, having already tolerated active disease between clinic appointments, before being eligible for therapy. A majority of patients (94%) registered in the BSRBR are recorded as having met this standard, although the veracity of recorded data is unclear – it is not audited and there is an incentive for clinicians, who judge that thresholds inappropriately control access to therapy, to state that patients have met the criteria.
• Guidance also recommends that, in order to continue therapy with TNF inhibitors, disease activity needs to decrease by a DAS28 score of 1.2 or be at, or below, 3.2 after 3 months of treatment. The BSR submission to NICE indicates that this may have been a typing error as a good DAS response is defined as a change of >1.2 \textit{and} a score below 3.2.\textsuperscript{85} DAS28 thresholds scores were derived originally from actual decisions taken in practice\textsuperscript{43} and their principal role is as outcome measures in clinical trials. Although these may be useful hurdles and good instruments for monitoring therapy, it has been argued that unthinking application of such thresholds devalues clinical judgements, especially since the DAS28 has some properties that undermine confidence in its value for individual decision making.\textsuperscript{90-93} In the BSRBR 41% of patients classified as non-responders on DAS thresholds continued with TNF inhibitors: indicating that clinicians and patients clearly felt that the modest improvement in DAS (mean improvement 0.3) and other health gains\textsuperscript{85} were sufficient to warrant continued drug use.

• Sequential use of TNF inhibitors, where patients fail to respond or experience an adverse reaction to one agent, was not recommended in previous guidance on the basis that there was no evidence supporting this practice. Since then many practicing clinicians have noted benefits for patients when switching agents. Some experiences have been published and demonstrate potential benefits for patients switching from any one of the three agents to another of these agents.\textsuperscript{94,95} BSR guidance (2005) cites some of this evidence without making any specific recommendations. Data from the BSRBR indicates that this practice is prevalent, despite current guidance.

• Updated BSR guidance considers, briefly, the use of dose changes and increased frequency of dosing for infliximab and adalimumab. A significant proportion of patients receiving infliximab experience increased disease activity after an initial good response. Clinicians have responded, in some cases, by reducing the interval between infusions such that patients are given 3 mg/kg of infliximab every 6 weeks instead of every 8 weeks, or by increasing the dose of infliximab to 5 mg/kg at 8 week intervals.\textsuperscript{96,97} Published observations indicate effective disease control by doing this but at significantly increased drug costs. A large series from Belgium, for example, showed that nearly a quarter of treated patients had dose increases\textsuperscript{74} whereas a US study showed that over 60% of patients
had dose increases. In addition the licence for adalimumab allows for increasing the dose from 40 mg every other week to once a week, effectively doubling the cost of therapy. It is unclear how commonly this is done in practice. By contrast increasing etanercept beyond a total of 50 mg per week (as one or two injections) does not appear to improve efficacy.

2.5 Degree of Diffusion & Anticipated Costs

By the end of 2004, 8455 patients with RA and 1081 with other rheumatic diseases, were treated with TNF inhibitors and were registered with the BSRBR. New patients were being added to the registry at a rate of 450 per month, in early 2004. If we estimate that currently around 8-10000 patients with RA are being treated with TNF inhibitors, at approximately £10000 per annum each, then the annual national costs of TNF inhibitors for RA is in the region of £80 to £100 million. We know these figures are rising and, given that only ~2% of patients with RA are currently on TNF inhibitors, there is the potential for future increases to be substantial.
3 EFFECTIVENESS

Summary
A comprehensive search for randomised controlled trials was undertaken. Studies were selected, assessed for quality and data extracted by two independent reviewers.

Twenty-nine trials met the inclusion criteria. One trial (BeSt) did not meet the inclusion criteria but is reported in detail as it is relevant to informing the decision on the most appropriate use of TNF inhibitors. Most trials were of good quality and compared one of the TNF inhibitors with placebo. Only three trials looked at a head-to-head comparison between a TNF inhibitor and methotrexate. No trial compared TNF inhibitors with each other.

When used alone, adalimumab was slightly less effective and etanercept was slightly more effective than methotrexate in patients who had not been treated with methotrexate or who had not previously failed methotrexate treatment.

All the three TNF inhibitors, either used alone (where licensed) or in combination with ongoing conventional DMARDs, were effective in controlling the signs and symptoms of RA compared to placebo in patients with who had had an inadequate response to conventional DMARDs.

Combination of a TNF inhibitor plus methotrexate was more effective than methotrexate alone in patients who had not been treated with methotrexate or who had not previously failed methotrexate treatment. The combination involving infliximab, however, was associated with an increased risk of serious infection.

Patients’ previous experience with the therapy has to be taken into account when interpreting treatment effects observed in trials, particularly when ‘combination therapy’ is involved. No clear relationship between disease duration and treatment effects was observed among limited evidence from trials.
3.1 Methods for reviewing effectiveness

3.1.1 Search strategy

Clinical effectiveness

The following resources were used to identify relevant studies:

- Searches of bibliographic databases:
  - Cochrane Library 2005 Issue 1
  - MEDLINE (Ovid) 1966 – February 2005, EMBASE (Ovid) 1980 – week 08 2005
  - Science Citation Index (ISI Web of Science) 1981-2005
- National Research Register 2005 Issue 1
- Internet sites of FDA and EMEA
- Manufacturer submissions to NICE 2005 appraisal process
- Citation lists
- Contact with experts and researchers

Searches used index and text words encompassing *rheumatoid arthritis, tumour necrosis factor, tumour necrosis factor receptors, anti-tumour necrosis factor, adalimumab, etanercept* and *infliximab*. Search filters were used in MEDLINE and EMBASE to identify randomised controlled trials (RCTs). Searches for adalimumab were not limited by date; searches for etanercept and infliximab started from 2001 as the previous reported had covered the earlier period. There were no restrictions by language. Full details of strategies are contained in Appendix 2, page 233.
3.1.2 Inclusion and exclusion criteria

Clinical effectiveness – efficacy outcomes

Inclusion criteria

- Randomised controlled trials (RCTs) that compare adalimumab, etanercept or infliximab, with any other agent including placebo in adult RA patients.
- Trial reports were only included if the recruitment of patients was complete.
- A trial had to be fully published as a paper or be available as a complete trial report to be included. Trial reports were requested on all major trials from the manufacturers.

Exclusion criteria

- Trials of adalimumab, etanercept or infliximab in juvenile arthritis, Crohn’s disease, psoriatic arthritis and other forms of spondyloarthritis.
- Trials of adalimumab, etanercept or infliximab comparing different doses or routes of administration without including another active or a placebo control group were only assessed for safety outcomes.
- Studies reporting solely on laboratory measures aimed at investigating disease, or treatment, mechanisms and which do not report relevant clinical outcomes.
- Observational studies of TNF inhibitor therapies that do not include a control group, except for information on adverse events.
- Trials only available as abstracts.

Clinical effectiveness – safety outcomes

Inclusion criteria

- RCTs that meet the inclusion criteria for the review on efficacy outcomes.
- In addition to RCTs, data from post-marketing surveillances, major observational studies and various registries including the British Society for Rheumatology Biologics Register (BSRBR) were used to inform the assessment of the safety of these three agents.
Based on the above inclusion and exclusion criteria, study selection was made independently by two reviewers. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

3.1.3 Data extraction strategy
Data included in the previous peer-reviewed, published, assessment report\(^1\) were taken directly from the report and incorporated into updated analyses. Data for outcomes that were not assessed in the previous assessment report, and additional data from new trials not included in the previous report were extracted independently by two reviewers using an agreed data extraction form. Results were extracted, where possible, for intention-to-treat populations as raw numbers, plus any summary measures with standard deviations, confidence intervals and p-values. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

3.1.4 Quality assessment strategy
The quality of RCTs was judged by adequacy of randomisation, allocation concealment, blinding, differential withdrawal between treatment arms, and use of intention-to-treat analysis. Two reviewers independently examined trial quality. Discrepancies were resolved by discussion with involvement of a third reviewer when necessary. Results of quality assessment were tabulated.

3.1.5 Data analysis

3.1.5.1 Outcomes of interest

Meta-analyses were carried out on selected key outcomes listed below, as specified in the review protocol (http://www.pcoph.bham.ac.uk/publichealth/wmhtac/pdf/protocols/Anti-TNF_2004_final_protocol%20.pdf).
Efficacy

- Proportions of patients meeting the ACR20, ACR50, ACR70 response criteria. Where ACR response was not reported, Paulus20 and Paulus50 were assumed to be equivalent to ACR20 and ACR50, respectively for the purposes of meta-analysis

- Swollen joint count (SJC)

- Patient’s global assessment of disease activity

- Health Assessment Questionnaire (HAQ)

- Disease activity score (DAS or DAS28)

- Accepted indices of joint damage (van der Heijde modified Sharp score)

Further descriptions of the ACR response criteria, HAQ, DAS, and modified Sharp score can be found in Appendix 1, page 229.

Tolerability

- Withdrawals for lack of efficacy

- Withdrawals due to adverse events

- Withdrawals for any reason

Safety

- Serious adverse events

- Serious infections

- Malignancy

Serious adverse events are defined as an adverse event that met any of the following criteria:

- fatal

- life-threatening

- results in an unplanned in-patient hospitalisation, or prolongs an existing hospitalisation

- significantly or permanently disabling

- a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalisation may still be considered serious adverse events if, based on appropriate medical
judgement, they require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Serious infections are defined as any infections that require hospitalisation or parenteral antimicrobial treatment. If the number of patients experiencing these events is not reported, the number of patients who experienced infections that were classified as serious adverse events is used instead. Figures of serious infection reported by study investigators without a clear definition are also included if the above information is not available.

Additional exploratory analyses on death, any infections, non-melanoma skin cancer, and all cancer excluding non-melanoma skin cancers were carried out.

3.1.5.2 Approach for meta-analysis

Each TNF inhibitor was meta-analysed separately. The primary analysis compared each TNF inhibitor at licensed dose (or its equivalent) with placebo or other active comparators using the latest follow-up data available from the randomised, controlled period of each trial. The doses included in the primary analysis are:

- Adalimumab: 40 mg every other week or 20 mg every week;
- Etanercept: 25 mg twice weekly, 50 mg once weekly, or 16 mg/m² twice weekly;
- Infliximab: 3 mg/kg at 0, 2, 6 weeks and then every 8 weeks.

Sensitivity analyses included TNF inhibitors at licensed doses and above, and at all doses including sub-licensed doses. Studies in which single injections or infusions were administered are not included in the primary analysis but are included in the all-dose sensitivity analyses. Duration of follow up for each trial is displayed on the forest plots of primary analysis for comparison. Additional analyses of results at 1 month, 3 months, 6 months, 12 months and beyond are also conducted for ACR20 response.
For each TNF inhibitor three comparisons were made:

(a) TNF inhibitor versus conventional DMARD
This ‘head-to-head’ comparison is most relevant for clinical practice. A fair head-to-head comparison requires that patients should not have previously tried any of the drugs being compared.

(b) TNF inhibitor versus placebo (with or without concomitant, ongoing DMARDs)
Trials that were included in this comparison typically recruited patients whose disease had been inadequately controlled by conventional DMARDs. The DMARDs that the patients had been taking prior to study entry (if any) were either stopped or continued during the trial and a TNF inhibitor or placebo given to patients. In both cases a TNF inhibitor is compared to placebo but the scenarios behind the comparisons are different. The former represents a comparison of stopping DMARDs versus replacing a DMARD with a TNF inhibitor. The latter represents a comparison of continuing a DMARD (which is, at best, partially effective) versus adding a TNF inhibitor to that DMARD.

To explore whether treatment effects differ between these two scenarios, the primary analysis of trials are displayed in the forest plots according to concomitant DMARD treatment. Studies in which patients stopped all concomitant DMARDs are placed on top of the plots and are labelled with a ‘(-)’ sign. These are followed by studies in which patients continued their existing DMARD treatment, which are labelled with a ‘(+’ sign. In a few studies the patients continued their ongoing antirheumatic therapy, which may have included DMARDs. These studies are labelled with a ‘(+/-)’ sign.

(c) Combination (TNF inhibitor + newly-initiated conventional DMARD) versus newly-initiated conventional DMARD alone
This analysis reports trials in which patients were naïve to, or had not previously failed treatment with the TNF inhibitor and the DMARD being compared. The only comparator DMARD used in such trials to date has been methotrexate. The effect size in these trials represents the additional treatment benefit (or harm) of the combination over the newly initiated methotrexate alone. In these trials there is a greater benefit to patients in the control
arm than seen in trials where the comparator is an established ongoing DMARD. It is thus necessary to distinguish between this analysis and that in (b), above, and we feel that it is inappropriate to cite a summary statistic combining these two different types of comparisons. However, for illustrative purpose, the forest plots of the primary analyses give both comparisons (b) and (c) on the same plot in order to illustrate the overall heterogeneity between these two types of ‘placebo vs. TNF inhibitor’ comparisons.

Although most trials contributed data to only one of the three comparisons described above, a few trials contributed to more than one. For example, the PREMIE trial compared adalimumab alone, MTX alone, and the combination of adalimumab + MTX in patients naïve to both treatments. The study therefore allowed two comparisons: adalimumab vs. MTX (comparison a), and combination of adalimumab + MTX vs. MTX (comparison c). We made no statistical adjustment for the multiple comparisons within a trial.

Although subgroup analyses according to disease duration (mean disease duration ≤ 3 years vs. > 3 years) were planned, on reviewing the data we felt they were insufficient to support this as disease duration relates closely to patients’ prior exposure to DMARD therapies, which was strongly associated with the type of trials that had been carried out. For example, trials which compared TNF inhibitors with placebo tended to recruit predominately RA patients with long disease duration and with prior exposure to multiple DMARDs, whereas trials which included genuine head-to-head comparison between TNF inhibitors and conventional DMARDs were predominately carried out in early RA patients.

3.1.5.3 Handling of data and presentation of results

For continuous outcomes, results are presented as a weighted mean difference (WMD). For binary outcomes, results are presented as relative risk (RR). Risk difference (RD) was also used to calculate numbers needed to treat (NNT).

For outcomes with continuous data, the decision about whether to use the change from baseline or the final result depended on whether data was available for a sufficient number of studies. Where possible, the standard deviation (SD) was taken directly from the reported results, or derived from the standard error of the mean (SEM) or confidence intervals (CIs). When only
the baseline SD was available, it was used as the SD for the final results as well. SDs for mean change from baseline, if not available, were imputed using baseline SD and final SD assuming an intercorrelation coefficient of 0.5. When only the median and interquartile ranges were reported, the median was used as the mean, and one half of the difference between the 1st and 3rd quartile was used as the SD. Where the SD could not be estimated from trial data using the above methods, an imputed SD was calculated from the baseline SD of other trials with the same intervention.

Many outcomes were meta-analysed, for brevity, only the summary results are presented. Forest plots of the primary analyses for the six key outcomes (ACR20; ACR50; ACR70; HAQ; serious adverse events; and malignancies) are shown. A fixed effects model was used unless trials demonstrate statistical heterogeneity, in which case a random effects model was also used. In such cases the most conservative result is presented.

3.2 Results for effectiveness review

3.2.1 Number and type of studies included

A total of 29 RCTs are included in this systematic review: adalimumab 9; etanercept 11; infliximab 9. One further trial (BeSt) is also described here.

The process of study selection is summarised in Figure 1. Thirty-six citations met inclusion criteria (kappa for two independent reviewers was 0.70, 95% CI 0.66-0.75): ten papers or conference abstracts describing further results from two trials (ERA and ATTRACT) included in the previous technology assessment report (TAR) and 26 papers or conference abstracts describing results from 15 RCTs not included in our previous review. For more details of excluded studies see Appendix 7, page 257.

Seven new RCTs were identified through manufacturer submissions and abstracts (not yet indexed in electronic databases) from conferences. Five met the inclusion criteria. Trial reports were obtained from the manufacturers for four of the trials (PREMIER, Codreanu et al 2003, Baumgartner et al 2004, and START) which are included in the systematic review. Schattenkirchner 1998 (adalimumab DE004) could not be included because
attempts to obtain the trial report from the manufacturer were unsuccessful. Two trials, ADORE\textsuperscript{107} and Behandel-Strategieën (BeSt) did not meet the inclusion criteria as they had TNF inhibitors in all arms thereby preventing appropriate comparisons between TNF inhibitors and other active comparators or placebo. However, although the BeSt study, which was a trial of DMARD sequences in RA, could not be included in meta-analyses we have chosen to describe this study in detail in the infliximab section (see Section 3.2.4), because it reports data that may inform the appropriate use of these agents.
Figure 1 Flow chart for study selection

1741 citations retrieved by electronic database search

1647 citations excluded on the basis of title and/or abstract

94 citations obtained

RCTs identified from other sources
  • Industry submissions 6
  • Conference abstracts 1

36 citations and 4 additional RCTs (unpublished or published in conference abstracts only) met inclusion criteria; these reported results from 2 RCT included in the previous TAR and 19 RCTs (see below) not included in the previous TAR
  • Adalimumab: 9
  • Etanercept: 5
  • Infliximab: 5

61 citations excluded after examination of full text publications/manuscripts/reports (see Appendix 6)

Reasons for exclusion
  • No appropriate comparison between TNF inhibitors and other active comparators or placebo 4
  • Neither full paper nor trial report available 1
  • Not including outcomes of interest (clinically important outcomes) 3
  • Interventions not including adalimumab, etanercept, or infliximab 3
  • Not RCTs (non-randomised studies, observational studies, case reports) 15
  • Review articles 10
  • News articles/commentaries/editorials 17
  • Irrelevant (conference news reports; cost studies) 8

RCTs included in the previous TAR
  • Etanercept: 6
  • Infliximab: 4

RCTs included in systematic review
  • Adalimumab: 9
  • Etanercept: 11
  • Infliximab: 9
3.2.2 Adalimumab

3.2.2.1 Descriptions of individual adalimumab trials

Nine trials comprising a total of 3387 patients, were included. Abbott Laboratories provided clinical study reports for five studies: ARMADA \(^{108}\), van de Putte 2004 \(^{109}\), PREMIER \(^{102}\), Keystone 2004a \(^{110}\), and STAR \(^{111}\). Data from these reports and additional trial data provided within the company submission are included. A list of these nine trials, the comparators and baseline patient characteristics are shown in Table 1. Trial quality, based on available data, is summarised in Table 2. In general the trials were of high quality.

In most trials patients met agreed disease classification criteria and active RA was defined on the basis of tender and swollen joint counts, and other parameters including ESR, CRP or morning stiffness. Two early phase trials \(^{112},^{113}\) used DAS scores for inclusion. Stable doses of oral prednisolone (\(\leq 10\) mg/day) and NSAIDs were allowed. Only one trial (PREMIER) \(^{102}\) recruited exclusively early RA patients (disease duration <3 years).

Excluding PREMIER, five trials had a treatment arm with the licensed dose of adalimumab: DE007; DE009; DE011; DE019; DE031. These trials are described below and key data from all trials is presented in tables. Mean disease duration in these trials was around 10 years. In DE031 adalimumab treated patients had a mean disease duration of 9 years compared with 12 years for the placebo group. Oral corticosteroids were used by 50%, or more, of patients in most treatment arms except in PREMIER in which over 35% of patients with early RA were on steroids. The number of tender and swollen joints required for entry varied between trials recruiting from European centres compared with US trials. For example ten swollen joints were required for entry into DE007 and DE011 compared with 6 in DE019 and DE031 (US studies). Baseline HAQ scores were also higher in the former studies indicating more functional limitation.
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions*</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>Mean number of previous DMARDs</th>
<th>On steroids %</th>
<th>On NSAIDs %</th>
<th>Mean baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DE001</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>den Broeder et al 2002</td>
<td>Placebo i.v. (1 dose)</td>
<td>31</td>
<td>55</td>
<td>11.9</td>
<td>3.7</td>
<td>77%</td>
<td>68%</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 0.5 mg/kg (1 dose)</td>
<td>17</td>
<td>54</td>
<td>11.0</td>
<td>3.6</td>
<td>53%</td>
<td>94%</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 1 mg/kg (1 dose)</td>
<td>18</td>
<td>58</td>
<td>11.2</td>
<td>3.9</td>
<td>78%</td>
<td>72%</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 3 mg/kg (1 dose)</td>
<td>18</td>
<td>54</td>
<td>10.8</td>
<td>3.9</td>
<td>67%</td>
<td>56%</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 5 mg/kg (1 dose)</td>
<td>18</td>
<td>59</td>
<td>14.5</td>
<td>4.4</td>
<td>78%</td>
<td>89%</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 10mg/kg (1 dose)</td>
<td>18</td>
<td>53</td>
<td>8.9</td>
<td>3.9</td>
<td>67%</td>
<td>72%</td>
<td>1.93</td>
</tr>
<tr>
<td><strong>DE005</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weisman et al 2003</td>
<td>Placebo i.v. (1 dose) + MTX (12.5-25mg/week, mean 17 mg/wk)</td>
<td>15</td>
<td>51</td>
<td>15</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 0.25 mg/kg (1 dose) + MTX (12.5-25 mg/week, mean 17 mg/wk)</td>
<td>9</td>
<td>50</td>
<td>17</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 0.5mg/kg (1 dose) + MTX (12.5-25 mg/week, mean 13 mg/wk)</td>
<td>9</td>
<td>56</td>
<td>13</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 1mg/kg (1 dose) + MTX (12.5-25 mg/week, mean 16 mg/wk)</td>
<td>9</td>
<td>51</td>
<td>16</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 3 mg/kg (1 dose) + MTX (12.5-25 mg/week, mean 15 mg/wk)</td>
<td>9</td>
<td>56</td>
<td>15</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 5 mg/kg (1 dose) + MTX (12.5-25 mg/week, mean 18 mg/wk)</td>
<td>9</td>
<td>54</td>
<td>18</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.4</td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventions*</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>Mean number of previous DMARDs</td>
<td>On steroids %</td>
<td>On NSAIDs %</td>
<td>Mean baseline HAQ score</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>DE007</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte et al 2003</td>
<td>Placebo s.c. weekly</td>
<td>70</td>
<td>50</td>
<td>9</td>
<td>3.5</td>
<td>77%</td>
<td>80%</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 20 mg weekly</td>
<td>72</td>
<td>54</td>
<td>10</td>
<td>4.1</td>
<td>76%</td>
<td>76%</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40 mg weekly</td>
<td>70</td>
<td>53</td>
<td>10</td>
<td>3.7</td>
<td>70%</td>
<td>81%</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 80 mg weekly</td>
<td>72</td>
<td>53</td>
<td>10</td>
<td>3.7</td>
<td>75%</td>
<td>78%</td>
<td>1.66</td>
</tr>
<tr>
<td><strong>DE009, ARMADA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinblatt et al 2003</td>
<td>Placebo s.c. every other week + MTX</td>
<td>62</td>
<td>56</td>
<td>11</td>
<td>3.0</td>
<td>58%</td>
<td>Not reported</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 20 mg every other week + MTX (12.5-25mg/week, mean 17 mg/wk)</td>
<td>69</td>
<td>54</td>
<td>13</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40 mg every other week + MTX (12.5-25mg/week, mean 16 mg/wk)</td>
<td>67</td>
<td>57</td>
<td>12</td>
<td>2.9</td>
<td>46%</td>
<td></td>
<td>1.55</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 80 mg every other week + MTX (12.5-25mg/week, mean 17 mg/wk)</td>
<td>73</td>
<td>56</td>
<td>13</td>
<td>3.1</td>
<td></td>
<td></td>
<td>1.55</td>
</tr>
<tr>
<td><strong>DE010</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rau et al 2004</td>
<td>Placebo s.c. &amp; i.v. (1 dose) + MTX (7.5-25mg/week, mean 14 mg/wk)</td>
<td>18</td>
<td>54</td>
<td>12</td>
<td>3.5</td>
<td>72%</td>
<td>94%</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>Adalimumab i.v. 1 mg/kg (1 dose) + MTX (7.5-25mg/week, mean 18 mg/wk)</td>
<td>18</td>
<td>52</td>
<td>11</td>
<td>3.4</td>
<td>72%</td>
<td>100%</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 1 mg/kg (1 dose) + MTX (7.5-25mg/week, mean 16 mg/wk)</td>
<td>18</td>
<td>53</td>
<td>11</td>
<td>3.3</td>
<td>83%</td>
<td>89%</td>
<td>1.33</td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventions*</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>Mean number of previous DMARDs</td>
<td>On steroids %</td>
<td>On NSAIDs %</td>
<td>Mean baseline HAQ score</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>DE011</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte et al 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe, Canada &amp; Australia, 52 centres, double-blind</td>
<td>Placebo s.c. weekly</td>
<td>110</td>
<td>54</td>
<td>12</td>
<td>3.6</td>
<td>67%</td>
<td>84%</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 20 mg every other week</td>
<td>106</td>
<td>53</td>
<td>9</td>
<td>3.7</td>
<td>70%</td>
<td>81%</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 20mg weekly</td>
<td>112</td>
<td>54</td>
<td>11</td>
<td>3.6</td>
<td>68%</td>
<td>75%</td>
<td>1.88</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40mg every other week</td>
<td>113</td>
<td>53</td>
<td>11</td>
<td>3.8</td>
<td>68%</td>
<td>82%</td>
<td>1.83</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40mg weekly</td>
<td>103</td>
<td>52</td>
<td>12</td>
<td>3.8</td>
<td>82%</td>
<td>77%</td>
<td>1.84</td>
</tr>
<tr>
<td><strong>DE013, PREMIER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breedveld et al 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America, Europe &amp; Australia, multicentre, double-blind</td>
<td>MTX (7.5-20 mg/week) weekly</td>
<td>257</td>
<td>52</td>
<td>0.8</td>
<td></td>
<td>35%</td>
<td>Not reported</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40 mg every other week</td>
<td>274</td>
<td>52</td>
<td>0.7</td>
<td></td>
<td>37%</td>
<td>1.63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40 mg every other week + MTX (7.5-20 mg/week) weekly</td>
<td>268</td>
<td>52</td>
<td>0.7</td>
<td></td>
<td>36%</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td><strong>DE 019</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keystone et al 2004a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA &amp; Canada, 89 centres, double-blind</td>
<td>Placebo s.c. + MTX (12.5-25mg/week, mean 17 mg/wk)</td>
<td>200</td>
<td>56</td>
<td>11</td>
<td>2.4</td>
<td>Not reported</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 20mg weekly + MTX (12.5-25mg/week, mean 16 mg/wk)</td>
<td>212</td>
<td>57</td>
<td>11</td>
<td>2.4</td>
<td>1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab s.c. 40mg every other week + placebo s.c. on alternate weeks + MTX (12.5-25mg/week, mean 17 mg/wk)</td>
<td>207</td>
<td>56</td>
<td>11</td>
<td>2.4</td>
<td>1.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions*</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>Mean number of previous DMARDs</th>
<th>On steroids %</th>
<th>On NSAIDs %</th>
<th>Mean baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DE 031, STAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furst et al 2003†††</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA &amp; Canada, 69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>centres, double-blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment &amp; follow-up: 24 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo s.c. + baseline standard anti-rheumatic therapy</strong></td>
<td>318</td>
<td>56</td>
<td>12</td>
<td></td>
<td></td>
<td>54%</td>
<td>64%</td>
<td>1.43</td>
</tr>
<tr>
<td><strong>Adalimumab s.c. 40mg every other week + baseline standard anti-rheumatic therapy</strong></td>
<td>318</td>
<td>55</td>
<td>9</td>
<td></td>
<td></td>
<td>51%</td>
<td>62%</td>
<td>1.37</td>
</tr>
</tbody>
</table>

*Some of the groups receiving active treatment also received matching placebo (where necessary) to maintain blinding. These placebo injections are not listed.

†Open-label, continuation study (DE003) in which patients in the placebo group were switched to receive adalimumab is not included in current review.

‡Patients received the first dose at baseline and the second dose after 4 weeks or on loss of response. Once the second dose was administered, the patient was considered to have completed the study and had the option to participate in a continuation study. This open-label continuation study (DE005X) in which placebo group was switched to receive adalimumab is not included in current review.

§Patients in the placebo group were switched to adalimumab 40 mg at week 12. Subsequent blinded and open-label continuation studies without placebo control are not included in current review.

¶A second double-blinded injection of randomised drug was given between 4 weeks and 3 months after the first injection according to patient’s response. Follow-up beyond 4 weeks and further 2.5-year open-label continuation study are not included in current review.

* Further open-label extension is not included in current review.
Table 2 Quality of included randomised controlled trials - adalimumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Truly random allocation/Remain on randomised treatment</th>
<th>Adequate allocation concealment</th>
<th>Blinding: Participants</th>
<th>Blinding: Investigators</th>
<th>Blinding: Assessors</th>
<th>Important differences in baseline characteristics between groups (item)</th>
<th>Important differences in completion rates between groups (% randomised patients completed)</th>
<th>Use of intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE001 den Broeder 2002</td>
<td>Placebo: 31 Adalimumab: 89</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DE005 Weisman 2003</td>
<td>Placebo: 15 Adalimumab: 45</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>Not applicable (sample size too small)</td>
<td>No</td>
</tr>
<tr>
<td>DE007 van de Putte 2003</td>
<td>Placebo: 70 Adalimumab: 214</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DE009 ARMADA, Weinblatt 2003</td>
<td>Placebo: 62 Adalimumab: 209</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>DE010 Rau 2004</td>
<td>Placebo: 18 Adalimumab: 36</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Study</td>
<td>Sample size</td>
<td>Truly random allocation/ Remain on randomised treatment</td>
<td>Adequate allocation concealment</td>
<td>Blinding: Participants</td>
<td>Investigators</td>
<td>Assessors</td>
<td>Important differences in baseline characteristics between groups (item)</td>
<td>Important differences in completion rates between groups (% randomised patients completed)</td>
<td>Use of intention-to-treat analysis</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>--------------------------------------------------------</td>
<td>--------------------------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>DE011 van de Putte 2004</td>
<td>Placebo: 110 Adalimumab: 434</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Placebo: 44% Adalimumab: 73%</td>
<td></td>
</tr>
<tr>
<td>DE013 PREMIER (Breedveld 2004)</td>
<td>MTX: 257 Adalimumab: 274 Combination: 268</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>MTX: 66% Adalimumab: 61% Combination: 76%</td>
<td></td>
</tr>
<tr>
<td>DE019 Keystone 2004a</td>
<td>Placebo: 200 Adalimumab: 419</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Placebo: 70% Adalimumab: 78%</td>
<td>Yes (except radiographic outcomes)</td>
</tr>
<tr>
<td>DE031 STAR (Furst 2003)</td>
<td>Placebo: 318 Adalimumab: 318</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Placebo: 91% Adalimumab: 91%</td>
<td></td>
</tr>
</tbody>
</table>
Van de Putte and colleagues 2003, DE007115

This 12-week, double-blind, multicentre study compared weekly s.c adalimumab 20, 40 or 80 mg with placebo without concomitant methotrexate. After eight weeks in the trial, patients in any treatment arms with ‘unbearable’ disease were allowed to enter a rescue arm, during which other standard RA therapies were permitted but adalimumab was not permitted until week 12. After 12 weeks placebo treated patients were given adalimumab 40 mg weekly for 40 weeks during a blinded continuation phase which is not included in this review. ACR20 response at week 12 was the primary endpoint. Methods of randomisation, allocation concealment and blinding were not clearly described.

ARMADA, Weinblatt and colleagues 2003, DE009108

This 24-week, double-blind, multicentre RCT compared adalimumab 20 mg every other week, 40 mg every other week, 80 mg every other week and placebo in patients receiving concomitant methotrexate. Treatment with methotrexate for at least six months, before entry, was required with the dose stable at between 10 to 25 mg/week for more than four weeks. A minimum of six swollen joints and nine tender joints, and prior treatment failure with at least one DMARD besides methotrexate but no more than four DMARDs, were required. The primary endpoint was ACR20 response at 24 weeks.

van de Putte and colleagues 2004, DE011109

This was a 26-week, double-blind, multicentre RCT compared adalimumab monotherapy (s.c. 20 mg every other week, 20 mg every week, 40 mg every other week or 40 mg every week) with placebo in patients who had failed at least one DMARD. Patients with at least 10 swollen joints and 12 tender joints were recruited. The primary endpoint was ACR20 response.

PREMIER, Breedveld and colleagues 2004, DE013102

This 2-year, double-blind, multicentre RCT compared treatment with methotrexate alone (started 7.5 mg/week and escalated to up to 20 mg/week), adalimumab alone (s.c. 40 mg every other week) or the combination of both in early RA patients (disease duration <3 years) who had not previously been treated with methotrexate. Patients with at least 8 swollen joints and 10 tender joints, were recruited. Patients previously treated with more than two DMARDs were not eligible. Sixty-eight percent of the randomised patients were DMARD
the comparison of ACR50 response at week 52 and change in modified total Sharp score from baseline to week 52 between the combination therapy and the methotrexate monotherapy only.

**Keystone and colleagues 2004a, DE019**

This 52-week, double-blind, multicentre trial compared adalimumab s.c. 40 mg every other week, 20 mg every week, and placebo in patients receiving concomitant methotrexate. Patients who were either rheumatoid factor positive or had at least one joint erosion on radiographs of the hands and feet were recruited. The primary endpoints were ACR20 response at 24 weeks, change in modified Sharp score at week 52; and change in HAQ at week 52.

**STAR, Furst and colleagues 2003, DE031**

This 24-week, double-blind, multicentre safety trial compared adalimumab s.c. 40 mg every other week with placebo in RA patients who continued to receive their standard antirheumatic therapy (including DMARDs). Concomitant DMARDs were permitted if doses had been stable for at least 28 days before screening, and a single increase in DMARD dosage was allowed at week 12 or subsequent visits if a patient failed to meet or maintain ACR20 response. Eighty-three percent of patients received at least one DMARD. The primary endpoint, safety, was assessed by types and frequencies of adverse events, physical examination findings, and standard laboratory test results.
3.2.2.2 Meta-analyses of adalimumab trials

The approaches to meta-analyses and data presentation are described in detail in section 3.1.5. The only adalimumab trial that recruited exclusively MTX naïve patients with disease duration < 3 years was the PREMIER\textsuperscript{102} trial and included three treatment arms which allow more than one comparisons: adalimumab versus methotrexate and combination (adalimumab + methotrexate) versus methotrexate.

**Adalimumab versus methotrexate**

The PREMIER\textsuperscript{102} trial is the only trial that included head-to-head comparison between adalimumab and a DMARD (MTX). The results are summarised in Table 3.

**Efficacy**

The only effectiveness result reaching conventional levels of statistical significance between adalimumab and MTX is radiographic joint damage. Patients treated with adalimumab had a smaller increase in modified Sharp score compared to those treated with MTX (mean difference over two years $-4.90, 95\% \text{ CI }$). However, given the multiple comparisons, this could be just a chance occurrence. Adalimumab appears to be marginally less effective than MTX in reducing disease activity as measured by other means, for example the ACR20 response (RR $= 0.88, 95\% \text{ CI } 0.75-1.03$) and ACR50 response (RR $= 0.86, 95\% \text{ CI } 0.70$ to $1.06$).

**Tolerability**

No significant difference was found between adalimumab and MTX.

**Safety**

One death occurred in the MTX arm while four occurred in the adalimumab arm. The number of patients with malignancy was similar (1 in the MTX arm and 4 in the adalimumab arm). More patients experienced serious adverse events in adalimumab arm although this did not reach statistical significance patients had serious infections in MTX arm compared to in the adalimumab arm.
### Table 3 Summary of 2-year results from PREMIER study - Adalimumab alone (licensed dose only) vs. MTX alone in MTX naïve patients

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>531</td>
<td>RR (fixed)</td>
<td>0.88 [0.75, 1.03]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>531</td>
<td>RR (fixed)</td>
<td>0.86 [0.70, 1.06]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>531</td>
<td>RR (fixed)</td>
<td>0.99 [0.75, 1.30]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>531</td>
<td>RD (fixed)</td>
<td>-0.07 [-0.15, 0.02]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>531</td>
<td>RD (fixed)</td>
<td>-0.06 [-0.14, 0.02]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>531</td>
<td>RD (fixed)</td>
<td>0.00 [-0.08, 0.07]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>1</td>
<td>335</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>1</td>
<td>329</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>1</td>
<td>328</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>DAS28-4, mean change from baseline</td>
<td>1</td>
<td>319</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
</tbody>
</table>
| Modified van de Heijde-Sharp score, mean change from baseline | 1 | 531 | WMD (fixed) | -4.90 
| Withdrawal for any reasons | 1 | 531 | RR (fixed) | 1.14 [0.91, 1.43] |
| Withdrawal due to lack of efficacy | 1 | 531 | RR (fixed) | 
| Withdrawal due to adverse events | 1 | 531 | RR (fixed) | 
| Death | 1 | 531 | RR (fixed) | 3.75 [0.42, 33.35] |
| Serious adverse events | 1 | 531 | RR (fixed) | 
| Malignancy – all | 1 | 531 | RR (fixed) | 
| Malignancy – skin cancer excluding melanoma | 1 | 531 | RR (fixed) | 
| Malignancy – all cancer excluding non-melanoma skin cancer | 1 | 531 | RR (fixed) | 
| Serious infection | 1 | 531 | RR (fixed) | 
| Any infection | 1 | 531 | RR (fixed) | 

Shaded cells indicate statistically significant result at P<0.05
**Adalimumab versus placebo**

Five trials\textsuperscript{108-111,115} included a comparison of adalimumab with placebo at licensed dose (or equivalent). Three additional trials\textsuperscript{112-114} included this comparison at above or under licensed doses. The results of primary analyses (licensed dose only) for the comparison between adalimumab and placebo are summarised in Table 4. Forest plots for the ACR20, ACR50, ACR70, HAQ, serious adverse events and malignancy are shown in the upper parts of Figure 2 to Figure 11, respectively.

**Efficacy**

Adalimumab at licensed dose is significantly more effective than placebo for all the efficacy outcomes included in the meta-analyses.

**Tolerability**

Significantly \textbullseye{} patients withdraw for any reasons and for lack of efficacy in the adalimumab group compared to placebo group. Slightly more patients withdraw due to adverse events in the adalimumab but these do not reach statistical significance.

**Safety**

Adalimumab is associated with a slight, but significantly increased, risk of any infection compared to placebo. It also appears to be associated with increased risk of death, malignancy, serious infections, although these do not reach statistical significance. No difference in the risk of serious adverse events was observed.

**Sensitivity analyses**

Results of sensitivity analyses that included licensed dose and above, and all doses, are listed in Table 63 – Page 238 and Table 64 – Page 239, Appendix 3 – Page 237. The results are in the same direction and very similar to the primary analysis. The increase in serious infection becomes statistically significant.
Table 4 Meta-analyses – Adalimumab s.c. licensed dose only vs. placebo (with or without ongoing conventional DMARDs), end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RR (fixed)</td>
<td>2.11 [1.84, 2.42]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RR (fixed)</td>
<td>3.58 [2.81, 4.58]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RR (fixed)</td>
<td>5.22 [3.45, 7.89]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RD (fixed)</td>
<td>0.28 [0.24, 0.32]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RD (fixed)</td>
<td>0.24 [0.20, 0.27]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1854</td>
<td>RD (random)</td>
<td>0.13 [0.09, 0.17]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1851</td>
<td>WMD (fixed)</td>
<td>-5.14 [-6.07, -4.21]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1850</td>
<td>WMD (fixed)</td>
<td>-1.62 [-1.89, -1.35]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1850</td>
<td>WMD (fixed)</td>
<td>-0.31 [-0.36, -0.26]</td>
</tr>
<tr>
<td>DAS28, mean change from baseline</td>
<td>2¹⁰⁹,¹¹⁵</td>
<td>476</td>
<td>WMD (fixed)</td>
<td>-1.12 [-1.37, -0.86]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1¹¹⁰</td>
<td>551</td>
<td>WMD (fixed)</td>
<td>-2.20 [-3.33, -1.07]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>1.37 [0.87, 2.16]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>2.02 [0.42, 9.59]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>1.05 [0.78, 1.41]</td>
</tr>
<tr>
<td>Death</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>3.44 [0.94, 12.60]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>2.11 [0.55, 8.06]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>2.92 [0.50, 17.13]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>2.35 [1.00, 5.53]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>1.18 [1.07, 1.29]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>5¹⁰⁸-¹¹¹,¹¹⁵</td>
<td>1861</td>
<td>RR (fixed)</td>
<td>2.35 [1.00, 5.53]</td>
</tr>
<tr>
<td>Any infection</td>
<td>4¹⁰⁸-¹¹¹</td>
<td>1719</td>
<td>RR (fixed)</td>
<td>1.18 [1.07, 1.29]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
Figure 2 ACR20 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

Review: Adalimumab for rheumatoid arthritis 2004
Comparison: 03 Adalimumab s.c. licensed dose only (40 mg every other week or equivalent) vs placebo, end of trial
Outcome: 01 ACR20 responder

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2003 (12 wks) (+)</td>
<td>36/71</td>
<td>7/70</td>
<td>1.92 [0.97, 3.82]</td>
<td>5.07 [2.42, 10.62]</td>
<td></td>
</tr>
<tr>
<td>van de Putte 2004 (26 wks) (+)</td>
<td>96/225</td>
<td>21/310</td>
<td>5.69 [2.23, 1.48, 3.36]</td>
<td>7.45 [2.67, 8.46]</td>
<td></td>
</tr>
<tr>
<td>STAR (24 wks) (+)</td>
<td>167/315</td>
<td>110/315</td>
<td>30.00 [2.12, 1.82]</td>
<td>4.55 [0.63, 0.76]</td>
<td></td>
</tr>
<tr>
<td>ARMADA (24 wks) (+)</td>
<td>49/97</td>
<td>9/62</td>
<td>5.35 [3.91, 8.57]</td>
<td>11.73 [2.37, 0.07]</td>
<td></td>
</tr>
<tr>
<td>Keystone 2004a (52 wks) (+)</td>
<td>238/419</td>
<td>48/200</td>
<td>59.30 [2.11, 1.84, 2.42]</td>
<td>56.90 [2.11, 1.84, 2.42]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1597</td>
<td>757</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 582 (Adalimumab), 105 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 23.64, df = 4 (P &lt; 0.0001), I² = 83.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 12.70 (P &lt; 0.00001), I² = 83.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.02 With concurrent, newly initiated MTX (adalimumab + MTX vs. MTX)
PREMIER [104 wks] (+) | 186/268 | 144/257 | 25.94 [0.33, 0.40] |
Subtotal (95% CI) | 268 | 257 | |
Test for heterogeneity: Chi² = 24.63, df = 4 (P < 0.0001), I² = 83.8% |
Test for overall effect: Z = 10.70 (P < 0.00001), I² = 83.8% |

<table>
<thead>
<tr>
<th>Outcome: 01 ACR20 responder</th>
</tr>
</thead>
</table>

Figure 3 ACR20 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

Review: Adalimumab for rheumatoid arthritis 2004
Comparison: 03 Adalimumab s.c. licensed dose only (40 mg every other week or equivalent) vs placebo, end of trial
Outcome: 01 ACR20 responder

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RD (fixed) 95% CI</th>
<th>Weight %</th>
<th>RD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2003 (12 wks) (+)</td>
<td>36/71</td>
<td>7/70</td>
<td>6.23 [0.23, 0.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2004 (26 wks) (+)</td>
<td>96/225</td>
<td>21/310</td>
<td>13.07 [0.24, 0.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR (24 wks) (+)</td>
<td>167/315</td>
<td>110/315</td>
<td>27.86 [0.18, 0.26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARMADA (24 wks) (+)</td>
<td>49/97</td>
<td>9/62</td>
<td>5.70 [0.53, 0.67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keystone 2004a (52 wks) (+)</td>
<td>238/419</td>
<td>48/200</td>
<td>23.94 [0.32, 0.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1597</td>
<td>757</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 582 (Adalimumab), 105 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 34.78, df = 5 (P &lt; 0.00001), I² = 85.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 11.04 (P &lt; 0.00001), I² = 85.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.02 With concurrent, newly initiated MTX (adalimumab + MTX vs. MTX)
PREMIER [104 wks] (+) | 186/268 | 144/257 | 23.20 [0.13, 0.22] |
Subtotal (95% CI) | 268 | 257 | |
Test for heterogeneity: Chi² = 25.01, df = 5 (P < 0.00001), I² = 85.6% |
Test for overall effect: Z = 11.04 (P < 0.00001), I² = 85.6% |
### Figure 4 ACR50 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

Review: Adalimumab for rheumatoid arthritis 2004
Comparison: 03 Adalimumab s.c. licensed dose only (40 mg every other week or equivalent) vs placebo, end of trial

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>Weight</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR [24 wks] (+)</td>
<td>11/215</td>
<td>55/315</td>
<td>0.20 [0.12, 0.32]</td>
<td>5.32</td>
<td>0.20 [0.12, 0.32]</td>
</tr>
<tr>
<td>Keystone 2004a [52 wks] (+)</td>
<td>166/419</td>
<td>18/200</td>
<td>13.44 [4.17, 42.68]</td>
<td>5.32</td>
<td>13.44 [4.17, 42.68]</td>
</tr>
<tr>
<td>Subtotal (95%) CI</td>
<td></td>
<td></td>
<td>1109</td>
<td>705</td>
<td></td>
</tr>
<tr>
<td>Total events: 360 (Adalimumab), 69 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for heterogeneity: Chi² = 50.80, df = 5 (P &lt; 0.00001), I² = 90.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>02 With concurrent, newly initiated MTX (adalimumab + MTX vs MTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIER [104 wks] (+)</td>
</tr>
<tr>
<td>Subtotal (95%) CI</td>
</tr>
<tr>
<td>Total events: 518 (Adalimumab), 179 (Control)</td>
</tr>
</tbody>
</table>

### Figure 5 ACR50 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

Review: Adalimumab for rheumatoid arthritis 2004
Comparison: 03 Adalimumab s.c. licensed dose only (40 mg every other week or equivalent) vs placebo, end of trial

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RD (fixed) 95% CI</th>
<th>Weight</th>
<th>RD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2004 [12 wks] (-)</td>
<td>17/71</td>
<td>1/70</td>
<td>16.76 [2.29, 122.56]</td>
<td>5.32</td>
<td>16.76 [2.29, 122.56]</td>
</tr>
<tr>
<td>STAR [24 wks] (+)</td>
<td>42/315</td>
<td>35/315</td>
<td>18.29 [1.84, 3.75]</td>
<td>5.32</td>
<td>18.29 [1.84, 3.75]</td>
</tr>
<tr>
<td>Keystone 2004a [52 wks] (+)</td>
<td>166/419</td>
<td>18/200</td>
<td>13.44 [4.17, 42.68]</td>
<td>5.32</td>
<td>13.44 [4.17, 42.68]</td>
</tr>
<tr>
<td>Subtotal (95%) CI</td>
<td>1109</td>
<td>705</td>
<td>41.30 [2.91, 4.58]</td>
<td>5.32</td>
<td>41.30 [2.91, 4.58]</td>
</tr>
<tr>
<td>Total events: 360 (Adalimumab), 69 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 13.33 (P &lt; 0.00001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>02 With concurrent, newly initiated MTX (adalimumab + MTX vs MTX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIER [104 wks] (+)</td>
</tr>
<tr>
<td>Subtotal (95%) CI</td>
</tr>
<tr>
<td>Total events: 518 (Adalimumab), 179 (Control)</td>
</tr>
</tbody>
</table>

For a natural reading, the data presents outcomes of ACR50 responder rate for Adalimumab vs placebo, including comparisons with and without concurrent MTX. The results show statistically significant improvements in response rates for Adalimumab compared to placebo, with broad confidence intervals and Z-scores indicating statistical significance.
**Figure 6 ACR70 RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2003 [12 wks] (+)</td>
<td>25/225</td>
<td>2/110</td>
<td>6.23</td>
<td>0.31 [0.04, 0.19]</td>
<td></td>
</tr>
<tr>
<td>STAR [24 wks] (+)</td>
<td>47/515</td>
<td>20/515</td>
<td>13.07</td>
<td>0.09 [0.04, 0.14]</td>
<td></td>
</tr>
<tr>
<td>ARMADA [24 wks] (+)</td>
<td>18/67</td>
<td>3/62</td>
<td>27.86</td>
<td>0.12 [0.07, 0.18]</td>
<td></td>
</tr>
<tr>
<td>Keystone 2004a [52 wks] (+)</td>
<td>92/419</td>
<td>8/200</td>
<td>2.61</td>
<td>0.61 [0.47, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1107</td>
<td>757</td>
<td>27.66</td>
<td>5.22 [3.49, 7.89]</td>
<td></td>
</tr>
<tr>
<td>Total events: 100 (Adalimumab), 24 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.84, df = 4 (P = 0.93), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 10.47 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 With concurrent, newly initiated MTX (adalimumab + MTX vs MTX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREMIER [104 wks] (+)</td>
<td>125/268</td>
<td>73/257</td>
<td>23.94</td>
<td>0.17 [0.13, 0.22]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1365</td>
<td>1104</td>
<td>25.60</td>
<td>0.14 [0.11, 0.18]</td>
<td></td>
</tr>
<tr>
<td>Total events: 315 (Adalimumab), 97 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 26.59, df = 5 (P &lt; 0.0001), I² = 81.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 10.62 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 7 ACR70 RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Adalimumab</th>
<th>Control</th>
<th>RD (fixed)</th>
<th>Weight</th>
<th>RD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Putte 2003 [12 wks] (+)</td>
<td>8/71</td>
<td>0/70</td>
<td>0.49</td>
<td>16.76 [6.09, 28.00]</td>
<td></td>
</tr>
<tr>
<td>STAR [24 wks] (+)</td>
<td>47/515</td>
<td>20/515</td>
<td>2.61</td>
<td>6.11 [1.47, 25.34]</td>
<td></td>
</tr>
<tr>
<td>ARMADA [24 wks] (+)</td>
<td>18/67</td>
<td>3/62</td>
<td>5.70</td>
<td>5.55 [1.79, 17.93]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1107</td>
<td>757</td>
<td>27.66</td>
<td>5.22 [3.49, 7.89]</td>
<td></td>
</tr>
<tr>
<td>Total events: 100 (Adalimumab), 24 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 8.13, df = 4 (P = 0.05), I² = 53.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.83 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 With concurrent, newly initiated MTX (adalimumab + MTX vs MTX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREMIER [104 wks] (+)</td>
<td>125/268</td>
<td>73/257</td>
<td>72.34</td>
<td>1.64 [1.30, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1365</td>
<td>1104</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 8 HAQ change – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)
(Confidential information removed)

Figure 9 Serious adverse events RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)
(Confidential information removed)
Figure 10 Serious adverse events RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

(Confidential information removed)

Figure 11 Malignancy RR – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)

(Confidential information removed)
Figure 12 Malignancy RD – Adalimumab licensed dose vs. placebo (including adalimumab + MTX vs. MTX)
(Confidential information removed)

Adalimumab + MTX versus MTX alone

Only the PREMIER\textsuperscript{102} trial included this comparison in MTX naïve, early RA, patients and the results are summarised in Table 5 below. The outcomes for ACR20, ACR50, ACR70, HAQ, serious adverse events, and malignancy are also displayed in the lower parts of Figure 2 to Figure 12 above.

Efficacy

The combination of adalimumab + MTX is more effective than MTX alone

Tolerability

Compared with MTX alone, the combination was associated with significantly withdrawal due to lack of efficacy and withdrawals for any reason. The combination was associated with a statistically non-significant increase in withdrawal due to adverse events.
Safety

The only statistically significant difference between the combination and MTX monotherapy among the safety outcomes meta-analysed is

There is also a non-significant increase in serious infection in the combination group compared to MTX group (RR = [redacted])
Table 5 Summary of 2-year results from PREMIER study – Combination of adalimumab (licensed dose only) + MTX vs. MTX alone in MTX naïve patients

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>1.24 [1.08, 1.42]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>1.38 [1.16, 1.64]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>1.64 [1.30, 2.07]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>525</td>
<td>RD (fixed)</td>
<td>0.13 [0.05, 0.22]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>525</td>
<td>RD (fixed)</td>
<td>0.16 [0.08, 0.25]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>525</td>
<td>RD (fixed)</td>
<td>0.18 [0.10, 0.26]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>1</td>
<td>369</td>
<td>WMD (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>1</td>
<td>366</td>
<td>WMD (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>1</td>
<td>367</td>
<td>WMD (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>DAS28, mean change from baseline</td>
<td>1</td>
<td>352</td>
<td>WMD (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1</td>
<td>525</td>
<td>WMD (fixed)</td>
<td>-8.50 [-]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>0.71 [0.54, 0.93]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>0.96 [0.06, 15.25]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>0.48 [0.09, 2.60]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
<tr>
<td>Any infection</td>
<td>1</td>
<td>525</td>
<td>RR (fixed)</td>
<td>-</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
3.2.3 Etanercept

3.2.3.1 Description of included etanercept trials

Eleven trials comprising a total of 3717 patients (3659 actually treated) were included. Clinical study reports were provided by Wyeth for ten of the studies: Moreland 1996116; Moreland 1997117; Moreland 1999118; ERA119, 120 Weinblatt 1999121; Wajdula 2000122; Codreanu 2003103; TEMPO123, 124; Keystone 2004b125; Baumgartner 2004.104 Additional data from these reports were included in this systematic review. The report by Lan et al126 was only available as a published paper.

A list of these trials, including comparators and baseline patient characteristics are shown in Table 6. Quality assessments of these trials, which are generally of high quality, are summarised in Table 7. In all trials, except Baumgartner 2004104, patients had active disease defined according to a number of tender and swollen joints and other parameters such as ESR and CRP. All patients met agreed disease classification criteria. Stable doses of oral prednisolone (≤10 mg/day) and NSAIDs were allowed. With the exception of the trial by Baumgartner et al104, patients with recent history of infection and significant comorbidity were excluded. Only one trial, ERA119, 120 recruited exclusively early RA patients. Key features for each of the studies are described below.
### Table 6 Included studies for etanercept and baseline patient characteristics

<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions$^a$</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Mean baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol 16.0002</strong></td>
<td><strong>Moreland et al 1996</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA, single centre, double-blind</td>
<td>Placebo single i.v. injection followed by s.c. injection twice weekly</td>
<td>4</td>
<td>54</td>
<td>19.8</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Etanercept 4 mg/m² single i.v. injection followed by 2 mg/m² s.c. injection twice weekly</td>
<td>3</td>
<td>56</td>
<td>5.3</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Etanercept 8 mg/m² single i.v. injection followed by 4 mg/m² s.c. injection twice weekly</td>
<td>3</td>
<td>38</td>
<td>4.3</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Etanercept 16 mg/m² single i.v. injection followed by 8 mg/m² s.c. injection twice weekly</td>
<td>3</td>
<td>53</td>
<td>4.7</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Etanercept 32 mg/m² single i.v. injection followed by 16 mg/m² s.c. injection twice weekly</td>
<td>3</td>
<td>62</td>
<td>6.3</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Protocol 16.0004</strong></td>
<td><strong>Moreland et al 1997</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA, multicentre, double-blind</td>
<td>Placebo s.c. twice weekly</td>
<td>44</td>
<td>55</td>
<td>71%&gt;5yr</td>
<td>34%</td>
<td>66%</td>
<td>73%</td>
<td>146$^c$</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 0.25 mg/m² twice weekly</td>
<td>46</td>
<td>54</td>
<td>76%&gt;5yr</td>
<td>MTX$^b$</td>
<td>59%</td>
<td>70%</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 2 mg/m² twice weekly</td>
<td>46</td>
<td>52</td>
<td>80%&gt;5yr</td>
<td>41% MTX</td>
<td>65%</td>
<td>80%</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 16 mg/m² twice weekly</td>
<td>44</td>
<td>52</td>
<td>80%&gt;5yr</td>
<td>30% MTX</td>
<td>77%</td>
<td>75%</td>
<td>135</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions*</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Mean baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol 16.0009</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moreland <em>et al</em> 1999</td>
<td>Placebo s.c. twice weekly</td>
<td>80</td>
<td>51</td>
<td>12</td>
<td>3.0</td>
<td>58%</td>
<td>84%</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 10 mg twice weekly</td>
<td>76</td>
<td>53</td>
<td>13</td>
<td>3.4</td>
<td>66%</td>
<td>67%</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly</td>
<td>78</td>
<td>53</td>
<td>11</td>
<td>3.3</td>
<td>81%</td>
<td>67%</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Protocol 16.0012</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERA, Bathan <em>et al</em> 2000; Genovese <em>et al</em> 2002</td>
<td>MTX (starting 7.5 and escalating to 20 mg/week by week 8; mean 19 mg/week) + placebo</td>
<td>217</td>
<td>49</td>
<td>1.0</td>
<td>0.6</td>
<td>41%</td>
<td>80%</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 10 mg twice weekly + placebo</td>
<td>208</td>
<td>50</td>
<td>0.9</td>
<td>0.5</td>
<td>42%</td>
<td>76%</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly + placebo</td>
<td>207</td>
<td>51</td>
<td>1.0</td>
<td>0.5</td>
<td>39%</td>
<td>86%</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Protocol 16.0014</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinblatt <em>et al</em> 1999</td>
<td>Placebo + ongoing MTX (12.5-25 mg/week; mean 18 mg/week)</td>
<td>30</td>
<td>53</td>
<td>13</td>
<td>2.8</td>
<td>70%</td>
<td>80%</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly + ongoing MTX (12.5-25 mg/week; mean 19 mg/week)</td>
<td>59</td>
<td>48</td>
<td>13</td>
<td>2.7</td>
<td>53%</td>
<td>75%</td>
<td>1.5</td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventions¹</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>No. of previous DMARDs</td>
<td>On steroids</td>
<td>On NSAIDs</td>
<td>Mean baseline HAQ score</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Protocol 0881A1-300-EU Wajdula 2000¹²² (The European Etanercept Investigators Group)</td>
<td>Placebo s.c. twice weekly</td>
<td>105</td>
<td>53</td>
<td>7.2</td>
<td>3.5</td>
<td>71%</td>
<td>85%</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 10 mg once weekly</td>
<td>122</td>
<td>53</td>
<td>6.9</td>
<td>3.2</td>
<td>77%</td>
<td>82%</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 10 mg twice weekly</td>
<td>110</td>
<td>54</td>
<td>6.8</td>
<td>3.0</td>
<td>71%</td>
<td>86%</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg once weekly</td>
<td>111</td>
<td>54</td>
<td>7.3</td>
<td>3.3</td>
<td>68%</td>
<td>83%</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly</td>
<td>111</td>
<td>53</td>
<td>7.5</td>
<td>3.6</td>
<td>70%</td>
<td>86%</td>
<td>1.8</td>
</tr>
<tr>
<td>Protocol 0881A1-309 Codreanu et al 2003¹⁰³</td>
<td>Sulfasalazine 2-3 g/day + placebo</td>
<td>50</td>
<td>53</td>
<td>5.6</td>
<td>2.1</td>
<td>32%</td>
<td>86%</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly + placebo</td>
<td>103</td>
<td>51</td>
<td>7.1</td>
<td>2.7</td>
<td>50%</td>
<td>82%</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Etanercept s.c. 25 mg twice weekly + sulfasalazine 2-3 g/day</td>
<td>101</td>
<td>51</td>
<td>6.5</td>
<td>2.3</td>
<td>40%</td>
<td>83%</td>
<td>1.6</td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventions⁵</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>No. of previous DMARDs</td>
<td>On steroids</td>
<td>On NSAIDs</td>
<td>Mean baseline HAQ score</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------------------</td>
<td>-----------------------</td>
<td>------------</td>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Protocol 0881A1-308-EU/AU TEMPO, Klareskog et al 2004¹²³,¹²⁴</td>
<td>MTX (starting 7.5, escalating to 20 mg/week if any painful/swollen joint; mean 18) + placebo Etanercept s.c. 25 mg twice weekly + placebo Etanercept s.c. 25 mg twice weekly + MTX (starting 7.5, escalating to 20 mg/week if any painful/swollen joint; mean 18)</td>
<td>228</td>
<td>53</td>
<td>6.8</td>
<td>2.3</td>
<td>64%</td>
<td>86%</td>
<td>1.7</td>
</tr>
<tr>
<td>Protocol 16.0036, Keystone et al 2004b¹²⁵</td>
<td>Placebo (55% with ongoing MTX, mean 14 mg/week) Etanercept s.c. 25 mg twice weekly (52% with ongoing MTX, mean 15 mg/week) Etanercept s.c. 50 mg once weekly (53% with ongoing MTX, mean 14 mg/week)</td>
<td>53</td>
<td>54</td>
<td>10.8</td>
<td>(Prior use)</td>
<td>89%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>153</td>
<td>52</td>
<td>8.2</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>214</td>
<td>53</td>
<td>9.0</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventionsa</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>No. of previous DMARDs</td>
<td>On steroids</td>
<td>On NSAIDs</td>
<td>Mean baseline HAQ score</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Protocol 0881A-100093</td>
<td>Placebo + MTX (12.5 – 20 mg / week)</td>
<td>29</td>
<td>51</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.2</td>
</tr>
<tr>
<td>Lan et al 2004126</td>
<td>Etanercept s.c. 25 mg twice weekly + MTX (same above)</td>
<td>29</td>
<td>48</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1.0</td>
</tr>
<tr>
<td>Taiwan, single centre, double-blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment &amp; follow-up: 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol 16.0029</td>
<td>Placebo s.c. twice weekly</td>
<td>269</td>
<td>60</td>
<td>10</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Baumgartner et al 2004184</td>
<td>Etanercept s.c. 25 mg twice weekly</td>
<td>266</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA, multicentre, double-blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment: 16 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up: 20 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Some of the groups receiving active treatment also received matching placebo (where necessary) to maintain blinding. These placebo injections are not listed.
bAll patients had received at least one previous DMARD but details are not reported. The values shown are percentages using methotrexate.
cOn this scale, 45 is best and 245 worst.
dThe placebo group switched to etanercept 25 mg twice weekly from week 8 and all treatment groups were followed up to week 16. The results from week 8 onwards are not included in current review.
### Table 7 Quality of included studies - etanercept

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Truly random allocation/ Remain on randomised treatment</th>
<th>Adequate allocation concealment</th>
<th>Blinding: Participants</th>
<th>Investigators</th>
<th>Assessors</th>
<th>Important differences in baseline characteristics between groups (% randomised patients completed)</th>
<th>Important differences in completion rates between groups (% randomised patients completed)</th>
<th>Use of intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreland 1996</td>
<td>Placebo:4 Etanercept: 12</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Sample size too small</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Moreland 1997</td>
<td>Placebo: 44 Etanercept: 136</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Placebo: 52% Etanercept: 76%</td>
</tr>
<tr>
<td>Moreland 1999</td>
<td>Placebo: 80 Etanercept: 154</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (concurrent steroids and NSAIDs)</td>
<td>Yes</td>
<td>Placebo: 33% Etanercept: 72%</td>
</tr>
<tr>
<td>ERA</td>
<td>MTX: 217 Etanercept: 415</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>MTX: 79% Etanercept: 82%</td>
</tr>
<tr>
<td>ERA First 12 months</td>
<td>MTX: 169 Etanercept: 343</td>
<td>Yes</td>
<td>-</td>
<td>No</td>
<td>No</td>
<td>No (except radiograph readers)</td>
<td>No</td>
<td>Yes</td>
<td>MTX: 59% Etanercept: 69%</td>
</tr>
<tr>
<td>Genovese 2002</td>
<td>Placebo: 30 Etanercept: 59</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Placebo: 80% Etanercept: 97%</td>
</tr>
<tr>
<td>Weinblatt 1999</td>
<td>Placebo: 105 Etanercept: 454</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Placebo: 81% Etanercept: 93%</td>
</tr>
<tr>
<td>Study</td>
<td>Sample size</td>
<td>Truly random allocation/ Remain on randomised treatment</td>
<td>Adequate allocation concealment</td>
<td>Blinding: Participants</td>
<td>Investigators</td>
<td>Assessors</td>
<td>Important differences in baseline characteristics between groups (% randomised patients completed)</td>
<td>Important differences in completion rates between groups (% randomised patients completed)</td>
<td>Use of intention-to-treat analysis</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------</td>
<td>--------------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Codreanu 2003(^{103})</td>
<td>SSZ: 50 Etanercept: 103 Etanercept + SSZ: 101</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>SSZ: 66% Etanercept: 91% Etanercept + SSZ: 93%</td>
</tr>
<tr>
<td>TEMPO</td>
<td>MTX: 228 Etanercept: 223 Etanercept + MTX: 231</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>MTX: 70% Etanercept: 76% Etanercept + MTX: 84%</td>
</tr>
<tr>
<td>Week 52 to week 100(^{120})</td>
<td>MTX: Etanercept: Etanercept + MTX:</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>MTX: Etanercept: Etanercept + MTX:</td>
</tr>
<tr>
<td>Keystone 2004(^{125})</td>
<td>Placebo: 53 Etanercept: 367</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Placebo: 94% Etanercept: 96%</td>
</tr>
<tr>
<td>Lan 2004(^{126})</td>
<td>Placebo: 29 Etanercept: 29</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Baumgartner 2004(^{104})</td>
<td>Placebo: 269 Etanercept: 266</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Placebo: Etanercept:</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
Moreland and colleagues 1996\textsuperscript{116}
Results from this study are not included in meta-analyses because of very small patient numbers (3 to 4 patients in each treatment group), short duration and imbalances in baseline patient characteristics (Table 6).

Moreland and colleagues 1997\textsuperscript{117}
This double-blind, multicentre RCT compared three doses of etanercept (s.c. 0.25, 2, or 16 mg/m\textsuperscript{2} body surface area twice weekly) with placebo for three months. Patients who had failed up to four DMARDs and had at least 10 swollen joints and 12 tender joints were included. Primary efficacy measures were percentage change from baseline to three months in swollen joint count, tender joint count, and total count of swollen or tender joints.

Moreland and colleagues 1999\textsuperscript{118}
This 6-month double-blind, multicentre RCT compared etanercept 10 mg or 25 mg s.c. twice weekly with placebo. Patients who had failed up to four DMARDs were recruited. At least 10 swollen joints and 12 tender joints were required at entry. The primary efficacy end points were ACR20 and ACR50 response at three and six months.

Wajdula and colleagues 2000 (The European Etanercept Investigators Study)\textsuperscript{122}
This double-blind, multicentre RCT compared four etanercept treatment regimens (s.c. 10 mg once weekly, 10 mg twice weekly, 25 mg once weekly, 25 mg twice weekly) with placebo. This study was planned to run for 6 months but the protocol was modified to a 3-month double-blind study after inception for reasons that were unclear. Patients with at least six swollen joints and 12 tender joints, and who had failed to respond to at least one DMARD were recruited. The primary efficacy endpoints were change from baseline in the number of swollen and painful joints at three months.

Etanercept early RA (ERA) trial, Bathon and colleagues 2000 \textsuperscript{119}, Genovese and colleagues 2002\textsuperscript{120}
This multicentre RCT compared etanercept s.c.10 mg twice weekly or 25 mg twice weekly with placebo. There was a 12-month double-blind phase and a further 12 months open-label phase. Results at 2 years were provided by the manufacturer and are referred to as the end of study results in this review unless otherwise specified. Recruited patients had RA for less than
3 years, at least 10 swollen joints and 12 tender joints, and were positive for rheumatoid factor or had at least three bony erosions on radiographs of hands, feet and wrists. Patients who had previously been treated with methotrexate were not eligible. Patients on other DMARDs at recruitment had a 4-week washout before entry. Fifty-nine percent of patients had never received a DMARD.

The primary clinical endpoint was ACR-N area under the curve (AUC) during the first six months, and the primary radiological endpoint was the change in modified Sharp scores over 12 months.

This trial was originally designed to show superiority of etanercept over methotrexate in preventing joint damage. However this goal was changed to that of showing equivalence of etanercept and methotrexate.

**TEMPO, Klareskog and colleagues 2004, van der Heijde and colleagues 2005**

This multicentre trial consisted of two periods. Period one was a 52-week double-blind RCT, followed by a double-blind extension of variable duration during which patients remained on randomised treatment. Two-year results were provided by the manufacturer and are referred to as the end of study results unless otherwise specified. TEMPO compared methotrexate alone (7.5 mg/week escalated to 20 mg/week if any tender or swollen joints remained), etanercept alone (s.c. 25 mg twice weekly), and a combination of the two. RA patients who had previously received methotrexate were allowed to enter (at the discretion of the investigator) provided that methotrexate had not been used within 6 months of study entry, had not been discontinued for lack of efficacy and had not caused toxicity.

Patients with disease durations between six months and 20 years who had failed at least one DMARD other than methotrexate were recruited. At least 10 swollen joints and 12 tender joints were required. The primary clinical endpoint was the 24-week AUC of the ACR-N. The 52-week change from baseline in total Sharp score was a conditional primary endpoint.

TEMPO appears to be the only trial in established RA (not early RA) that genuinely compares a conventional DMARD with a TNF inhibitor. However around 42% of patients in each arm of this trial had previously tried methotrexate. It is not at all clear why these individuals
discontinued methotrexate in the face of active disease if, as stated in the entry criteria, the drug was not ineffective nor toxic.

**Codreanu and colleagues 2003**[^103]

There is only a published abstract[^103] for this multi-centre trial. The 24-week results were provided by the manufacturer and are referred to as the end of study results. The trial compared sulfasalazine alone (2-3 g/day), etanercept alone (s.c. 25 mg twice weekly), and the combination of both in RA patients who were not adequately controlled while having received sulfasalazine. The primary endpoint was ACR20 response at 24 weeks.

**Lan and colleagues 2004**[^126]

This was a single centre, 12-week RCT that compared etanercept (s.c. 25 mg twice weekly) to placebo in patients who had been receiving stable doses (12.5 to 20 mg/week) of methotrexate for at least four weeks. Patients with duration of RA longer than one year, with at least six swollen joints and six tender joints despite methotrexate treatment were recruited. The baseline HAQ score of the patients in this trial (average 1.1) was better than other etanercept trials. The primary endpoints were reduction in the number of swollen and tender joints from baseline to 12 weeks. Details of randomisation, allocation concealment and blinding were not described in the published paper and no trial report was made available.

**Keystone and colleagues 2004b**[^125]

This 16-week multicentre RCT compared s.c. etanercept 50 mg once weekly, s.c. etanercept 25 mg twice weekly, and placebo. Placebo treated patients received etanercept 25 mg twice weekly at eight weeks and thus results from week eight onwards were excluded from this review. Patients with at least six swollen joints and six tender joints were recruited. Patients were allowed to continue with stable doses of methotrexate (≤25 mg/week) but other DMARDs were not allowed. Approximately half of the patients in each treatment group were...
receiving concomitant methotrexate. The primary efficacy endpoint was the ACR20 response. Etanercept 50 mg once weekly was compared to placebo at week eight and the comparative efficacy of the two etanercept treatment regimens was also studied.

**Baumgartner and colleagues 2004**

This 16-week multicentre safety trial compared etanercept s.c. 25 mg twice weekly and placebo in adult RA patients, with at least one qualifying comorbid condition including diabetes, chronic obstructive pulmonary diseases and recent infections. Randomisation was stratified by presence of diabetes. Patients in this trial were older than those in other etanercept trials.

The overall prior and concurrent DMARD use was not reported, The primary endpoint was the incidence of medically important infections. No efficacy outcomes were measured.

The study was, however, terminated early due to the low incidence of medically important infections observed in the study.
3.2.3.2 Meta-analyses of etanercept trials

The principles of analysis and data presentation of etanercept trials are the same as those for adalimumab and are described in section 3.1.5. Two trials (TEMPO\textsuperscript{123} and Codreanu 2003\textsuperscript{103}) included three treatment arms which allow more than one comparison.

**Etanercept versus conventional DMARD**

Three trials (ERA trial\textsuperscript{119}, TEMPO\textsuperscript{123}, and Codreanu 2003\textsuperscript{103}) included comparisons between etanercept and a conventional DMARD. Only the ERA trial, however, allows a genuine head-to-head comparison between etanercept and MTX in early RA patients who were naïve to both treatments. Around 40\% of patients in TEMPO had previously taken methotrexate without experiencing treatment failure due to lack of efficacy or toxicity. This, in theory, could introduce bias in favour of MTX. These patients, however, had not continued the MTX treatment for at least six months prior to the study. The reasons for this and their potential impact on study results are not clear. The investigators performed subgroup analyses and found no significant interaction between previous use of MTX and treatment effects in terms of ACR responses, DAS and total Sharp score.\textsuperscript{123} The trial by Codreanu and colleagues (2003)\textsuperscript{103} recruited patients who had had an inadequate response to sulfasalazine, and thus this trial should not be regarded as a head-to-head comparison. This section therefore focuses on the results from ERA (Table 8) and TEMPO (Table 9). The outcomes for ACR20, ACR50, ACR70, HAQ, serious adverse events, and malignancy from all the three trials are also shown in the lower parts of Figure 13 to Figure 23.

**Efficacy**

Although the mean disease duration for the patients was only one year in the ERA trial compared with over six years in the TEMPO trial, the results from these two studies are remarkably similar – no statistical heterogeneity between the studies was found in any of the outcomes that were meta-analysed. Overall the results demonstrate that etanercept monotherapy is marginally more effective than methotrexate in improving RA symptoms and physical function. The differences between etanercept and MTX for ACR20 response and
modified sharp score are statistically significant in both studies, while the difference for ACR50 response is significant only in the TEMPO trial.

_Tolerability_

Etanercept monotherapy appears to be better tolerated than MTX monotherapy. Fewer patients withdrew either due to lack of efficacy or because of adverse events in etanercept treated groups.

_Safety_

No significant differences between etanercept and MTX were found.

_Subgroup analyses_

In addition to the subgroup analyses of prior use of MTX, extensive analyses were also performed in the TEMPO trial to explore potential interactions between disease duration and treatment effects.

_Codreanu 2003_\(^{103}\)

The comparison between etanercept and sulfasalazine in sulfasalazine partial responders/non-responders is summarised in Table 65 - Page 240, Appendix 3. The results resemble those observed in trials comparing etanercept and placebo (described in the following section), which show etanercept is significantly more effective and better tolerated.
Table 8 Summary of 2-year results from ERA study – Etanercept alone vs. MTX alone in MTX naïve patients
<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>1.22 [1.06, 1.40]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>1.16 [0.94, 1.44]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>1.23 [0.89, 1.70]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>424</td>
<td>RD (fixed)</td>
<td>0.13 [0.04, 0.22]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>424</td>
<td>RD (fixed)</td>
<td>0.07 [-0.03, 0.16]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>424</td>
<td>RD (fixed)</td>
<td>0.05 [-0.03, 0.14]</td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>1</td>
<td>424</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>1</td>
<td>424</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>1</td>
<td>424</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1</td>
<td>424</td>
<td>Not estimable</td>
<td>No data available</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline (1 year result)</td>
<td>1</td>
<td>417</td>
<td>WMD (fixed)</td>
<td>-0.97 [-1.65, -0.29]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>0.63 [0.48, 0.84]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>0.73 [0.40, 1.34]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>0.58 [0.32, 1.06]</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>3.14 [0.13, 76.75]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>No data available</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td>0.82 [0.31, 2.15]</td>
</tr>
<tr>
<td>Any infection</td>
<td>1</td>
<td>424</td>
<td>RR (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
### Table 9 Summary of 2-year results from TEMPO study – Etanercept alone vs. MTX alone in MTX naïve patients/responders

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td>1.28 [1.06, 1.54]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td>1.47 [1.15, 1.89]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td>1.46 [1.00, 2.14]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>451</td>
<td>RD (fixed)</td>
<td>0.12 [0.03, 0.21]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>451</td>
<td>RD (fixed)</td>
<td>0.14 [0.05, 0.23]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>451</td>
<td>RD (fixed)</td>
<td>0.08 [0.00, 0.15]</td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>1</td>
<td>451</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>1</td>
<td>451</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>1</td>
<td>451</td>
<td>WMD (fixed)</td>
<td>-0.10 [-0.23, 0.03]</td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1</td>
<td>451</td>
<td>WMD (fixed)</td>
<td>-0.10 [-0.11, -0.05]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline (1 year result)</td>
<td>1</td>
<td>424</td>
<td>WMD (fixed)</td>
<td>-2.28 [-4.11, -0.45]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>1</td>
<td>451</td>
<td>RR (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
### Figure 13 ACR20 RR – Etanercept licensed dose vs. other active treatment

#### Review:
Etanercept for rheumatoid arthritis 2004

#### Comparison:
03 Etanercept s.c. licensed dose only (25 mg twice weekly) vs other active treatment

#### Outcome:
01 ACR20 responder

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Partial responders to comparator DMARD (sulfasalazine)</td>
<td>126/223</td>
<td>101/228</td>
<td>40.98</td>
<td>1.28</td>
<td>1.04, 1.54</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>149/207</td>
<td>128/217</td>
<td>51.28</td>
<td>1.22</td>
<td>1.06, 1.40</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td>430</td>
<td>445</td>
<td>82.97</td>
<td>1.24</td>
<td>1.11, 1.39</td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.79 (P = 0.0002)</td>
<td>5.33</td>
<td>495</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 275 (Etanercept), 229 (Control)</td>
<td>90</td>
<td>103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.79 (P = 0.0002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 351 (Etanercept), 243 (Control)</td>
<td>126/223</td>
<td>101/228</td>
<td>41.98</td>
<td>0.13</td>
<td>0.04, 0.22</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>149/207</td>
<td>128/217</td>
<td>51.28</td>
<td>0.13</td>
<td>0.04, 0.22</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td>430</td>
<td>445</td>
<td>86.66</td>
<td>0.13</td>
<td>0.04, 0.18</td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.85 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Figure 14 ACR20 RD – Etanercept licensed dose vs. other active treatment

#### Review:
Etanercept for rheumatoid arthritis 2004

#### Comparison:
03 Etanercept s.c. licensed dose only (25 mg twice weekly) vs other active treatment

#### Outcome:
01 ACR20 responder

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RD (fixed)</th>
<th>Weight</th>
<th>RD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Partial responders to comparator DMARD (sulfasalazine)</td>
<td>126/223</td>
<td>101/228</td>
<td>44.68</td>
<td>0.12</td>
<td>0.03, 0.21</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>149/207</td>
<td>128/217</td>
<td>41.98</td>
<td>0.13</td>
<td>0.04, 0.22</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td>430</td>
<td>445</td>
<td>86.66</td>
<td>0.13</td>
<td>0.04, 0.18</td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.85 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 275 (Etanercept), 229 (Control)</td>
<td>90</td>
<td>103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.79 (P = 0.0002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 351 (Etanercept), 243 (Control)</td>
<td>126/223</td>
<td>101/228</td>
<td>41.98</td>
<td>0.13</td>
<td>0.04, 0.22</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>149/207</td>
<td>128/217</td>
<td>51.28</td>
<td>0.13</td>
<td>0.04, 0.22</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td>430</td>
<td>445</td>
<td>86.66</td>
<td>0.13</td>
<td>0.04, 0.18</td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.85 (P = 0.0001)</td>
<td>5.33</td>
<td>495</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 15 ACR50 RR – Etanercept licensed dose vs. other active treatment
(Confidential information removed)

Figure 16 ACR50 RD – Etanercept licensed dose vs. other active treatment
(Confidential information removed)

Figure 17 ACR70 RR – Etanercept licensed dose vs. other active treatment
(Confidential information removed)
Figure 18 ACR70 RD – Etanercept licensed dose vs. other active treatment
(Confidential information removed)

Figure 19 HAQ change – Etanercept licensed dose vs. other active treatment
(Confidential information removed)
Figure 20 Serious adverse events RR – Etanercept licensed dose vs. other active treatment
(Confidential information removed)

Figure 21 Serious adverse events RD – Etanercept licensed dose vs. other active treatment
(Confidential information removed)
Figure 22 Malignancy RR – Etanercept licensed dose vs. other active treatment
(Confidential information removed)

Figure 23 Malignancy RD – Etanercept licensed dose vs. other active treatment
(Confidential information removed)
Etanercept versus placebo

Eight trials\textsuperscript{104,117,118,121,122,125,126} compared etanercept at licensed dose (or equivalent) to placebo. Three of the trials\textsuperscript{117,118,122} also included sub-licensed doses. No trial included above licensed dose. Results of the primary analyses (licensed dose) are summarised in Table 10, and are also shown in the upper parts of Figure 24 to Figure 33.

Efficacy

Etanercept was significantly more effective than placebo. Figure 24 shows a pattern of decreasing effect size for ACR20 in terms of relative risk in trials in which patients: (1) were not receiving any concurrent DMARDs; (2) were receiving concurrent DMARDs which had failed to provide adequate disease control; and (3) were receiving concurrent, newly initiated methotrexate. This pattern, however, is not clearly observed for other outcome measures, nor is it observed in trials of other TNF inhibitors.

Tolerability

Etanercept is better tolerated than placebo.

Safety

There were no significant differences between etanercept and placebo. In the trial by Baumgartner et al (2004),\textsuperscript{104} which recruited patients with comorbidity, five deaths occurred in etanercept arm compared to one in the placebo arm.
Sensitivity analysis

Results of sensitivity analysis which included sub-licensed doses are summarised in Table 66, page 242, Appendix 3. These are consistent with the primary analysis.
Table 10 Meta-analyses – Etanercept s.c. licensed dose only vs. placebo (with or without ongoing conventional DMARDs), end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>7</td>
<td>1172</td>
<td>RR (fixed)</td>
<td>3.59 [2.89, 4.46]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>7</td>
<td>1172</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>6</td>
<td>1084</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>7</td>
<td>1172</td>
<td>RD (fixed)</td>
<td>0.48 [0.42, 0.53]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>7</td>
<td>1172</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>6</td>
<td>1084</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>7</td>
<td>1178</td>
<td>WMD (random)</td>
<td>-6.75 [-8.95, -4.56]</td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>7</td>
<td>1178</td>
<td>WMD (fixed)</td>
<td>-2.49 [-2.74, -2.24]</td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>6</td>
<td>1055</td>
<td>WMD (fixed)</td>
<td>-0.50 [-0.59, -0.42]</td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1</td>
<td>150</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>No data available</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>7</td>
<td>1657</td>
<td>RR (fixed)</td>
<td>0.37 [0.29, 0.46]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>6</td>
<td>1237</td>
<td>RR (fixed)</td>
<td>0.19 [0.13, 0.28]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>7</td>
<td>1657</td>
<td>RR (fixed)</td>
<td>0.80 [0.49, 1.30]</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>1657</td>
<td>RR (fixed)</td>
<td>2.22 [0.50, 9.80]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5</td>
<td>1353</td>
<td>RR (fixed)</td>
<td>1.25 [0.75, 2.08]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>6</td>
<td>1569</td>
<td>RR (fixed)</td>
<td>0.44 [0.11, 1.68]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>6</td>
<td>1569</td>
<td>RR (fixed)</td>
<td>0.98 [0.17, 5.59]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>6</td>
<td>1569</td>
<td>RR (fixed)</td>
<td>0.19 [0.02, 1.71]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>7</td>
<td>1627</td>
<td>RR (fixed)</td>
<td>0.78 [0.37, 1.62]</td>
</tr>
<tr>
<td>Any infection</td>
<td>6</td>
<td>1569</td>
<td>RR (fixed)</td>
<td>1.00 [0.87, 1.14]</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
Shaded cells indicate statistically significant result at P<0.05

Figure 24 ACR20 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waddula 2000 [12 wks] (-)</td>
<td>76/109</td>
<td>12/100</td>
<td>15.23</td>
<td>5.50 [3.37, 9.02]</td>
<td></td>
</tr>
<tr>
<td>Keystone 2004b [8 wks] (+/-)</td>
<td>182/367</td>
<td>10/53</td>
<td>5.43</td>
<td>2.63 [1.49, 4.64]</td>
<td></td>
</tr>
<tr>
<td>Lan 2004 [12 wks] (+)</td>
<td>26/129</td>
<td>10/29</td>
<td>5.38</td>
<td>2.60 [1.55, 4.36]</td>
<td></td>
</tr>
<tr>
<td>Weinblatt 1996 [24 wks] (+)</td>
<td>42/59</td>
<td>8/30</td>
<td>5.71</td>
<td>2.67 [1.44, 4.94]</td>
<td></td>
</tr>
<tr>
<td>Codreanu 2003 [24 wks] (+)</td>
<td>14/100</td>
<td>14/50</td>
<td>10.05</td>
<td>2.64 [1.67, 4.18]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>786</td>
<td>386</td>
<td>46.29</td>
<td>3.59 [2.89, 4.46]</td>
<td></td>
</tr>
<tr>
<td>Total events: 479 (Etanercept), 69 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 11.95 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 40.99, df = 7 (P &lt; 0.00001), I² = 82.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

02 With concurrent, newly initiated MTX (etanercept + MTX vs MTX)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>RR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>TEMPO [100 wks] (+)</td>
<td>152/231</td>
<td>101/228</td>
<td>54.72</td>
<td>1.49 [1.25, 1.77]</td>
<td></td>
</tr>
<tr>
<td>Total events: 152 (Etanercept), 101 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.49 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 25 ACR20 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RD (fixed)</th>
<th>Weight</th>
<th>RD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 With (+) or without (-) concurrent, ongoing conventional DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moreland 1997 [12 wks] (-)</td>
<td>152/231</td>
<td>101/228</td>
<td>6.42</td>
<td>0.61 [0.45, 0.78]</td>
<td></td>
</tr>
<tr>
<td>Waddula 2000 [12 wks] (-)</td>
<td>76/109</td>
<td>12/100</td>
<td>15.23</td>
<td>0.58 [0.47, 0.68]</td>
<td></td>
</tr>
<tr>
<td>Moreland 1998 [20 wks] (-)</td>
<td>46/78</td>
<td>9/60</td>
<td>11.53</td>
<td>0.48 [0.35, 0.61]</td>
<td></td>
</tr>
<tr>
<td>Keystone 2004b [8 wks] (+/-)</td>
<td>182/367</td>
<td>10/53</td>
<td>15.52</td>
<td>0.31 [0.19, 0.42]</td>
<td></td>
</tr>
<tr>
<td>Lan 2004 [12 wks] (+)</td>
<td>26/129</td>
<td>10/29</td>
<td>4.23</td>
<td>0.55 [0.35, 0.76]</td>
<td></td>
</tr>
<tr>
<td>Weinblatt 1996 [24 wks] (+)</td>
<td>42/59</td>
<td>8/30</td>
<td>5.81</td>
<td>0.45 [0.25, 0.64]</td>
<td></td>
</tr>
<tr>
<td>Codreanu 2003 [24 wks] (+)</td>
<td>14/100</td>
<td>14/50</td>
<td>9.73</td>
<td>0.46 [0.31, 0.61]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>786</td>
<td>386</td>
<td>66.49</td>
<td>0.46 [0.32, 0.53]</td>
<td></td>
</tr>
<tr>
<td>Total events: 479 (Etanercept), 69 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 14.77, df = 6 (P &lt; 0.02), P = 59.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 14.77 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

02 With concurrent, newly initiated MTX (etanercept + MTX vs MTX)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Etanercept</th>
<th>Control</th>
<th>RD (fixed)</th>
<th>Weight</th>
<th>RD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>TEMPO [100 wks] (+)</td>
<td>152/231</td>
<td>101/228</td>
<td>33.51</td>
<td>0.22 [0.13, 0.30]</td>
<td></td>
</tr>
<tr>
<td>Total events: 152 (Etanercept), 101 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.74 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
Figure 26 ACR50 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)

Figure 27 ACR50 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)
Figure 28 ACR70 RR – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)

Figure 29 ACR70 RD – Etanercept licensed dose vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)
Figure 30 HAQ change – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)

Figure 31 Serious adverse events RR – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)
Figure 32 Serious adverse events RD – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)

Figure 33 Malignancy RR – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)
Figure 34 Malignancy RD – Etanercept licensed dose only vs. placebo (including etanercept + MTX vs. MTX)
(Confidential information removed)

Etanercept + MTX versus MTX
Only the TEMPO trial\textsuperscript{123} included this comparison and the results are summarised in Table 11 and are also shown in the lower parts of Figure 24 to Figure 34.

Efficacy
The combination of etanercept + MTX was significantly more effective than MTX monotherapy.*

Tolerability
The combination was** patients withdrew due to lack of efficacy and for any reason in the combination group.

Safety
*the safety outcomes being meta-analysed. Nevertheless, serious adverse events and malignancy occurred**
<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td>1.49 [1.25, 1.77]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td>1.92 [1.52, 2.41]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td>2.53 [1.82, 3.54]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>459</td>
<td>RD (fixed)</td>
<td>0.22 [0.13, 0.30]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>459</td>
<td>RD (fixed)</td>
<td>0.27 [0.19, 0.36]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>459</td>
<td>RD (fixed)</td>
<td>0.25 [0.17, 0.33]</td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>1</td>
<td>459</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Patients’ global assessment, end of study result</td>
<td>1</td>
<td>459</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>1</td>
<td>459</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1</td>
<td>459</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline (1 year result)</td>
<td>1</td>
<td>430</td>
<td>WMD (fixed)</td>
<td>-3.34 [-5.12, -1.56]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin</td>
<td>1</td>
<td>459</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>cancer</td>
<td></td>
<td>RR (fixed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---</td>
<td>--------------</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>1</td>
<td>459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>1</td>
<td>459</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at $P<0.05$
3.2.4 Infliximab

3.2.4.1 Description of included infliximab trials

Nine trials comprising a total of 2835 patients (2823 actually treated) were included in meta-analyses. A pre-publication manuscript of the BeSt study was made available by the investigators but did not meet our inclusion criteria. However because of its importance it is described in detail, but the data are not used in meta-analyses. Clinical study reports were provided by Schering-Plough for three of the studies: (ATTRACT128-130, ASPIRE131, and START105). Additional data from these reports were included in this systematic review. Data were available only from published papers for the remaining six studies (Elliott 1994132, Maini 1998133, Kavanaugh 2000134, Durez 2004135, Taylor 2004136, and Quinn 2005137).

Treatment comparators and baseline patient characteristics are shown in Table 12. Quality assessments of trials are summarised in Table 13. In most trials active RA was defined by six or more swollen joints (10 for ASPIRE) with additional criteria related to tender joints, ESR, CRP and morning stiffness. Taylor 2004136 and Quinn 2005137 focused on ultrasonographic and MRI outcomes respectively. Low dose oral steroids (<10 mg/day prednisolone) and NSAIDs were allowed at stable doses. DMARDs other than methotrexate were not allowed except in the START trial.105 Three trials (ASPIRE131, Taylor 2004136 and Quinn 2005137) recruited exclusively early RA patients. Key features for studies that included the licensed dose of infliximab are described below.
### Table 12 Description of included randomised controlled trials and baseline patient characteristics – infliximab

<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs (mean)</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elliott et al 1994</strong></td>
<td>Placebo (single i.v. infusion 0.1% albumin)</td>
<td>24</td>
<td>48</td>
<td>9.0</td>
<td>3.7</td>
<td>Not</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Europe, 4 centres, double-blind</td>
<td>Infliximab single i.v. infusion 1 mg/kg</td>
<td>25</td>
<td>56</td>
<td>7.5</td>
<td>2.8</td>
<td>Not</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Infliximab treatment:</td>
<td>Infliximab single i.v. infusion 10 mg/kg</td>
<td>24</td>
<td>51</td>
<td>7.3</td>
<td>3.1</td>
<td>Not</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

<p>| <strong>Maini et al 1998</strong> | Placebo (i.v. 0.1% albumin) + MTX 7.5 mg/week | 14 | 49 | 7.6 | 2 | 50% | Not | Not reported | Not reported |
| Europe, 6 centres, double-blind | Infliximab i.v. 1 mg/kg + MTX 7.5 mg/week | 14 | 54 | 14.3 | 2 | 43% | Not | Not reported | Not reported |
| Infliximab treatment: | Infliximab i.v. 1 mg/kg without MTX | 15 | 49 | 7.6 | 3 | 67% | Not | Not reported | Not reported |
| five infusions at | Infliximab i.v. 3 mg/kg | 14 | 47 | 7.8 | 2.5 | 50% | Not | Not reported | Not reported |
| | | 15 | 50 | 11.1 | 2 | 29% | Not | Not reported | Not reported |
| | | 15 | 56 | 9.7 | 2 | 60% | Not | Not reported | Not reported |</p>
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 2, 6, 10 and 14 weeks Duration of follow-up: 26 weeks</td>
<td>mg/kg + MTX 7.5 mg/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 3 mg/kg without MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 10 mg/kg + MTX 7.5 mg/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 10 mg/kg without MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C0168T22 ATTRACT, Maini et al 1999\textsuperscript{128}, Lipsky et al 2000\textsuperscript{129} North America and Europe, 34 centres, double-blind Infliximab treatment:</td>
<td>Placebo (0.1% albumin or saline) + MTX (median 15 mg/week)</td>
<td>88</td>
<td>51</td>
<td>11</td>
<td>(Mean)\textsuperscript{b}</td>
<td>2.5</td>
<td>64%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 3 mg/kg every 8 weeks + MTX (median 15 mg/week)</td>
<td>86</td>
<td>54</td>
<td>10</td>
<td></td>
<td>2.8</td>
<td>63%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 3 mg/kg every 4</td>
<td>87</td>
<td>54</td>
<td>11</td>
<td></td>
<td>2.5</td>
<td>58%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Infliximab i.v. 3 mg/kg every 4</td>
<td>81</td>
<td>52</td>
<td>12</td>
<td></td>
<td>2.5</td>
<td>65%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>repeated infusion at 0, 2, 6 then every 8 weeks until week 54&lt;sup&gt;a&lt;/sup&gt;</td>
<td>weeks + MTX (median 15 mg/week) Infliximab i.v. 10 mg/kg every 8 weeks + MTX (median 15 mg/week) Infliximab i.v. 10 mg/kg every 4 weeks + MTX (median 15 mg/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study and description</td>
<td>Interventions</td>
<td>No. of patients</td>
<td>Mean age (years)</td>
<td>Mean disease duration (years)</td>
<td>No. of previous DMARDs</td>
<td>On steroids</td>
<td>On NSAIDs</td>
<td>Baseline HAQ score (Mean)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Kavanaugh et al 2000&lt;sup&gt;34&lt;/sup&gt; United States, 3 centres, double-blind Infliximab treatment: single i.v. infusion</td>
<td>Placebo (single i.v. infusion 0.1% albumin) + MTX 10 mg/week</td>
<td>7</td>
<td>45</td>
<td>4.9</td>
<td>Not reported</td>
<td>2/7</td>
<td>4/7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Infliximab single i.v. infusion 5 mg/kg + MTX 10 mg/week</td>
<td>7</td>
<td>47</td>
<td>7.4</td>
<td></td>
<td>5/7</td>
<td>7/7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Infliximab single i.v. infusion 10 mg/kg + MTX 10 mg/week</td>
<td>7</td>
<td>53</td>
<td>7.5</td>
<td></td>
<td>5/7</td>
<td>6/7</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Infliximab single i.v. infusion 20 mg/kg + MTX 10 mg/week</td>
<td>7</td>
<td>37</td>
<td>4.9</td>
<td></td>
<td>6/7</td>
<td>5/7</td>
<td>1.5</td>
</tr>
<tr>
<td>C0168T29 ASPIRE, St. Clair et al 2004&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Placebo + MTX (starting 7.5 and increasing to 20 mg/week by week 8)</td>
<td>282</td>
<td>50</td>
<td>0.9</td>
<td>DMARD naïve</td>
<td>65%</td>
<td>38%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>359</td>
<td>51</td>
<td>0.8</td>
<td></td>
<td>71%</td>
<td>37%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
</table>
| North America, Europe and Israel, multicentre, double-blind Infliximab treatment: repeated infusion at 0, 2, 6 then every 8 weeks until week 46 | Infliximab i.v. 3 mg/kg every 8 weeks + MTX (as above)  
Infliximab i.v. 6 mg/kg every 8 weeks + MTX (as above) | 363 | 50 | 0.9 | | 68% | 39% | 82% | 1.5 |
| Durez et al 2004 | Methylprednisolone 1 g single IV infusion + MTX 10-15 mg/week | 15  
12 | (Median) 56  
48 | (Median) 12  
10 | (Median) 3  
3 | Not reported  
Not reported | | (Median) 1.5  
1.3 |
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab treatment: three infusions at weeks 0, 2, 6 Duration of follow-up: 14 weeks</td>
<td><strong>Infliximab i.v. 3 mg/kg + MTX (as above)</strong></td>
<td>12</td>
<td>51</td>
<td>1.6</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
| Taylor et al 2004¹³⁻¹⁸ | **Placebo (normal saline) + MTX (starting 12.5 to 17.5 mg/week, increasing to 25 mg/week if needed)**  
**Infliximab i.v. 5 mg/kg every 8 weeks + MTX (as above)** | 12              | 51               | 1.6                          | Not reported           | Not reported           | Not reported | Not reported       |
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up: 54 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C0168T41</strong></td>
<td>Placebo + MTX (mean)</td>
<td>363</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>START, Yocum et al 2004</td>
<td>Infliximab i.v. 3 mg/kg + MTX (mean)</td>
<td>360</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-centre, double-blind</td>
<td>Infliximab i.v. 10 mg/kg + MTX (mean)</td>
<td>361</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab treatment: four infusion at 0, 2, 6 and 14 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up: 22 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quinn et al 2005</strong></td>
<td>Placebo + MTX (mean)</td>
<td>10</td>
<td>53</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>Not reported</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study and description</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Mean disease duration (years)</th>
<th>No. of previous DMARDs</th>
<th>On steroids</th>
<th>On NSAIDs</th>
<th>Baseline HAQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK, single centre, double-blind Infliximab treatment: repeated infusion at 0, 2, 6 then every 8 weeks until week 46 Duration of follow-up: 54 weeks</td>
<td>Infliximab i.v. 3 mg/kg every 8 weeks + MTX (as above) (starting 7.5 and increasing to 15-25 mg/week according to clinical response)</td>
<td>10</td>
<td>51</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Extension study with continuous treatment and follow-up to 102 weeks not included in current review; see text for details.*

*Excluding MTX.*

*Open label, non-comparative extension with 3 additional infusion of infliximab 10 mg/kg at weeks 12, 20, and 28 and follow-up to week 40 not included in current review.*

*Patients in placebo arm switched to infliximab 3 mg/kg at week 22 and all group continued treatments for 46 weeks. Results beyond 22 weeks are not included in current review.*

*Open label extension and follow-up to 104 weeks not included in current review as other DMARDs could be introduced during the extension.*
### Table 13 Quality of included randomised controlled trials – infliximab

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Truly random allocation/ Remain on randomised treatment</th>
<th>Adequate allocation concealment</th>
<th>Blinding: Participants</th>
<th>Blinding: Investigators</th>
<th>Blinding: Assessors</th>
<th>Important differences in baseline characteristics between groups (item)</th>
<th>Important differences in completion rates between groups (% randomised patients completed)</th>
<th>Use of intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliott 1994[132]</td>
<td>Placebo: 24 Infliximab: 49</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No (only one patient withdrew &amp; replaced)</td>
<td>Yes</td>
</tr>
<tr>
<td>Maini 1998[133]</td>
<td>Placebo: 14 Infliximab: 87</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes (HAQ)</td>
<td>Yes</td>
<td>Unclear (Yes for Paulus response)</td>
</tr>
<tr>
<td>Kavanaugh 2000[134]</td>
<td>Placebo: 7 Infliximab: 21</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Not applicable (sample size too small)</td>
<td>No</td>
<td>No (except ACR responses)</td>
</tr>
<tr>
<td>ATTRACT</td>
<td>Placebo: 88 Infliximab: 340</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes (except radiographic and safety outcomes)</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Truly random allocation/ Remain on randomised treatment</th>
<th>Adequate allocation concealment</th>
<th>Blinding: Participants</th>
<th>Investigators</th>
<th>Assessors</th>
<th>Important differences in baseline characteristics between groups (item)</th>
<th>Important differences in completion rates between groups (% randomised patients completed)</th>
<th>Use of intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 102</td>
<td>Placebo: 28 Infliximab: 231</td>
<td>Partially&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>Partially&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Partially&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Partially&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(61% randomised patients entering extension)</td>
<td>Yes (except SF-36, radiographic and safety outcomes)</td>
<td>Yes (except SF-36, radiographic and safety outcomes)</td>
</tr>
<tr>
<td>(Maini 2004&lt;sup&gt;130&lt;/sup&gt;, Clinical study report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>START, Yocum 2004</td>
<td>Placebo: 363 Infliximab: 721</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear (withdrawal at week 22 not reported)</td>
<td>Yes</td>
</tr>
<tr>
<td>ASPIRE, St Clair 2004</td>
<td>Placebo: 291 Infliximab: 749</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No&lt;sup&gt;b&lt;/sup&gt; Placebo: 82% Infliximab: 86%</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Clinical study report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor 2004&lt;sup&gt;136&lt;/sup&gt;</td>
<td>Placebo: 12 Infliximab: 12</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No (one patient withdrew but did not state which arm)</td>
<td>No</td>
</tr>
<tr>
<td>Durez 2004&lt;sup&gt;135&lt;/sup&gt;</td>
<td>Methylprednisolone: 15 Infliximab: 12</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Truly random allocation/ Remain on randomised treatment</th>
<th>Adequate allocation concealment</th>
<th>Blinding: Participants</th>
<th>Investigators</th>
<th>Assessors</th>
<th>Important differences in baseline characteristics between groups (item)</th>
<th>Important differences in completion rates between groups (% randomised patients completed)</th>
<th>Use of intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn 2005</td>
<td>Placebo: 10</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Infliximab: 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 10/10</td>
<td>Infliximab: 9/10</td>
</tr>
</tbody>
</table>

* Only 28 (32%) of the those allocated MTX in year one continued compared with 231 (68%) of those on infliximab plus MTX. For ethical reasons the study was unblinded at week 54. Unblinding occurred in 12% of patients prior to completion of all HAQ evaluations. Ninety-four of the 259 patients had a gap of more than 8 weeks between treatments because of the timing of the protocol amendment. The mean length of time that infliximab was suspended was 19.4 weeks.

* Prior to unblinding, forty-five patients at two study sites were excluded from the efficacy analysis (16 in the MTX-placebo group, 14 in the MTX-3 mg/kg infliximab group and 15 in the MTX-6 mg/kg infliximab group) because their study data could not be verified with source documents.
Maini and colleagues 1998\textsuperscript{133}

This 26-week, multicentre, double-blind RCT compared three doses of i.v. infliximab (1, 3 or 10 mg/kg, with or without ongoing methotrexate 7.5 mg/week) with placebo plus ongoing methotrexate. Patients who had taken methotrexate at a dose of 7.5 mg to 15 mg per week for at least 6 months, with at least six swollen joints were recruited. Other DMARDs were not permitted. The primary efficacy measurement was the total time (in weeks) that a patient exhibited a Paulus 20\% response.

ATTRACT, Maini and colleagues 1999\textsuperscript{128}, Lipsky and colleagues 2000\textsuperscript{129}

This double-blind, multicentre, RCT compared four dosing regimens of infliximab (i.v. 3 mg/kg or 10 mg/kg, at 0, 2, 6 weeks and then every 4 or 8 weeks) with placebo combined with concomitant methotrexate therapy. Patients who had been receiving methotrexate for at least three months and had been stable at 12.5 mg/week or more before screening were recruited. At least six swollen joints and six tender joints were required. The primary endpoint was ACR20 response at week 30.

The study was planned to run for 54 weeks but it was extended by a protocol amendment to 102 weeks based on FDA guidance.\textsuperscript{130} A clinical study report for the two-year results was provided by the manufacturer. Results beyond week 54 were not included in meta-analyses for the following reasons: first, there was a substantial difference in the proportion of patients entering the second year between treatment arms (32\% for the placebo + methotrexate arm and 68\% for the infliximab + methotrexate arms combined); second, treatment was unblinded for 12\% of the patients before completion of all HAQ evaluations; third, ninety-four of the 259 patients in the infliximab groups had a treatment gap between first year and second year of more than eight weeks (mean 19.4 weeks) because of the timing of the protocol amendment. Consequently, the 54-week results are referred to as the "end of study" results in meta-analyses, unless otherwise specified.
ASPIRE, St Clair and colleagues 2004\textsuperscript{131}

This 54-week, double-blind, multicentre RCT which compared treatment with methotrexate alone (starting at 7.5 mg/week and escalated to 20 mg/week) and infliximab (i.v. 3 mg/kg or 6 mg/kg every 8 weeks) with methotrexate. Only patients with early RA, disease duration of three months to 3 years, were included. A minimum of 10 swollen joints and 12 tender joints were required. Patients who had received more than three doses of methotrexate or received other DMARDs within four weeks of study entry were not eligible.

Forty-five patients from two study sites out of 1049 randomised patients were excluded from efficacy analysis because the data could not be verified with source documents. The study had three primary endpoints: ACR-N from baseline to week 54 (for reduction of signs and symptoms); van der Heijde modification of the total Sharp score (for radiographic progression of joint damage); and change from baseline in HAQ scores averaged over weeks 30-54 (for improvement in physical function). The safety outcomes for this trial were reported and analysed according to actual treatment that the patient had received.

Durez and colleagues 2004\textsuperscript{135,138}

This small open-label, single centre RCT compared a single i.v. pulse of methylprednisolone (1 gram) with three i.v. infusions (at weeks 0, 2 and 6) of infliximab 3 mg/kg in patients receiving concurrent methotrexate (10-15 mg/week). Patients with disease for more than one year and at least six swollen joints and six tender joints were recruited and followed for 14 weeks. The primary endpoint was not stated although various disease activity measures and serum matrix metalloproteinase-3 (MMP-3) were evaluated. Methods of randomisation, allocation concealment, patient withdrawals and use of intention-to-treat analysis were not clearly described.
START, Yocum and colleagues 2004
This double-blind, multicentre safety trial compared infliximab, at two doses (i.v. 3 mg/kg or 10 mg/kg, at week 0, 2, 6, then every 8 week thereafter), and placebo in patients receiving concurrent methotrexate. Patients were treated for 46 weeks but patients in the placebo group were switched to receive infliximab 3 mg/kg every 8 weeks at week 22. Thus results beyond week 22 are excluded from this review and the 22-week results are referred to as the end of trial results. This trial has only been published as an abstract. Only HAQ data are currently included in our meta-analysis as the manufacturer made the clinical study report available just before the completion of the final draft of this assessment report.

Quinn and colleagues 2005
This small double-blind, single centre RCT compared methotrexate alone (started 7.5 mg/week and escalated to up to 25 mg/week depending on disease activity) and methotrexate combined with i.v. infliximab 3 mg/kg every 8 weeks. Patients with early RA, judged to have a poor prognosis were treated for 12 months, with a further open-label phase up to 24 months. The latter data are not included in this review as other DMARDs could be introduced during the extension. RA patients with symptoms for less than 12 months and no previous treatment with DMARDs or oral corticosteroids were recruited. Metacarpophalangeal joint disease and poor prognosis according to a scoring system based on rheumatoid factor positivity, genetic markers, CRP, gender, and HAQ
score were required. The primary endpoint was MRI-measured synovitis at week 14. Allocation concealment was not clearly stated.

**BeSt (Behandel-Strategieën) study, Goekoop-Ruiterman and colleagues**¹³⁹-¹⁴¹
This important trial compared four strategies for using DMARDs, rather than individual drugs. Patients with RA diagnosed within 2 years were recruited. Because patients received infliximab in all arms, this trial does not meet the inclusion criteria defined in our protocol, which sought comparatives studies of TNF inhibitors against alternative treatments. Nor can its results be incorporated meaningfully in the meta-analyses. Nevertheless we report it in detail here, as it is important evidence to inform guidance on appropriate use of infliximab. The primary endpoints of the BeSt study were HAQ and radiographic joint damage according to the Sharp-van der Heijde score after 1 year of follow-up. A sequence of drug treatments was strictly defined and patients moved along the sequence of therapies based on their response. Those who did not achieve a DAS score of 2.4 or less, based on evaluation of 44 joints (Appendix 1, page 229) moved to the next step in the defined sequence. A sustained response to therapy, defined as DAS of ≤2.4 for six months, led to a tapering of drug treatment that was strictly specified and included contingencies for disease relapse.

This trial was co-sponsored by Schering-Plough and the Dutch College of Health Insurance. Drugs used in the treatment strategies were:

**Group 1: Sequential monotherapy (126 patients):**

- Methotrexate; methotrexate (25 mg/week); sulfasalazine 2 g/day; leflunomide 20 mg/day.
Group 2: Step-up combination therapy (121 patients):

- Methotrexate; methotrexate 25 mg/week; methotrexate 25 mg/week and sulfasalazine 2 g/day; methotrexate 25 mg/week and sulfasalazine 2 g/day and hydroxychloroquine 400 mg/day;

Group 3: Initial combination with prednisolone (133 patients):

- Methotrexate, sulfasalazine 2 g/day and prednisolone (60 mg reducing to 7.5 over 7 weeks);

Group 4: Initial combination with infliximab (128 patients):

Methotrexate and infliximab starting at 3 mg/kg (licensed schedule)
A total of 508 patients were randomly allocated to a treatment strategy and assessed every 3 months who was blinded to treatment allocation.

Key outcomes of this study are shown in the Table 14. Patients in groups 3 and 4 improved more rapidly than in groups 1 and 2 (p<0.001), but at 1 year differences were less marked (p<0.009). No statistically significant differences were found on comparing group 1 to 2 and on comparing group 3 to group 4. Similarly, significantly less radiographic progression (p<0.007 or less) was seen in groups 3 and 4 compared with groups 1 and 2, at 1 year.
The data for groups 1 and 2 are inconsistent with clinical experience and published data for MTX in early RA. The authors concluded that initial combination therapy with infliximab or prednisolone had significant advantages over sequential monotherapy with DMARDs or step-up combination DMARD use.
Table 14  Key outcomes for the BeSt study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1 Sequential monotherapy</th>
<th>Group 2 Step-up combination</th>
<th>Group 3 Initial combination with prednisolone</th>
<th>Group 4 Initial combination with infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.4 (***</td>
<td>1.4 (***</td>
<td>1.4 (***</td>
<td>1.4 (***</td>
</tr>
<tr>
<td>3 months</td>
<td>1.0 (***</td>
<td>1.0 (***</td>
<td>0.6 (***</td>
<td>0.6 (***</td>
</tr>
<tr>
<td>12 months</td>
<td>0.7 (***</td>
<td>0.7 (***</td>
<td>0.5 (***</td>
<td>0.5 (***</td>
</tr>
<tr>
<td>DAS44 (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.5 (***</td>
<td>4.5 (***</td>
<td>4.4 (***</td>
<td>4.3 (***</td>
</tr>
<tr>
<td>3 months</td>
<td>3.5 (***</td>
<td>3.5 (***</td>
<td>2.4 (***</td>
<td>2.6 (***</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in total Sharp-van der Heijde score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.0 (******)</td>
<td>2.5 (******)</td>
<td>1.0 (******)</td>
<td>0.5 (******)</td>
</tr>
</tbody>
</table>
3.2.4.2 Meta-analysis of infliximab results

The principles of analysis and data presentation of infliximab trials are the same as described in section 3.1.5.

Infliximab vs. other active treatment

The license for infliximab stipulates that infliximab has to be used in conjunction with MTX, thus head-to-head comparison between infliximab and methotrexate is not considered here. However, relevant data from a small, dose-ranging study\textsuperscript{133} are summarised in Table 67, 244, Appendix 3. Infliximab 3 mg/kg at 0, 2, 6 weeks was more effective in all efficacy outcomes than single i.v. infusion of methylprednisolone (1 g) in a small open-label RCT by Durez and colleagues (2004).\textsuperscript{135}

Infliximab vs. placebo (with concurrent, ongoing MTX)

Two trials (START\textsuperscript{105} and ATTRACT\textsuperscript{129}) compared infliximab at licensed dose to placebo in patients who had had an inadequate response to MTX treatment. The results for these primary analyses (licensed dose) are summarised in Table 15 and the upper parts of Figure 35 to Figure 44. Additional data from a small, dose-ranging study\textsuperscript{132} for the comparison between infliximab alone (not licensed use) and placebo without concomitant MTX are not considered here but are summarised in Table 67, page 244, Appendix 3.

Efficacy

Infliximab is significantly more effective than placebo

\begin{itemize}
\item Efficacy
\end{itemize}

Tolerability

Infliximab is better tolerated than placebo.

Safety

\begin{itemize}
\item Safety
\end{itemize}

were found between infliximab and placebo in all the safety outcomes being meta-analysed.
Sensitivity analyses

Three trials (Maini 1998\textsuperscript{133}, Kavanaugh 2000\textsuperscript{134} and Taylor 2004\textsuperscript{136} included comparisons between infliximab and placebo at doses or dosing schedules other than that in the license. Sensitivity analyses which include patients from these trials are summarised in Table 68 (licensed dose and above) and Table 69 (all doses including sub-licensed dose), page 247, Appendix 3. Results are generally consistent with the primary analyses. However, when above licensed doses are included, infliximab was associated with a slight, 

in any infection

Contrary to the observations from TEMPO trial, data from ATTRACT trial indicated that there was
### Table 15 Meta-analyses – Infliximab i.v. licensed dose only vs. placebo with ongoing MTX in MTX partial responders/non-responders, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>858</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>830</td>
<td>WMD (fixed)</td>
<td>-5.08 [-6.23, -3.94]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>829</td>
<td>WMD (fixed)</td>
<td>-1.52 [-1.89, -1.15]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>818</td>
<td>WMD (fixed)</td>
<td>-0.27 [-0.35, -0.19]</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>No data available</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1¹²⁹</td>
<td>135</td>
<td>WMD (fixed)</td>
<td>-5.70 [-8.58, -2.82]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1¹²⁹</td>
<td>174</td>
<td>RR (fixed)</td>
<td>0.53 [0.36, 0.80]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1¹²⁹</td>
<td>174</td>
<td>RR (fixed)</td>
<td>0.54 [0.33, 0.90]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1¹²⁹</td>
<td>174</td>
<td>RR (fixed)</td>
<td>0.73 [0.24, 2.21]</td>
</tr>
<tr>
<td>Death</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>895</td>
<td>RR (fixed)</td>
<td>0.33 [0.05, 2.06]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>895</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>895</td>
<td>RR (fixed)</td>
<td>2.48 [0.49, 12.70]</td>
</tr>
<tr>
<td>Malignancy – skin cancer</td>
<td>2¹⁰⁵,₁₂⁹</td>
<td>895</td>
<td>RR (fixed)</td>
<td>1.49 [0.25, 8.80]</td>
</tr>
<tr>
<td>excluding melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>$2^{105,129}$</td>
<td>895</td>
<td>RR (fixed)</td>
<td>2.32 [0.34, 15.62]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>$2^{105,129}$</td>
<td>895</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>$2^{105,128}$</td>
<td>896</td>
<td>RR (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at $P<0.05$
Figure 35 ACR20 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)

Figure 36 ACR20 RD – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)
Figure 37 ACR50 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)

Figure 38 ACR50 RD – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)
Figure 39 ACR70 RR – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)

Figure 40 ACR70 RD – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)
Figure 41 HAQ change – Infliximab licensed dose only vs. placebo (with concurrent MTX)

(Confidential information removed)

Figure 42 Serious adverse events RR - Infliximab licensed dose vs. placebo (with concurrent MTX)

(Confidential information removed)

Figure 43 Serious adverse events RD - Infliximab licensed dose vs. placebo (with concurrent MTX)

(Confidential information removed)
Figure 44 Malignancy RR – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)

Figure 45 Malignancy RD – Infliximab licensed dose vs. placebo (with concurrent MTX)
(Confidential information removed)
Infliximab + MTX vs. MTX (newly initiated MTX)

ASPIRE\textsuperscript{131} and the study by Quinn and colleagues (2005)\textsuperscript{137} compared the combination of infliximab and MTX with MTX alone in MTX naïve, early RA patients. The results of primary analyses (at licensed dose) are summarised in Table 16 and are also shown in the lower parts of Figure 35 to Figure 45.

**Efficacy**

Infliximab combined with MTX is more effective than MTX alone. The differences between the combination and MTX monotherapy are statistically significant for all the efficacy outcomes being meta-analysed except patient’s global assessment of disease activity.

**Tolerability**

The combination is associated with significantly fewer withdrawals due to lack of efficacy (RR = 0.21, 95% CI 0.09 to 0.47) but significantly more withdrawals due to adverse events (RR = 2.99 (95% CI 1.49 to 6.03).

**Safety**

The combination is associated with a significantly increased risk of serious infection (RR = 2.74, 95% CI 1.12 to 6.70). No significant differences were found for other safety outcomes being meta-analysed.

**Sensitivity analyses**
Results which include additional patients treated with above licensed dose (6 mg/kg every eight weeks) in the ASPIRE trial are summarised in Table 70, Appendix 3. Data are generally consistent with primary analyses and show slightly increased effect size for efficacy outcomes except modified Sharp score. When the above licensed dose is included, the combination of infliximab + MTX is associated with an increased risk of both serious infection (RR = 2.59, 95% CI 1.11 to 6.04) and patients developed malignancy in the 6 mg/kg group compared with in the 3 mg/kg group in the ASPIRE trial.
Table 16 Meta-analyses – Combination of infliximab (i.v. licensed dose only) + MTX vs. MTX alone in MTX naïve patients, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RR (fixed)</td>
<td>1.17 [1.02, 1.34]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RR (fixed)</td>
<td>1.44 [1.18, 1.76]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RR (fixed)</td>
<td>1.57 [1.20, 2.05]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RD (fixed)</td>
<td>0.09 [0.01, 0.17]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RD (fixed)</td>
<td>0.14 [0.07, 0.22]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>2[131,137]</td>
<td>645</td>
<td>RD (fixed)</td>
<td>0.12 [0.05, 0.19]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>1[131]</td>
<td>540</td>
<td>WMD (fixed)</td>
<td>-3.28 [-4.55, -2.01]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>1[131]</td>
<td>536</td>
<td>WMD (fixed)</td>
<td>-0.79 [-1.08, -0.51]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>2[131,137]</td>
<td>563</td>
<td>WMD (fixed)</td>
<td>2.99 [1.49, 6.03]</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>2[131,137]</td>
<td>549</td>
<td>WMD (fixed)</td>
<td>2.74 [1.12, 6.70]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1[131]</td>
<td>641</td>
<td>WMD (fixed)</td>
<td>1.27 [0.84, 1.92]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1[131]</td>
<td>665</td>
<td>RR (fixed)</td>
<td>0.39 [0.04, 4.29]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1[131]</td>
<td>665</td>
<td>RR (fixed)</td>
<td>2.99 [1.49, 6.03]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>2[131,137]</td>
<td>685</td>
<td>RR (fixed)</td>
<td>1.27 [0.84, 1.92]</td>
</tr>
<tr>
<td>Death</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>1.27 [0.84, 1.92]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>1.27 [0.84, 1.92]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>2.74 [1.12, 6.70]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>2.74 [1.12, 6.70]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1[131]</td>
<td>663</td>
<td>Not estimable</td>
<td>No event</td>
</tr>
<tr>
<td>Serious infection</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>2.74 [1.12, 6.70]</td>
</tr>
<tr>
<td>Any infection</td>
<td>1[131]</td>
<td>663</td>
<td>RR (fixed)</td>
<td>2.74 [1.12, 6.70]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
3.3 Summary of effectiveness review and additional evidence

Results of primary meta-analyses (licensed dose only) for the three TNF inhibitors for the key outcomes are summarised in Table 17. A brief description for each type of comparison is provided below.

3.3.1 TNF inhibitors versus DMARDs

Volume of evidence

Only one adalimumab trial (PREMIER\textsuperscript{102}, n=531 in the relevant arms) and two etanercept trials (ERA\textsuperscript{119}, n=424 and TEMPO\textsuperscript{123}, n=451) allow head-to-head comparison between a TNF inhibitor (at licensed dose) and MTX. No trial compared a TNF inhibitor with other conventional DMARDs.

Direction of effect

Adalimumab monotherapy was marginally less effective than MTX monotherapy in reducing RA symptoms and improving physical function in early RA patients naïve to MTX treatment, and did not offer better tolerability over MTX. By contrast, etanercept alone was slightly more effective than MTX alone in early RA patients who are naïve to MTX treatment and in patients with longer disease duration who have no history of treatment failure with MTX. Etanercept was better tolerated than MTX in these patients. Both adalimumab and etanercept were significantly more effective than MTX in slowing radiographic joint damage but the clinical relevance of these differences is unclear. No significant differences between MTX and adalimumab and etanercept were found for the safety outcomes, including: deaths; serious adverse events; malignancy; serious infections; any infections. However, this may be due to the relatively small number of patients included in the analyses. Large pragmatic trials and careful post-marketing surveillance, including record linkage studies, are needed to compare the relative safety of TNF inhibitors compared to MTX and other DMARDs.
Table 17 Summary of the results of primary analyses for key outcomes included in this review (CIC)

<table>
<thead>
<tr>
<th>TNF inhibitor &amp; population</th>
<th>ACR20 RR* [95% CI] ( &amp; NNT)</th>
<th>ACR70 RR* [95% CI] ( &amp; NNT)</th>
<th>HAQ change Mean difference[95% CI]</th>
<th>Modified sharp score Mean difference[95% CI]</th>
<th>Withdrawal for any reasons RR* [95% CI]</th>
<th>Serious adverse events RR* [95% CI]</th>
<th>Serious infections RR* [95% CI] ( &amp; NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-TNF versus MTX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (early RA)</td>
<td>0.88 [0.75, 1.03]</td>
<td>0.99 [0.75, 1.30]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept (early RA)</td>
<td>1.22 [1.06, 1.40]</td>
<td>1.23 [0.89, 1.70]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept (established RA)</td>
<td>1.28 [1.06, 1.54]</td>
<td>1.46 [1.00, 2.14]</td>
<td>-0.10 [-0.23, 0.03]</td>
<td>-2.28 [-4.11, -0.45]/ 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-TNF versus placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (established RA)</td>
<td>2.11 [1.84, 2.42]</td>
<td>5.22 [3.45, 7.89]</td>
<td>-0.31 [-0.36, -0.26]</td>
<td>-2.20 [-3.33, -1.07]/ 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept (established RA)</td>
<td>3.59 [2.89, 4.46]</td>
<td>NNT 2.1 [1.9, 2.4]</td>
<td>-0.50 [-0.59, -0.42]</td>
<td>No data available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (established RA)</td>
<td></td>
<td></td>
<td>-0.27 [-0.35, -0.19]</td>
<td>-5.70 [-8.58, -2.82]/ 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-TNF + MTX versus MTX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab + MTX (early RA)</td>
<td>1.24 [1.08, 1.42]</td>
<td>1.64 [1.30, 2.07]</td>
<td></td>
<td></td>
<td>-4.40 [-6.14, -2.66]/ 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept +</td>
<td>1.49 [1.25, 1.77]</td>
<td>2.53 [1.82, 3.54]</td>
<td>-0.40 [-0.52, -0.28]</td>
<td>-3.34 [-5.12, -1.56]/ 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX (established RA)</td>
<td>NNT 4.5 [3.3, 7.7]</td>
<td>NNT 4.0 [3.0, 5.9]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab + MTX (early RA)</td>
<td>1.17 [1.02, 1.34]</td>
<td>1.57 [1.20, 2.05]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNT 11.1 [5.9, 100]</td>
<td>NNT 8.3 [5.3, 20.0]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-3.28 [-4.55, -2.01] / 1 year

0.87 [0.64, 1.19] 1.27 [0.84, 1.92]

2.74 [1.12, 6.70]

NNH 25 [16.7, 10]
3.3.2 TNF inhibitors versus placebo

Volume of evidence

The majority of RCTs included in this review compared TNF inhibitors with placebo. Five adalimumab trials\textsuperscript{108,111,115} involving 1861 patients, eight etanercept trials\textsuperscript{103,104,117,118,121,122,125,126} involving 1715 patients, and two infliximab trials\textsuperscript{105,129} involving 895 patients were included in the primary meta-analyses.

Direction of effect

All the three TNF inhibitors were significantly more effective in controlling the symptoms of RA, improving physical function and retarding radiographic joint damage and were associated with few treatment withdrawals compared to placebo. Use of above licensed doses slightly increased the treatment effect for adalimumab and infliximab, but was associated with increased risk of any infection and serious infections. More patients treated with adalimumab and infliximab had cancer but this did not reach statistical significance. No increased risk of infection or malignancy was found for etanercept compared with placebo.

3.3.3 Combination of TNF inhibitor + MTX versus MTX

Volume of evidence

Four trials compared a TNF inhibitor (at licensed dose) combined with MTX to MTX alone in patients naïve to, or who had not previously failed methotrexate: PREMIER\textsuperscript{102} (n=525) for adalimumab; TEMPO\textsuperscript{123} (n=459) for etanercept; ASPIRE\textsuperscript{131} (n=665) for infliximab; Quinn \textit{et al} 2005\textsuperscript{137} (n=20) for infliximab.

Direction of effect

A TNF inhibitor combined with methotrexate was significantly more effective than MTX monotherapy in controlling RA symptoms, improving physical function, and slowing radiographic joint damage for all the three TNF inhibitors. Fewer patients on combination therapy withdrew from treatment, but the difference was not statistically significant for the infliximab combination, which was associated with nearly a three-fold increase in withdrawal due to adverse events (RR = 2.99, 95% CI 1.49 to 6.03) and serious infections (RR = 2.74, 95% CI 1.12 to 6.70). Adalimumab combined with methotrexate was associated with a
Risks of serious infection and withdrawal due to adverse events were also compared to MTX alone, but these did not reach statistical significance. In safety outcomes were found between etanercept combined with MTX and MTX alone.

3.3.4 Additional information on effectiveness and safety

This section summarised additional evidence that is not included in meta-analyses. Information cited in this section is collated from FDA reports, published reviews and observational studies, summaries of product characteristics, and submissions from the British Society for Rheumatology (BSR) and manufacturers of TNF inhibitor to NICE. Lack of appropriate, unbiased comparison groups is a major problem for the validity of comparative results from non-RCTs. This should be borne in mind when interpreting observational data. Issues related to tuberculosis and blood monitoring have been discussed in section 2.3.4, page 35 and are not described here.

Mortality

Mortality data from long-term follow-up programmes for patients treated with adalimumab and etanercept were reviewed by FDA in 2003. The observed death rates in the follow-up programmes, adjusted for age and sex, were lower than that would be expected among US general populations and do not indicate a higher death rate with TNF inhibitor treatments.

Malignancies including lymphomas

A significant increase in the incidence of lymphoma compared with general population was noted for all the three TNF inhibitors in the 2003 FDA review. Controversy remains with regard to whether the observed higher incidences indicate additional risk due to TNF treatment, or whether they are in line with the increased risk of lymphoma observed in RA patients with high inflammatory activity. In general, the incidence of other types of malignancies in TNF inhibitor treated patients was found to be similar to, or lower than that observed in general population and other RA populations.
Congestive heart failure

Adalimumab and infliximab are contraindicated in moderate to severe heart failure (New York Heart Association class III or IV). Two RCTs (not included in our systematic review) that evaluated the use of etanercept in the treatment of congestive failure were terminated early due to lack of efficacy, and data from one of these trials suggested a possible tendency towards worsening of congestive heart failure and increased all-cause mortality in patients treated with etanercept.\textsuperscript{151,152} In another trial that evaluated the use of infliximab in congestive heart failure, no clinical benefit was observed and high dose infliximab (10 mg/kg at 0, 2, 6 weeks) was associated with an increased risk for a composite outcome that included death from any cause and hospitalisation for heart failure (hazard ratio 2.84, 95% CI 1.01 to 7.97).\textsuperscript{153}

Pulmonary fibrosis

In an investigation of pulmonary fibrosis and associated death, BSRBR found that there was a two to three fold increase in mortality for patients with pulmonary fibrosis at baseline compared to those without it among all patients (including TNF treated and control group) with 6 month’s follow-up data.\textsuperscript{85} As the vast majority the patients with pulmonary fibrosis at baseline were in the TNF treated groups and only one death associated with pulmonary fibrosis occurred in the control group, it was not possible to conclude whether there is a potential association between TNF treatment and death associated with pulmonary fibrosis.

Combination of TNF inhibitors with anakinra

Results from a RCT (not included in this systematic review, see Appendix 7) by Genovese and colleagues (2004)\textsuperscript{154} suggest that combination therapy with etanercept plus anakinra provided no treatment benefit over etanercept alone, and was associated with an increased risk of serious infections (0% for etanercept alone an 3.7-7.4% for combination therapy). The combination of TNF inhibitors and anakinra is therefore not recommended.
4 HEALTH ECONOMICS

Summary of review of existing economic evaluations

A comprehensive search for existing economic evaluations was undertaken. These were assessed for quality using the Consensus on Health Economic Criteria.

Existing economic evaluations
Ten published economic evaluations and 4 unpublished economic evaluations, of which only 3 were available electronically, were identified and reviewed. All were of high quality meeting at least 15 of the 19 quality assessment criteria. All but one used a decision alaytic model. Most gave ICERs that suggested that the use of TNF inhibitors were under the threshold normally considered to be the limit for cost-effectiveness. Direct comparisons of the ICERs between the studies is not possible because of their different approaches to modelling, different time horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used. Many of the estimates for effectiveness were derived from single trials, or a subset of trials rather than a systematic review and meta-analysis of relevant trial and observational data.

Although most were of high quality, none of them used all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context.

The aim of this section is to assess the cost-effectiveness of adalimumab, etanercept and infliximab for treating RA from a National Health Services (NHS) perspective.

This section of the report has three components:

- a review of existing economic evaluations of the use of TNF inhibitors in RA
• a technical commentary on the decision-analytic models used in the economic analyses reported in the manufacturers’ submissions to NICE
• a description of the Birmingham Rheumatoid Arthritis Model and the economic analyses of TNF inhibitors used singly or sequentially in RA patients, undertaken by the authors

4.1 Systematic review of economic evaluations

4.1.1 Method

Search strategy

The searches for clinical effectiveness were amplified to identify existing economic models and information on costs, cost effectiveness and quality of life from the following sources:
• Bibliographic databases
  o MEDLINE (Ovid) 1966 – Feb 2005, EMBASE (Ovid) 1980 – week 09 2005
  o Cochrane Library (NHSEED) 2005 Issue 1
  o HEED Feb 2005
• Internet sites of national economic units
• Internet sites of regulatory authorities, e.g. FDA, EMEA

Time and language limits were as for clinical effectiveness searches. Systematic reviews of DMARDs were sought to inform the economic analysis and provide a context for biological TNF inhibitors. The search strategy was based on the Aggressive Research Intelligence Facility (ARIF) search protocol for reviews which includes the Cochrane Library, Clinical Evidence, MEDLINE, Bandolier, health technology assessment databases and in-house databases. Full details of search strategies are contained in Appendix 4 Searches – economic evaluations, page 250, Appendix 5 Searches – decision analytic models, page 253 and Appendix 6 Searches – systematic reviews of DMARDs, page 255.
Inclusion and exclusion criteria

The review is an update of our previous report. Inclusion and exclusion criteria applied for economic searches are shown in Table 18.

Table 18 Inclusion criteria for the review on cost-effectiveness

<table>
<thead>
<tr>
<th>Study design</th>
<th>Cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis; cost studies (UK only), quality of life studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>People with RA; other forms of arthritis are excluded</td>
</tr>
<tr>
<td>Intervention</td>
<td>Etanercept, infliximab or adalimumab.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Disease-modifying antirheumatic drugs (DMARDs)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Quality of life estimates, cost estimates, cost-effectiveness</td>
</tr>
</tbody>
</table>

Study selection, data extraction, and quality assessment strategy

An experienced health economist applied the inclusion and exclusion criteria. Data were extracted by one reviewer using a pre-designed data extraction form and were independently check by a second reviewer. Data on the following was sought:

- Study characteristics, such as form of economic analysis, population, interventions, comparators, perspective, time horizon, and modelling used.
- Effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting, and key assumptions.
- Results and sensitivity analyses.

These characteristics and the main results of included economic evaluations are summarised in subsequent tables. The quality of included studies and industry submissions was assessed using the Consensus on Health Economic Criteria (CHEC-list). The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and
valuation, decision modelling, discounting, allowance for uncertainty and presentation of results were all evaluated as part of this process.

### 4.1.2 Results of systematic review of economic evaluations

Ten published studies, including one by the current authors (Jobanputra et al 2002), met the inclusion criteria. Given that Jobanputra et al 2002 describes the initial version of BRAM which is updated in this report, it will not be further discussed here. Key features of the nine other studies are summarised in Table 19, below. In addition, all 3 manufacturers submitted economic analyses and models. These submissions are reviewed in detail in section 4.1.4 of this chapter. Details of the 9 studies are presented in Appendix 9, page 267 using a simplified version of the Drummond & Jefferson checklist. A summary of the incremental cost-effectiveness ratios (ICERs) for TNF inhibitors reported in published papers is provided in Table 20.

#### Table 19 Summary of published economic analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>TNF inhibitor(s) considered</th>
<th>Form of economic analysis</th>
<th>Model used</th>
<th>Time horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobelt et al (2004)</td>
<td>Etanercept, infliximab</td>
<td>Cost utility</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Drug</td>
<td>Comparator</td>
<td>Study</td>
<td>Date</td>
<td>Time horizon</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>DMARD sequence</td>
<td>Bansback(^{163})</td>
<td>2005</td>
<td>Lifetime</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMARD sequence</td>
<td>Brennan(^{157,165})</td>
<td>2004</td>
<td>Lifetime</td>
</tr>
<tr>
<td></td>
<td>DMARD sequence</td>
<td>Bansback(^{163})</td>
<td>2005</td>
<td>Lifetime</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline level (failed</td>
<td>Kobelt(^{160})</td>
<td>2004</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>at least 2 DMARDs,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>including methotrexate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Kobelt(^{164})</td>
<td>2005</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMARD sequence</td>
<td>Jobanputra(^{1})</td>
<td>2002</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Drug</td>
<td>Comparator</td>
<td>Study</td>
<td>Date</td>
<td>Time horizon</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>Usual treatment, leflunomide,</td>
<td>Welsing&lt;sup&gt;162&lt;/sup&gt;</td>
<td>2004</td>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy leflunomide,</td>
<td>Choi **&lt;sup&gt;156&lt;/sup&gt;</td>
<td>2002</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>methotrexate, sulfasalazine,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no second line agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Placebo and methotrexate</td>
<td>Wong&lt;sup&gt;155&lt;/sup&gt;</td>
<td>2002</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Kobelt&lt;sup&gt;159&lt;/sup&gt;</td>
<td>2003</td>
<td>10 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline level (failed at</td>
<td>Kobelt&lt;sup&gt;160&lt;/sup&gt;</td>
<td>2004</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>least 2 DMARDs, including</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methotrexate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD sequence</td>
<td>Bansback&lt;sup&gt;163&lt;/sup&gt;</td>
<td>2005</td>
<td>Lifetime</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD sequence</td>
<td>Jobanputra&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2002</td>
<td>Lifetime</td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>Chiou&lt;sup&gt;161&lt;/sup&gt;</td>
<td>2004</td>
<td>1 year</td>
<td></td>
</tr>
</tbody>
</table>

*Industry sponsored studies are highlighted in shaded cells.

** Cost-effectiveness analysis, all other studies are cost-utility analyses
Four economic evaluations only considered etanercept compared to specified DMARDs or sequences of DMARDs (see Table 21). Three studies were cost-utility analyses, with the cost-effectiveness ratio (ICER) reported as cost per quality adjusted life year (QALY) gained (see Table 21). In addition to cost/QALY, Welsing and colleagues (2004)\textsuperscript{162} also considered cost per patient year in three Disease Activity Score (DAS28) states. Choi and colleagues (2002)\textsuperscript{156} used the ACR20 response and a weighted average of proportions of patients achieving ACR70, ACR50 and ACR20 (ACR weighted response, ACR70WR) and reported the cost-effectiveness ratio as cost per ACR20 or ACR70WR. Brennan et al (2004)\textsuperscript{157} carried out the analysis from a health care perspective, whereas the other studies included direct and indirect costs. The four studies differed in how etanercept use was modelled: Choi et al (2002)\textsuperscript{156} considered etanercept alone over a short time period of six months; Brennan et al (2004)\textsuperscript{157} placed etanercept as third line therapy in a DMARD sequence over a patient lifetime; Welsing et al (2004)\textsuperscript{162} considered three different etanercept pathways (etanercept first, then switch to conventional DMARDs if there is no response; leflunomide followed by etanercept if there is no response to leflunomide (Lef-Etan); and finally, etanercept switching to leflunomide with non-response (Etan-Lef)). Kobelt et al (2005)\textsuperscript{164} considered etanercept alone and etanercept combined with methotrexate.

Two studies found high ICERs. Choi et al (2002)\textsuperscript{156} suggested that recommendations regarding use depended on whether an ICER over $40,000 per ACR20 or ACR70WR was considered acceptable. Welsing et al (2004)\textsuperscript{162} recommended use of etanercept following leflunomide after 2 other DMARDs (where the first is methotrexate) had failed. In contrast, Brennan et al (2004)\textsuperscript{157,165} reported a much lower ICER and suggested “etanercept was cost-effective when compared with non-biologic agents”. Kobelt et al (2005)\textsuperscript{164} reported the ICER for etanercept in combination with methotrexate to be within the “acceptable range”. Each study used a different modelling approach. Choi and colleagues (2002)\textsuperscript{156} used a simple decision tree structure and modelled costs and outcomes over 6 months. Welsing and colleagues (2004)\textsuperscript{162} and Kobelt and colleagues (2005)\textsuperscript{164} used a Markov model structure with a 5 year time horizon and a 5 and 10 year time horizon respectively. Brennan and colleagues (2004)\textsuperscript{157} developed an individual patient-level simulation model to calculate lifetime costs and outcomes. RCT data were used to model outcomes; it has been suggested that observational data are a more realistic representation of outcomes in practice and therefore more suitable for CE analyses.\textsuperscript{166}
Table 21 Published etanercept economic analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Patient group</th>
<th>Comparator(s)</th>
<th>Base case ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al (2002)¹⁵⁶</td>
<td>Not stated</td>
<td>RA</td>
<td>4 monotherapy comparators:</td>
<td>Etanercept vs. sulfasalazine:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- leflunomide</td>
<td>$41,900 per ACR20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- methotrexate</td>
<td>Etanercept vs. methotrexate:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- sulfasalazine</td>
<td>$40,800 per ACR70WR</td>
</tr>
<tr>
<td>Welsing et al (2004)¹⁶²</td>
<td>Not stated (but used data from Wyeth)</td>
<td>RA</td>
<td>2 comparators:</td>
<td>Etanercept alone was dominated by leflunomide/etanercept combinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- usual treatment</td>
<td>Vs usual treatment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- leflunomide</td>
<td>€163,556 per QALY for Lef-Etan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€297,151 per QALY for Etan-Lef</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vs leflunomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€317,627 per QALY for Lef-Etan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€517,061 per QALY for Etan-Lef</td>
</tr>
<tr>
<td>Brennan et al (2004)¹⁵⁷,¹⁶⁵</td>
<td>Not stated (but 2 authors from Wyeth)</td>
<td>RA</td>
<td>DMARD sequence</td>
<td>£16,330 per QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment for 2 years, extrapolation to 10 years: Etan-MTX €37,331 per QALY.</td>
<td>Treatment for 2 years, extrapolation to 5 years: Etan-MTX €54,548 per QALY.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment for 10 years: Etan-MTX €46,494 per QALY.</td>
<td>Treatment for 5 years, extrapolation to 10 years. Etan-MTX €47,316 per QALY.</td>
</tr>
</tbody>
</table>
Each study took different approaches, for example, the evaluation undertaken (cost-effectiveness or cost utility analysis), the treatment comparators and the time horizon chosen (each used a different time horizon varying from 6 months to lifetime). Kobelt et al used a cycle length of 1 year, which is not clinically relevant. A cycle length of around 4 months is more clinically relevant as decisions about the efficacy of DMARDs are generally made over this time. Three analyses were from a societal perspective, an approach that leads to a more favourable ICER. If a treatment is more effective, then patients are more able to work thus leading to lower indirect costs. The Choi et al study did not calculate cost per QALYs therefore comparison with other results is not possible.

Two of the ten identified published studies report an economic analysis of infliximab in combination with methotrexate (see Table 22); and were sponsored by the manufacturer Schering-Plough. Both studies were cost-utility analyses using a societal perspective and the comparator explored was methotrexate alone. The quality of life (QoL) data used by Wong et al\textsuperscript{158} was based on self-reported global health using a visual analogue scale (VAS) from the ATTRACT trial and the ARAMIS database. However, there are problems with VAS such as context bias and end point aversion and the method is not truly preference based. Other methods are more appropriate, for example using a utility measure such as EQ-5D. Therefore results should be treated with some caution. Costs were obtained from the ARAMIS database, based on a North American population and are not directly transferable to a UK perspective, and the analysis was carried out from a societal perspective. The study authors concluded that infliximab with methotrexate was cost-effective, especially when including indirect costs of loss of productivity. However, cost-effectiveness is dependent on the ICER threshold of the decision maker. The effectiveness data used by the Kobelt et al study is from observational data only, and uses a societal perspective therefore giving a more favourable ICER. This perspective also leads to a large difference in ICERs between the UK and Sweden as this difference was driven by indirect costs. Differences arose due to higher average salary and more generous long-term illness benefits in Sweden, plus a lower proportion of UK patients in advanced HAQ states had taken early retirement compared with Sweden. A Markov model was used in both studies, with Wong et al (2002)\textsuperscript{158} projecting 54 week results of a randomised controlled trial to a lifetime horizon and Kobelt et al (2003)\textsuperscript{159} producing results for a 10 year
time horizon. The latter uses a one-year cycle length, which is not clinically appropriate as a patient may change DMARDs over a much shorter period of time.

Table 22 Published infliximab economic analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Patient group</th>
<th>Comparator(s)</th>
<th>Base case ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al</td>
<td>Schering-Plough, Centocor Corp,</td>
<td>RA</td>
<td>Placebo and methotrexate</td>
<td>$30,500 per QALY</td>
</tr>
<tr>
<td>(2002)</td>
<td>National Institutes for Health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobelt et al</td>
<td>Schering Plough</td>
<td>RA</td>
<td>Methotrexate</td>
<td>For 1 year of treatment: €3,440 per QALY in Sweden</td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td></td>
<td>€34,800 per QALY in UK</td>
</tr>
</tbody>
</table>

The remaining four cost-effectiveness analyses considered more than one TNF inhibitor therapy (see Table 23). Kobelt et al (2004)\(^{160}\) reported a cost-utility analysis using patient level direct costs and effectiveness using data from a cohort of 160 patients. Patients received etanercept (n=113) or infliximab (n=47) but drug allocation was not randomised. Data were shown for use of a TNF inhibitor compared with resource use and quality of life for the year before treatment (baseline). Jobanputra et al considered etanercept and infliximab in comparison with a DMARD sequence. This work formed the economic evaluation of the previous NICE appraisal for TNF inhibitor drugs undertaken by the current authors and will therefore not be described further. Bansback et al (2005)\(^{163}\), funded by Abbott Laboratories, used a patient-level simulation model to conduct cost-utility analyses from a health care perspective. The model builds on two previous RA models.\(^{157}\) Etanercept and adalimumab were considered as monotherapies and in combination with methotrexate, with two separate analyses for adalimumab plus methotrexate. The second analysis contained additional information from a larger adalimumab trial in a pooled analysis. Infliximab was only considered in combination with methotrexate. Results were presented as ICERs versus traditional DMARDs for two separate groups: an ACR50 response which corresponded to a good DAS28 response; and an ACR20 response which corresponded to a moderate DAS28 response. Using such dichotomous data, unfortunately, does not reflect clinical reality, or practice, as many patients may continue, or cease, therapy despite such thresholds and actual
drug continuation rates from observational studies are more appropriate for modelling. Chiou et al (2004)\textsuperscript{167} used a decision tree to carry out a cost-utility analysis of anakinra, adalimumab, etanercept and infliximab used alone or in combination with methotrexate during one year. Separate analyses were conducted for monotherapies and combination therapies. A preference weight was attached to each of the 16 health states representing a combination of the level of adverse effects and ACR response criteria. However, preference weights were derived from VAS visual analogue scales, which is not ideal.

Kobelt et al (2004)\textsuperscript{160} reported QALYs within the generally accepted threshold of €50,000 per QALY, however analysis was from a societal perspective, therefore results are not directly relevant to a UK health care perspective. Bansback et al (2005)\textsuperscript{163} suggested that adalimumab was cost-effective for the treatment of moderate to severe RA and was at least as cost-effective as etanercept or infliximab; but there was uncertainty about which drug was the most cost-effective. In addition, they concluded that with the exception of infliximab, the cost results were in a range normally considered cost-effective in Europe. Chiou et al (2004)\textsuperscript{167} found anakinra to be the least cost-effective option, and etanercept (as monotherapy and combined with methotrexate) was dominant over other TNF inhibitors. Compared with anakinra, both etanercept treatment regimens were below US$15,000 per QALY. However, the study is US based and uses USA health care costs, therefore the results cannot be applied to the UK.

Direct comparison of these ICERs is inappropriate as the analyses are very different in terms of treatment comparators and time horizons. The Kobelt et al\textsuperscript{164} analysis is without modelling, Bansback et al\textsuperscript{163} conduct modelling over a patient’s lifetime and Chiou et al\textsuperscript{167} model over one year. Modelling the response over a one year cycle is not clinically appropriate, especially as it is assumed treatment will continue over this period with no switching of therapy. In reality, patients will switch from one drug to another in a period much smaller than one year due to lack of response or adverse effects. In addition, Chiou et al is the only study that does not use traditional DMARDs as the comparator using anakinra monotherapy instead. However, anakinra was not recommended for routine use in the NHS by NICE in its November 2003 guidance (http://www.nice.org.uk/pdf/TA072guidance.pdf) because of its poor incremental cost-effectiveness which was over £100K/QALY.\textsuperscript{3}
Table 23 Published economic analyses for more than one TNF inhibitor therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsor</th>
<th>Patient group</th>
<th>Comparator(s)</th>
<th>Base case ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etanercept, infliximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jobanputra (2002)¹</td>
<td>NHS HTA programme</td>
<td>RA</td>
<td>DMARD sequence</td>
<td>Etanercept £83,095 per QALY</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infliximab £115,937 per QALY</td>
</tr>
</tbody>
</table>
| Kobelt et al (2004)¹⁶⁰ | Österlund and Kock Foundations, the King Gustav V 80 year fund, Reumatikerförbundet | RA             | Baseline level (failed at least 2 DMARDs, including methotrexate) | After 3 months treatment: €43,500 per QALY  
|                        |                                              |                |                                    | After 6 weeks treatment: €36,900 per QALY                                    |
| **Etanercept, infliximab, adalimumab** |
| Chiou et al (2004)¹⁶⁷ | Not stated                                   | RA             | Anakinra                           | US$13,387 per QALY (Etanercept alone)                                          |
|                        |                                              |                |                                    | Adalimumab alone dominated                                                     |
|                        |                                              |                |                                    | US$7,925 per QALY (Etanercept + MTX)                                           |
|                        |                                              |                |                                    | Adalimumab + MTX and infliximab + MTX dominated                                |
| Bansback et al (2005)¹⁶³ | Abbott Laboratories                         | RA             | DMARD sequence                    | ACR50/DAS28 good:                                                             |
|                        |                                              |                |                                    | €34,167 per QALY (Adalimumab+MTX)                                              |
|                        |                                              |                |                                    | €34,922 per QALY (Adalimumab+MTX ₣)                                           |
|                        |                                              |                |                                    | €35,760 per QALY (Etanercept + MTX)                                            |
|                        |                                              |                |                                    | €48,333 per QALY (Infliximab + MTX)                                            |
|                        |                                              |                |                                    | €41,561 per QALY (Adalimumab)                                                  |
|                        |                                              |                |                                    | €36,927 per QALY (Etanercept)                                                  |
|                        |                                              |                |                                    | ACR20/DAS28 moderate:                                                          |
|                        |                                              |                |                                    | €40,875 per QALY (Adalimumab+MTX)                                              |
|                        |                                              |                |                                    | €44,018 per QALY (Adalimumab+MTX ₣)                                           |
|                        |                                              |                |                                    | €51,976 per QALY (Etanercept + MTX)                                            |
|                        |                                              |                |                                    | €64,935 per QALY (Infliximab + MTX)                                            |
4.1.3 Summary of review of existing economic evaluations

- Results of published economic evaluations vary: some analyses suggest that use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, others report very high ICERs.
- A direct comparison of ICERs between studies is not possible because of different approaches to modelling, in particular time horizon, cycle length, country of origin, perspective chosen, source of preference weights and comparator drugs.
- Many of the previous analyses are based on clinical estimates that are derived from single trials, or a small number of trials, rather than a formal systematic review, meta-analysis of evidence, or observational data of effectiveness in clinical practice.
- Drug manufacturers have sponsored four published analyses, with a further two having links with a drug company. Two studies do not state the sponsors of the study. The two remaining studies were not linked with any drug manufacturers.
- Each study was considered to be of adequate quality, in terms criteria in the CHEC-list where at least 15 of 19 were met by all. All fulfilled criteria related to design and conduct, i.e. each study was a cost effectiveness evaluation addressing a clearly defined research question applied to a clearly defined population. An appropriate perspective was chosen in each and the outcomes identified were relevant and were measured appropriately. Incremental analyses, to which appropriate sensitivity analyses had been applied, were reported without exception.
- Quality assessment criteria that were not met included failure to report the following: discounted future costs and benefits in two studies; potential conflicts of interest in five studies; competing interests in two studies; the generalisability of results in one study and ethical and distributional issues in any of the included studies.
- All but one economic analysis used a decision analytic model. Published models vary in some important aspects; for example, the type of model used, whether switching of
therapy is considered, drug combinations, comparator therapies and time horizon and cycle length.

- One study carried out a cost-effectiveness analysis using patient-level data on costs and outcomes from a patient cohort. However results for two separate TNF inhibitors were combined.

- Six studies report costs that include both those from a health care perspective and indirect costs including losses of productivity; inclusion of these productivity costs improves the cost-effectiveness of TNF inhibitors.

- One study carried out a cost-effectiveness analysis, with the remaining nine conducting a cost-utility analysis. Two studies obtained preference weights from VAS, considered to be a less acceptable method for obtaining preference. The remaining seven studies used EQ-5D, in some cases using regression analysis to convert HAQ scores to EQ-5D.

- In model-based analyses, costs and benefits were modelled over a number of different time horizons: 6 months (one study); 1 year (one study), 5 years (one study), 10 years (two studies) and lifetime (four studies). However there was no association between ICER values and time horizon used.
4.1.4 Review of industry cost-effectiveness submissions

A detailed summary of the economic analyses and models included in the company submissions is reported in this section. All three companies provided an electronic model. The methods used in the economic analyses are presented in Table 24 below.

Table 24: Summary of methods used in industry economic analyses

<table>
<thead>
<tr>
<th>Submission features</th>
<th>Abbott Laboratories Adalimumab (Humira®)</th>
<th>Wyeth Etanercept (Enbrel®)</th>
<th>Schering-Plough Infliximab (Remicade®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice of TNF inhibitor</td>
<td>Adalimumab in combination with methotrexate</td>
<td>Six-line drug sequence with etanercept/methotrexate combination 1st line, 2nd line or 3rd line</td>
<td>Infliximab in combination with methotrexate</td>
</tr>
<tr>
<td>Comparator</td>
<td>Three line drug sequence without use of adalimumab</td>
<td>Six line drug sequence without use of etanercept</td>
<td>Methotrexate alone</td>
</tr>
<tr>
<td>Patient characteristic(s)</td>
<td>Patients with RA, average age 55, 77% female who have failed 3 DMARDs including methotrexate</td>
<td>Patients with RA, average age 53, (in line with patients in TEMPO trial)</td>
<td>Two patient groups: (1) active RA despite treatment with DMARDs, (2) severe active early RA</td>
</tr>
<tr>
<td>Form of analysis</td>
<td>Cost-utility analysis</td>
<td>Cost-utility analysis</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Model used</td>
<td>Patient based transition-state model with 10,000 patients</td>
<td>Markov model with 6-monthly cycles and 10,000 patients</td>
<td>Markov model with 6 monthly cycles, based on ARAMIS</td>
</tr>
<tr>
<td>Time horizon of model</td>
<td>Lifetime</td>
<td>Lifetime</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Base-case results</td>
<td>£17,860 per QALY</td>
<td>1st line: £16,000 per QALY 2nd line: £20,000 per QALY 3rd line: £18,000 per QALY</td>
<td>Methotrexate experienced: £6,228 per QALY Methotrexate naïve: £16,766 per QALY Methotrexate naïve with high CRP: £13,000 per QALY</td>
</tr>
</tbody>
</table>
4.1.5 **Abbott submission (adalimumab)**

A patient-based, state-transition model was developed to assess the cost-effectiveness of adalimumab in combination with methotrexate compared with a sequence of traditional DMARDs in patients with moderate to severe RA. The main treatment sequences considered are shown below. Adalimumab monotherapy and other TNF inhibitors were also explored and results presented in the report. The 1\textsuperscript{st} to 3\textsuperscript{rd} line therapies are not stated here as the analysis assumed that patients had failed three DMARDs including methotrexate.

<table>
<thead>
<tr>
<th>Therapy line</th>
<th>Treatment sequence (4\textsuperscript{th} line)</th>
<th>Comparator sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>4\textsuperscript{th}</td>
<td>Adalimumab + Methotrexate</td>
<td>Gold</td>
</tr>
<tr>
<td>5\textsuperscript{th}</td>
<td>Gold</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>6\textsuperscript{th}</td>
<td>Leflunomide</td>
<td>Ciclosporin + Methotrexate</td>
</tr>
<tr>
<td>7\textsuperscript{th}</td>
<td>Ciclosporin + Methotrexate</td>
<td>Rescue</td>
</tr>
<tr>
<td>8\textsuperscript{th}</td>
<td>Rescue</td>
<td>Rescue</td>
</tr>
</tbody>
</table>

The model used 6-monthly cycles in which patients can experience a number of events. In the first 6-month period on a therapy a patient can: have a positive response to treatment; have a negative response to treatment; suffer a serious adverse event; or die. In subsequent periods a patient can: have continued efficacy; have a loss of efficacy; suffer a serious adverse event; or die. Therefore at the end of a cycle the patient can: continue on the same therapy; withdraw and proceed to the next therapy when a negative response, loss of efficacy or serious adverse event has occurred; or die.

The model run was for 10,000 patients, and applied a single baseline profile rather than sampling individual patient characteristics. The baseline characteristics were set to reflect patients in adalimumab trials. Patients had a mean age of 54.7 year, 77% were female, with a baseline HAQ of 1.6 and a mean DMARD use of 3. However, assuming a fixed HAQ score at baseline ignores the heterogeneity of response.

Data used in the base case analyses came from trials where the comparator was methotrexate, with the exception of the data for DMARDs. Here an observational study (Geborek et al) of
leflunomide was used and was assumed to be representative of all DMARDs. It is inappropriate to use leflunomide data derived from populations that had failed 2 DMARDs to represent all DMARDs, particularly in early RA. This is because this observational study looks at RA patients who had failed at least 2 DMARDs before testing leflunomide, etanercept or infliximab. In addition, using annual withdrawal rates for leflunomide from this study and assuming that this applies to all DMARDs is inappropriate. No meta-analyses of biological trials were undertaken for their analysis, and main trial data for each of the TNF inhibitors was used instead.

Clinical advice recommended that strategies where dose escalation with infliximab occurred should be excluded due to greatly increased cost whilst adding very little benefit. The analysis in this report also does not consider dose escalation, therefore the ICERs reported for infliximab will underestimate drug costs. In reality, dose escalation is common and ideally should be incorporated in CE analyses.

ACR50 data were used in the base case to determine response rate on each therapy, with patient level trial data used for adalimumab and published data for other DMARDs. Average improvement in HAQ for ACR20, ACR50 and ACR70 responders was available from the adalimumab trials. This data was not available for other DMARDs therefore an assumption was made that HAQ improvement would be the same as for adalimumab and independent of treatment. The calculated HAQ change, categorised by response, is shown in Table 25. Long-term change in HAQ was obtained from a systematic review, assuming a slight progression of disability over time, with data for a successful response recalculated to account for the variation in patient numbers in the studies. However, to assume year on year decrease in HAQ response in early disease is problematic as HAQ is very labile in the first 5 years of disease. Withdrawal from treatment was assumed to change the HAQ score by the equivalent amount of the initial improvement, therefore giving a slightly higher HAQ score that at baseline but due to gradual progression of disability. Data for non-responders was based on an observational study by Young et al.46 This study does not report specifically on DMARD responders and non-responders and it is unclear how this data was obtained. Also, the study is a hospital based study of early RA patients where data was collected annually. As HAQ is especially labile in this population, single annual measurements have limited reliability.
Table 25 HAQ changes by response type

<table>
<thead>
<tr>
<th>ACR improvement</th>
<th>Observed HAQ change</th>
<th>HAQ change given baseline of 1.6</th>
<th>New HAQ score for responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20%</td>
<td>-6.4%</td>
<td>-0.102</td>
<td>1.498</td>
</tr>
<tr>
<td>20-50%</td>
<td>-34.7%</td>
<td>-0.555</td>
<td>1.045</td>
</tr>
<tr>
<td>50-70%</td>
<td>-57.0%</td>
<td>-0.912</td>
<td>0.688</td>
</tr>
<tr>
<td>70%+</td>
<td>-64.6%</td>
<td>-1.034</td>
<td>0.566</td>
</tr>
</tbody>
</table>

Patient HAQ scores are updated every 6 months and the mean level of HAQ improvement was obtained from clinical trial data and published literature. HAQ scores are converted to QALYs by using regression of HAQ against utility from trial data. The relationship between HAQ and utility scores was given as $U = 0.76 - (0.28 \times \text{HAQ}) + 0.05 \times \text{Female}$. This relationship was derived from analysis of Health Utility Index 3 data obtained from the adalimumab trials.

Data on the incidence of mild, moderate and serious adverse events were estimated from an observational study. The same study and a review provided data on long-term withdrawal; the limitations of using data from Geborek et al are discussed above. Mortality risk for patients with RA was adjusted by HAQ score, and Gompertz models were fitted, with the minimum age set at 50. The 6 monthly hazard rate was calculated in the model for patients’ age and mid-point HAQ score during each therapy line. This simplification may be acceptable, however, exploratory analyses would be worthwhile to test this assumption.

Resource use and costs were derived from published data, costing BSR guidelines and expert clinical opinion. In addition, some health care resource utilisation was estimated based on HAQ-DI scores. Costs and benefits were discounted at 6% and 1.5% respectively. Costs were calculated from a health care perspective. Both simple one-way and probabilistic sensitivity analyses were undertaken.

The base-case results using ACR50 suggest that adalimumab is cost-effective as 4th line therapy, with an ICER of £17,860. A total of 32 one-way sensitivity analyses were conducted all giving ICERs under £30,000 per QALY. Probabilistic sensitivity analysis showed
adalimumab in combination with methotrexate to have a 99.8% probability of being cost-effective at a willingness to pay threshold of £30,000 per QALY. Comparison with etanercept gave a lower ICER of £14,388 and a 96% probability of being cost-effective at £30,000 per QALY.

Secondary analyses were also reported. Using an ACR20 response the cost per QALY for adalimumab plus methotrexate was £19,251. Cost-effectiveness ratios at different lines of entry were also explored for ACR50 and ACR20.

The ICERs for ACR50 are:
- 1st line: £19,095 per QALY
- 2nd line: £18,166 per QALY
- 3rd line: £18,479 per QALY

The ICERs for ACR20 are:
- 1st line: £21,228 per QALY
- 2nd line: £19,794 per QALY
- 3rd line: £19,596 per QALY

The study concluded that adalimumab “should be considered cost-effective when compared against conventional DMARDs” and on the basis of this “the cost-effectiveness of adalimumab is very similar to that of etanercept and infliximab.”

4.1.6 Wyeth submission (etanercept)

A sequential model was developed whereby a simulated patient receives a given treatment until DMARD switching occurs as a result of either failure of effectiveness or serious adverse events. The main treatment sequences considered are shown below but others were explored and not presented in the report.
<table>
<thead>
<tr>
<th>Therapy line</th>
<th>Treatment sequence</th>
<th>Comparator sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Etanercept + Methotrexate</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Methotrexate</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>Sulfasalazine</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Leflunomide</td>
<td>Gold</td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Gold</td>
<td>DMARD (non-specified)</td>
</tr>
<tr>
<td>6&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Salvage therapy</td>
<td>Salvage therapy</td>
</tr>
</tbody>
</table>

The submission indicates that “the aim of the economic model and treatment sequences was to demonstrate that etanercept + MTX is a cost-effective intervention when used earlier in the management of RA, i.e. 1<sup>st</sup> and 2<sup>nd</sup> line”. Etanercept and methotrexate were used in combination as “the body of evidence suggests that combination therapy is more effective than monotherapy”. Using combination data, however, will weigh ICERs in favour of etanercept since patients responding to combined therapy, if they are DMARD naïve, have the opportunity of responding to two agents and many may have responded to MTX alone.

The model uses 6-monthly cycles and allows patients to experience: changes in disease severity; enter a remission state; develop drug tolerance problems; experience a serious adverse event; or die. At the end of each 6-month cycle the patient can:

- Change disease severity;
- Experience a serious adverse event;
- Switch treatment therapy; or
- Die.

The model run consisted of 10,000 hypothetical patients, followed until death. Costs were calculated from the perspective of a health care provider. The main driver of the model result is the patient’s disease severity. Disease severity determines several factors in the model including the likelihood of switching therapy, health-related utility and mortality. HAQ was used to represent disease severity as it was not practical to measure both HAQ and DAS28 scores simultaneously. However for the purpose of ‘switching thresholds’ a relationship

Last amended: 11 October 2005
between HAQ and DAS28 was required and changes in HAQ score were used as a proxy for changes in the DAS28. Perhaps here it would have been more appropriate to use actual switching rates from clinical observation rather than this conversion which potentially introduces more uncertainty into the model. A baseline HAQ of 1.74 was obtained from the TEMPO trial. Using a fixed HAQ at start of treatment has limitations and the heterogeneity of response is not taken into account. Patients’ HAQ scores are updated every 6 months, with the changes based on evidence from clinical trials and other published sources (see Table 26 for estimates).

A robust approach was applied, where distributions rather than point estimates were used in order to introduce a random element into HAQ change. The HAQ change estimates were derived from the TEMPO study for etanercept, MTX and combination therapy. The HAQ change for unspecified DMARD was based on the TICORA trial. This is inappropriate since data for individual drugs is available. The initial HAQ change for sulfasalazine assumed -0.29. This improvement is based on an intention to treat analysis of trial data and HAQ improvement for those that continue drug was -0.43. For the purposes of economic modelling we are interested in those that continue treatment since those who do not are accounted for elsewhere. Thus a figure of -0.29 underestimated the benefit of continuing with sulfasalazine. Data from trials such as TEMPO represents ideal responses and the data may not reflect outcomes in routine care. For other therapies, the estimates were based on “published sources” and where data was not available for six-month changes, estimates were converted to six-month rates using a simple formula. In all cases, the first six months change was accounted for when calculating medium-term changes. Patients in remission were assumed to experience different HAQ changes compared to those not in remission. However, the definition of remission is problematic, and the change in HAQ may have been sufficient to represent remission without assuming further treatment benefits in modelling.
Serious adverse events (SAEs) in the model were dependent on the treatment received. Their occurrence affected costs, utility and the likelihood of switching therapy. SAEs were assumed to occur for one cycle only. “Due to lack of reliable evidence for this parameter, it was assumed that one-third of patients who experience a SAE would switch therapies during that (6 month) period.” This assumption would be unnecessary if actual data on switching were used and the probability of switching may actually be much higher than a third. In addition, SAEs and switching appear to be able to occur with salvage therapy, but is it unclear how or why this happens.

Table 26: HAQ Change Parameters

<table>
<thead>
<tr>
<th></th>
<th>Etan</th>
<th>MTX</th>
<th>Etan+MTX</th>
<th>SSZ</th>
<th>Gold</th>
<th>Infl+MTX</th>
<th>DMARD</th>
<th>Adal</th>
<th>Lef</th>
<th>Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial HAQ change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>-0.690</td>
<td>-0.650</td>
<td>-0.890</td>
<td>-0.290</td>
<td>-0.430</td>
<td>-0.080</td>
<td>-0.270</td>
<td>-0.560</td>
<td>-0.500</td>
<td>-0.040</td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium-term non-remission – mean HAQ change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>-0.005</td>
<td>-0.001</td>
<td>-0.052</td>
<td>0.075</td>
<td>0.045</td>
<td>-0.087</td>
<td>-0.080</td>
<td>-0.030</td>
<td>0.000</td>
<td>0.200</td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Remission – mean HAQ change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>-0.0276</td>
<td>-0.0037</td>
<td>-0.0145</td>
<td>0.075</td>
<td>0.045</td>
<td>-0.087</td>
<td>-0.080</td>
<td>-0.030</td>
<td>0.000</td>
<td>0.200</td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-term change per cycle</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>0.00</td>
<td>0.02</td>
<td>0.00</td>
<td>0.10</td>
<td>0.10</td>
<td>0.00</td>
<td>0.1</td>
<td>0.00</td>
<td>0.10</td>
<td>0.28</td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMARD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 27 Serious adverse events parameters

<table>
<thead>
<tr>
<th></th>
<th>Etan</th>
<th>MTX</th>
<th>Etan+MTX</th>
<th>SSZ</th>
<th>Gold</th>
<th>Infl+MTX</th>
<th>DMARD</th>
<th>Adal</th>
<th>Lef</th>
<th>Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of SAE</td>
<td>0.07</td>
<td>0.07</td>
<td>0.05</td>
<td>0.07</td>
<td>0.06</td>
<td>0.10</td>
<td>0.06</td>
<td>0.07</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Probability of switching if SAE</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Switching occurs for one of two reasons: lack of effectiveness or occurrence of an SAE. The treatment switch criteria used in the model were:

- If a patient does not have an initial (i.e. first 6 months) improvement of 0.3468 in HAQ.
- If, after an initial improvement, the patient’s HAQ worsens by 0.3468 over 12 months or 0.3468 over a 6-month period.

Mortality rates for RA were assumed to be 1.63 times that of the general population of the same age. The change in mortality rate was adjusted taking change in HAQ into account. Inflating the already increased mortality on the basis of HAQ appears to introduce double-counting and is therefore inappropriate. Utility weights were assumed to vary linearly with HAQ score (i.e. \( U = 0.76 + \text{(HAQ x -0.28)} \)). This was further adjusted to consider SAEs – with a loss of 0.05 for each SAE experienced, but this assumption for a six-month period for someone experiencing a SAE appears to be an underestimate.

Resource use and cost data were taken from expert opinion and national sources. One blood test per year is assumed for those on TNF inhibitors and two for those on DMARDs. However if those on TNF inhibitors are to receive methotrexate, then more frequent blood tests (e.g. monthly) are likely. This larger number of blood tests would apply to both arms. Rituximab is suggested for the salvage therapy with a six-month cost of almost £900. This is in contrast with the equivalent ‘palliation’ used in other analyses where costs are much lower, which may be a more accurate reflection of reality. For the base case, costs were discounted at 6% and QALYs at 1.5%. Simple one-way sensitivity analysis was undertaken on HAQ changes, mortality rate,
SAE utility, cost, discount rates and switching threshold. The upper value for initial change in HAQ on etanercept of -1.3 appears to be rather high.

The base-case results suggest that etanercept is cost-effective 1st line. The ICERs indicate:

- 1st line: £16,000 per QALY
- 2nd line: £20,000 per QALY
- 3rd line: £18,000 per QALY

Sensitivity analysis results are interpreted as showing that the results for all three models (1st, 2nd and 3rd line) are “relatively robust to changes in key parameters”.

4.1.7 Schering-Plough submission (infliximab)

The economic analysis presented in this submission assessed the cost-effectiveness of infliximab in combination with methotrexate compared to methotrexate alone in patients with severe RA. Data on effectiveness were drawn from the ATTRACT and ASPIRE trials and so the patient populations seen in those trials were assumed for the modelling work: patients with active RA despite DMARD use; patients with severe active early RA. The perspective adopted was that of the NHS and PSS.

To estimate the long-term consequences of RA and model the natural history of RA, a Markov model was used based on the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS). This is not described in detail in the report. ARAMIS is a North American database consisting of 4,258 prospectively enrolled patients with RA from 9 centres followed for over 17,000 patient years. The issue here is how a population of patients seen in private practices in the US and Canada between 1981 and 1995 can reflect practice in the NHS in 2005. The model has states defined in terms of HAQ score (e.g. HAQ 0.1-1.0) and states defined in terms of treatments (e.g. methotrexate and one or more DMARD). Each health state, in terms of disability score and treatment, determines the transitional probability. During any cycle, patients may change or retain the same treatment, with the exception that the other treatments could not change to infliximab+methotrexate. It is unclear why a change to
infliximab and methotrexate is not permitted as this is a fairly common practice for people not doing well on a DMARD. An assumption was made that when infliximab was continued beyond the trial duration, the HAQ score would be preserved but not improved, and would be discontinued with worsening HAQ or side effects. HAQ in RA or in the normal population tends to decline with age, therefore assuming long-term stability is unreasonable.

Clinically significant radiographic progression was determined from cohort data using the smallest detectable difference (SDD) based on the OMERACT definition. Although SDD is an important starting point for determining whether radiographic changes are clinically meaningful, it is by no means accepted that the two are the same. In addition, the SDD needs to be determined for each trial since it is a statistical concept and depends on the performance of two or more assessors in a particular setting, so SDD from different settings vary considerably. Patient were divided into radiographic SDD progressors and non-progressors, with progressors having higher mean HAQ scores due to physical disability from the progressing disease. Therefore an absence of radiographic progression improved HAQ by 0.27 after 5-6 years. But since there is a relationship between HAQ and radiographic change, and since HAQ changes are incorporated into the model, it appears that HAQ improvements are being double-counted.

Radiographic data were used in the model such that evidence of radiographic stabilisation was applied to the Markov as increasing the chance that a patient would remain in the same HAQ group, thereby decreasing the annual likelihood of HAQ progression. However, radiographic changes are likely to be greater in early RA and it is unreasonable to assume similar changes could apply to the ATTRACT trial population. This analysis also calibrated the model to assume benefits 5 years from trial onset. Radiographic benefit was applied to patients treated more than 6 weeks, so patients who discontinued infliximab where no ACR20 response was evident by week 14 did not receive this benefit. Most patients in trials do not show radiographic changes. Therefore assuming this radiographic benefit several years later in patients with 6 weeks of treatment and an ACR20 response at 14 weeks is rather generous.

Estimates of the impact of infliximab on disease progression were obtained from the ATTRACT trial and from the ASPIRE trial, with the likelihood of improved or worsened HAQ
score estimated from the methotrexate and methotrexate/infliximab arms of the trials. However using all arms of infliximab/methotrexate regardless of dose or dosing interval from ATTRACT may weigh in favour of infliximab as, although outcomes looked similar, patients on 10mg/kg of infliximab did appear to be doing better. Health state values were derived from Kobelt et al (2002) with a conversion of HAQ to utility based on personal communication with Kobelt, as follows:

- HAQ 0 = 0.819
- HAQ 0.1-1.0 = 0.682
- HAQ 1.1-2.0 = 0.454
- HAQ 2.1-3.0 = 0.192

UK-based sources for resource use data and for unit costs were used (the ERAS study). Discount rates of 6% for costs and 1.5% for benefits were applied. A wide range of one-way and multi-way sensitivity analyses were undertaken.

**Table 28 Base case CE results (Schering-Plough)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Incremental cost (£)</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate experienced (ATTRACT)</td>
<td>17,370</td>
<td>2.79</td>
<td>6,228</td>
</tr>
<tr>
<td>Methotrexate naïve (ASPIRE)</td>
<td>23,808</td>
<td>1.42</td>
<td>16,766</td>
</tr>
<tr>
<td>Methotrexate naïve with high CRP (ASPIRE)*</td>
<td>23,926</td>
<td>1.84</td>
<td>13,000</td>
</tr>
</tbody>
</table>

* Represent early progressive RA

The results are interpreted as yielding “costs per QALY that fall well within the range of such estimates for health care interventions typically funded in the UK. The high CRP subset has a better cost-effectiveness ratio because of faster radiological progression compared to the overall ASPIRE group.”
The sensitivity analyses looked at stopping rules, discount rates, RA mortality assumptions, utility scores, resource use and radiographic stabilisation. ACR20 was used for the stopping rules in this analysis, however the stopping rule recommended by NICE stipulates use of DAS28 scores only. Although the two are related, it is not clear that ACR20 can substitute for DAS28 changes in practice. Assumptions concerning the duration of radiographic benefit were shown to be a possible driver of the CE results.

Summary of industry submissions:

- The submission by Wyeth suggests that etanercept is highly cost-effective.
- The submission by Schering-Plough suggests that infliximab is highly cost-effective.
- The submission by Abbott suggests that adalimumab is highly cost-effective.
- All three submissions report a model-based cost-utility analysis with a lifetime horizon, and all three have undertaken extensive sensitivity analyses. The results of all sensitivity analyses broadly support the base case findings of support for the use of the new therapy/product in question.
- Two of the three submissions (those from Wyeth and Abbott Laboratories) have considered drug sequences and the use of the new therapy as part of an existing sequence.
4.2 Economic analysis used in this report

**Summary of the Birmingham economic evaluation**

- A simulation model, which considered improvements in quality of life and mortality, but assumed no effect of the TNF inhibitors on the need for joint replacement, was used.

- For use in accordance with current NICE guidance, as the third DMARD in a sequence of DMARDs, the base-case ICER depended on whether the effectiveness data was taken from early RA or late RA patients as shown below (in clinical practice there will be a mixture of both). Sensitivity analyses showed that the results were most sensitive to figures for HAQ progression on TNF inhibitors and the effectiveness of DMARDs, but not particularly sensitive to changes in mortality ratios used per unit HAQ.

<table>
<thead>
<tr>
<th>TNF Inhibitor</th>
<th>Comparator</th>
<th>Cost/QALY Late RA</th>
<th>Cost/QALY Early RA</th>
<th>Sensitivity analyses - late RA data (early RA data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (no MTX)</td>
<td>Dominated</td>
<td>£55K</td>
<td>£56K (£27K)</td>
<td>Dominated (£101K)</td>
</tr>
<tr>
<td>Etanercept (no MTX)</td>
<td>£93K</td>
<td>£45K</td>
<td>£30K (£23K)</td>
<td>£505K (£79K)</td>
</tr>
<tr>
<td>Adalimumab (with MTX)</td>
<td>£169K</td>
<td>£45K</td>
<td>£40K (£25K)</td>
<td>Dominated (£70K)</td>
</tr>
<tr>
<td>Etanercept (with MTX)</td>
<td>£94K</td>
<td>£42K</td>
<td>£30K (£22K)</td>
<td>£608K (£69K)</td>
</tr>
<tr>
<td>Infliximab (with MTX)</td>
<td>Dominated</td>
<td>£49K</td>
<td>£61K (£26K)</td>
<td>Dominated (£75K)</td>
</tr>
</tbody>
</table>

- TNF inhibitors are most cost-effective when used last in a sequence of DMARDs giving an ICER for etanercept of £32k/QALY which was substantially lower than the ICERs for adalimumab (£67k/QALY) or infliximab (£69k/QALY). Suggesting that, other things being equal, etanercept should be the TNF inhibitor of choice.

- First-line use in early RA gave ICERs over £100k/QALY for etanercept and adalimumab and infliximab was dominated by the base strategy.

- For sequential use of TNF inhibitors, only etanercept was clinically worth using as a second or third TNF inhibitor. It produced an ICER of £88k/QALY or higher. Adalimumab and infliximab were dominated by base strategy when used as the second or third TNF inhibitors.
The main aim of the analysis was to assess the cost-effectiveness of adding a TNF inhibitor to an existing treatment pathway for rheumatoid arthritis compared to the same pathway without that TNF inhibitor. The costs are from an NHS perspective.

The analysis was conducted using an updated version of the Birmingham Rheumatoid Arthritis Model (BRAM), which was further developed starting from the most recent previous version (used in the assessment of anakinra).

The BRAM is an individual sampling model. The model was devised to reflect the typical real clinical patient pathway. A large number of virtual patient histories are simulated with the accumulation of costs and QALYs. The basic model structure is shown in Figure 46 followed by a complete description of the model structure.
Patients are assumed to follow a sequence of treatments (single or combination therapy) which involves: starting a treatment; spending some time on that treatment; quitting the treatment if it is toxic or ineffective; and starting the next treatment. The pattern is then repeated. Any patient who has started and had to quit all the active treatments moves on to palliation. Patients’ HAQ scores are assumed to improve (decrease) on starting a treatment; this improvement is lost on quitting the treatment, which may be for reasons either of toxicity or loss of effectiveness. HAQ scores can range from 0 (best) to 3 (worst) and are constructed such that the smallest measurable change in disability is 0.125 (see Appendix 1, page 229 for further details of the HAQ). Reflecting observed data, while on any treatment, a patient’s
condition is assumed to decline slowly over time; this is modelled as periodic increases of 0.125 in HAQ score.

All patients are followed through to death. Mortality risk is assumed to depend on current HAQ score, as well as age and sex.

There are two important improvements from previous versions of the BRAM. Firstly, there is individual variation in HAQ improvement on starting treatment. Secondly, time on treatment includes explicit consideration of early quitting, with early quitting due to lack of effectiveness being correlated to poor HAQ improvement on starting treatment.

**4.2.1 Strategies compared using the BRAM**

**4.2.1.1 Baseline for comparison**

Before considering how TNF inhibitors could be included in treatment strategies, it is convenient to describe the baseline strategy without TNF inhibitors.

The baseline strategy, based on our previous survey of all rheumatology consultants in the UK, starts with methotrexate (MTX) as single therapy. If methotrexate is stopped on grounds of toxicity, it is followed by sulfasalazine (SSZ) as single therapy, otherwise by the combination of methotrexate plus sulfasalazine. Similarly, if this combination is quit on grounds of toxicity, it is followed by leflunomide (LEF). But, if the methotrexate-sulfasalazine combination lacks efficacy, hydroxychloroquine (HCQ) is added to the combination. These rules are shown in Table 29 under the header “Moves dependent on toxicity”. For most other treatments, the choice of treatment next in sequence, and the move to the next agent, simply depends on drug cessation – for whatever reason. For example, sulfasalazine as single therapy, in the table below, is always followed by leflunomide, as shown under the header “Always move to”. In the case of ciclosporin (CyA), the preferred next treatment is the combination of ciclosporin plus methotrexate. However, this combination cannot be offered if ciclosporin has just been quit on grounds of toxicity, nor can it be offered if methotrexate was earlier quit for toxicity. This is shown under “Relevant toxicity”. Palliation (Pall) is the treatment of last resort and therefore cannot be quit. The other abbreviations used in the following tables are AZA for azathioprine, DPen for penicillamine and GST for injectable gold.
Table 29 Basic structure of the model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>If toxic, move to</td>
</tr>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
</tr>
<tr>
<td>SSZ</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td></td>
<td>MTX+SSZ</td>
<td>LEF</td>
</tr>
<tr>
<td>MTX+SSZ+HCQ</td>
<td></td>
<td>LEF</td>
<td>MTX+SSZ+HCQ</td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td></td>
<td>CyA or MTX*</td>
<td>DPen</td>
</tr>
<tr>
<td>CyA+MTX</td>
<td></td>
<td></td>
<td>CyA+MTX</td>
</tr>
<tr>
<td>DPen</td>
<td></td>
<td></td>
<td>Pall</td>
</tr>
</tbody>
</table>

* We assume that toxicity of MTX+SSZ(+HCQ) would not preclude the use of the combination CyA+MTX. (Because of the paucity of data for toxicity in the case of MTX+SSZ+HCQ and the individual components of MTX+SSZ. This simplifying assumption is unlikely to be significant.

The structure as shown in this table is more general than the structure used in previous versions of the BRAM: all our previous strategies can be described by tables of this form.

4.2.1.2 Comparisons

For clarity, the word “comparison” is reserved for an analysis comparing two options. The phrase “strategy set” is used for a collection of strategies (treatment sequences) with a common initial sequence and divergence point.

4.2.1.2.1 Single TNF inhibitors (vs. no TNF inhibitor)

In these strategy sets only one TNF inhibitor is used. There are six options in each case: adalimumab alone; etanercept alone; each of the three TNF inhibitors combined with methotrexate; and the comparator option without TNF inhibitors. These produce a total of fifteen possible comparisons: five (“major comparisons”) relate to including each TNF inhibitor singly within a sequence without TNF inhibitors and ten (“minor comparisons”) relate to comparisons between different TNF inhibitors.
A. *Single TNF inhibitor at the start*

In this strategy set, the divergence point is at the start of the sequence, i.e. patients are treated with a TNF inhibitor before any other DMARD (see Table 30, options at divergence point are shaded). Option 1 starts with adalimumab followed by methotrexate. Option 2 starts with etanercept followed by methotrexate. Option 3 starts with adalimumab in combination with methotrexate followed by sulfasalazine (it would be clinically inappropriate to use methotrexate as single therapy after failing this combination). Similarly, options 4 and 5 start with etanercept and infliximab, respectively, in combination with methotrexate. Option 6, the comparator, starts with methotrexate. Each of options 1, 2, and 6 continues with the complete baseline strategy, while options 3, 4, and 5 join this strategy from sulfasalazine, thus avoiding the early combinations with methotrexate. It is assumed that the combination of ciclosporin with methotrexate would still be available in this case. When the model is run, initial characteristics for (virtual) patients are sampled from the starting distribution. Each patient is then run independently through each of the four options and differences in costs and QALYs between options are recorded. This process is repeated for a sufficiently large number of patients to produce a statistically stable comparison between each pair of options.
### Table 30 Strategy set with TNF inhibitors at the start

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>If toxic, move to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Otherwise, move to</td>
</tr>
<tr>
<td>Option 1</td>
<td>Adal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>Etan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 3</td>
<td>Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>SSZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 4</td>
<td>Etan+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>SSZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 5</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>SSZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 6</td>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
</tr>
<tr>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>MTX+SSZ</td>
<td>LEF</td>
<td>MTX+SSZ+HCQ</td>
</tr>
<tr>
<td>MTX+SSZ+HCQ</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### B. Single TNF inhibitor as third-line therapy

In this strategy set, TNF inhibitors are considered as third-line therapy, i.e. after two DMARDs including methotrexate have been tried – in accordance with current NICE guidance.

Each (virtual) patient is started on methotrexate. Patients who quit methotrexate on grounds of toxicity move to single therapy sulfasalazine. Those who quit for any other reason move to the
combination methotrexate plus sulfasalazine. Any patient who dies while still on one of the
treatments mentioned so far is discarded from the analysis and replaced by a new (virtual)
patient starting again from the beginning with methotrexate. Any patient who fails on
sulfasalazine (or methotrexate plus sulfasalazine) has reached the divergence point between the
options (see Table 31, below, options after divergence point are shaded). The patient’s
characteristics at this moment are stored for future use, and the patient is run through the rest of
option 1, continuing with adalimumab and then leflunomide, and so on.

Costs and QALYs are counted only from the divergence point, and are discounted to the
divergence point. The patient characteristics at the divergence point are retrieved, and the
patient is run through option 2, starting with etanercept followed by leflunomide. Once the
costs and QALYs for option 2 have been calculated, the patient characteristics at the
divergence point are again retrieved, and the patient is run through option 3, starting this time
with the combination adalimumab plus methotrexate, except that if methotrexate has been quit
on grounds of toxicity, adalimumab monotherapy is given instead. In either case, this therapy
is followed by leflunomide. Option 4 is similar to option 3, with etanercept instead of
adalimumab. In option 5, the combination infliximab plus methotrexate is given immediately
after the divergence point.

In practice, patients who had quit methotrexate on grounds of toxicity would not be given a
combination of infliximab and methotrexate (option 5). We have assumed that such patients
would be given infliximab as single therapy, although we recognise that infliximab is often
combined with other agents such as leflunomide or azathioprine in clinical practice. We have
further assumed that the effectiveness of infliximab without methotrexate in these
circumstances is similar to infliximab with methotrexate. To compensate for a bias in favour
of infliximab introduced by this assumption, the cost for the combination is also used. (The
cost of methotrexate forms only a small part of the cost of this combination.) Thus, in the
model, the data set for the combination infliximab plus methotrexate is used regardless of the
reason for quitting methotrexate. Option 5 continues with leflunomide, and so on. Finally,
option 6 involves the use of leflunomide immediately after the divergence point. Differences
between options are stored and the process is repeated for a sufficiently large number of
patients.
### Table 31 Strategy set with TNF inhibitors in third place

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 3</td>
<td>MTX</td>
<td>Adal</td>
<td>Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 4</td>
<td>MTX</td>
<td>Etan</td>
<td>Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 5</td>
<td>Infl+MTX*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 6</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The data set for this combination is used in the model, regardless of the reason for quitting methotrexate.

**C. Single TNF inhibitors as last active therapy**

In this strategy set, patients are run through the whole of the baseline strategy if necessary. Any patient who dies while still on active therapy is discarded from the analysis and replaced by a new patient. Any patient who fails on all the conventional DMARDs used in the baseline strategy reaches the divergence point (see Table 32, options at divergence point are shaded).
Thus, in this strategy TNF inhibitors are used are treatments of last resort. As before, the patient’s characteristics at the divergence point are stored before the patient starts on option 1 (adalimumab followed by palliation). The patient is then restarted from the divergence point and run through each of the other options.

**Table 32 Strategy set with TNF inhibitors as last active therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>MTX+SSZ</td>
<td>LEF</td>
<td>MTX+SSZ+HCQ</td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ+HCQ</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CYA+MTX</td>
<td>DPen</td>
<td>Divergence pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Adal</td>
<td>Adal</td>
<td>Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>Etan</td>
<td>Etan</td>
<td>Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>Option 3</td>
<td>MTX</td>
<td>Adal</td>
<td>Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Option 4</td>
<td>MTX</td>
<td>Etan</td>
<td>Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>Option 5</td>
<td>Infl+MTX*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 6</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Last amended: 11 October 2005_
4.2.1.2.2 Strategies including two TNF inhibitors consecutively

Here the relevant decision is, having used one TNF inhibitor, whether to use a second TNF inhibitor or to revert to conventional DMARDs. We consider only the case where the first TNF inhibitor is used as third-line therapy, and we consider adalimumab and etanercept only as single therapy. Any one of the three TNF inhibitors could be the first choice. Thus there are three strategy sets to consider, each with three options.

The first of these strategy sets, shown in Table 33 starts with methotrexate, followed by sulfasalazine (with or without methotrexate) and then adalimumab. The divergence point comes immediately after adalimumab. Options 1 and 2 are to treat with etanercept and infliximab, respectively, if adalimumab fails and then continue the baseline strategy from leflunomide onwards. In the comparator, option 3, adalimumab is followed by leflunomide and the baseline strategy. The equivalent strategy sets for other choices of first TNF inhibitor are shown in Table 71 and Table 72 in Appendix 8, page 260.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td></td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
</tr>
<tr>
<td>SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 3</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td></td>
<td>CyA or MTX</td>
<td>DPEN</td>
<td>CyA+MTX</td>
</tr>
</tbody>
</table>
4.2.1.2.3 Strategies including all three TNF inhibitors consecutively

Here the relevant decision is, having used two TNF inhibitors, whether to use a third TNF inhibitor or to revert to conventional DMARDs. Again we are considering only the case where the first TNF inhibitor is used as third-line therapy, i.e. after sulfasalazine and methotrexate have been tried (according to current NICE guidance), and we consider adalimumab and etanercept only as single therapy. Any one of the three TNF inhibitors could be the first fixed choice, with either of the other two as the second fixed choice. Thus there are six strategy sets to consider, each with two options.

The strategy set shown in Table 34 starts with methotrexate, followed by sulfasalazine (with or without methotrexate) and then adalimumab followed by etanercept. The divergence point comes immediately after etanercept. Option 1 is to use infliximab after this and then continue the baseline strategy from leflunomide onwards; option 2 is to forgo infliximab and continue directly with leflunomide. The other five strategy sets which are similar are given in Table 73, Table 74, Table 75, Table 76 and Table 77 in Appendix 8, page 260.
Table 34 Strategy set: adalimumab and etanercept possibly followed by infliximab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td></td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
</tr>
<tr>
<td>SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.2.2 Data used in the BRAM

The main source of data is the current review for TNF inhibitors and published literature for other data.

Initial Patient Data

Table 35 shows the initial age and sex distribution, based on UK data from Wiles et al. 169

Table 35 Initial age and sex distribution

<table>
<thead>
<tr>
<th>age</th>
<th>15 – 24</th>
<th>25 – 34</th>
<th>35 – 44</th>
<th>45 – 54</th>
<th>55 – 64</th>
<th>65 – 74</th>
<th>75 – 84</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>0.9</td>
<td>2.5</td>
<td>5.4</td>
<td>8.3</td>
<td>9.0</td>
<td>6.8</td>
<td>5.1</td>
<td>38</td>
</tr>
<tr>
<td>female</td>
<td>1.5</td>
<td>4.0</td>
<td>8.8</td>
<td>13.7</td>
<td>14.7</td>
<td>10.9</td>
<td>8.4</td>
<td>62</td>
</tr>
</tbody>
</table>

The starting distribution of HAQ scores, shown in Table 36 is also based on Wiles et al. 169

Table 36 Starting distribution of HAQ scores
### Starting treatments

In previous versions of the BRAM, the HAQ improvement (decrease) on starting any treatment was fixed as a multiple of 0.125. In this version, the HAQ improvement has been allowed to vary between individual patients in the model, and is modelled as a multiplier of the original HAQ. An example of the method used is shown here for the case of leflunomide.

Data available were baseline HAQ mean 1.03, standard deviation 0.62, and HAQ improvement mean 0.48 (SD 0.5).

An Excel spreadsheet was set up to create a starting population of 10,000 virtual patients with HAQ scores drawn from a normal distribution with mean and standard deviation supplied by the user. Each generated HAQ score was converted to the nearest legitimate value (multiples of 0.125 in the range 0 to 3). The parameters supplied were adjusted to compensate for the effect of this conversion, so that the mean and standard deviation of the population generated correspond to the data.

A beta distribution was found to match the given mean and standard deviation for HAQ improvement. The parameters are shown in Table 37, while Figure 47 displays the simulated population. Each square within the graph represents a possible pair of values of starting HAQ and HAQ on treatment: the darker the square, the larger the number of simulated patients with that pair of HAQ values. It can be seen that there is a high proportion of patients with equal HAQ on treatment compared to before treatment. In this example, the sampled population contains a large number of zero initial HAQ values. These are omitted from the graphs, but included in the calculations relating to HAQ improvement.
### Table 37 Fitting beta distribution to HAQ change data for leflunomide

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial HAQ parameters</td>
<td>1.01</td>
<td>0.66</td>
</tr>
<tr>
<td>Initial HAQ sampled</td>
<td>1.03</td>
<td>0.62</td>
</tr>
<tr>
<td>HAQ improvement</td>
<td>0.48</td>
<td>0.50</td>
</tr>
<tr>
<td>Beta parameters</td>
<td>0.57</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Table 38 shows the parameters found for the beta distributions. Two sets of figures are given for each of the TNF inhibitors – one for early RA, and one for late RA. The columns headed $a$ and $b$ are the actual parameters of the distribution, while the column headed mean gives the mean value of the distribution. Since the distribution is for a multiplier giving HAQ improvement, the higher the mean, the more effective the treatment. Consider for example a patient with HAQ before treatment equal to 2.5. The effect of a treatment with mean 0.6 will lie somewhere between two extremes. One extreme is that all patients have HAQ reduced by $0.6 \times 2.5 = 1.5$, so that HAQ on treatment would be 1.0, while the other extreme is that 60% of patients have HAQ reduced to zero, while the other 40% have no change in HAQ. Where values of $a$ and $b$ are both less than 1, as is generally the case for the values used here, the distribution is close to the second of these cases.
### Table 38 Beta distributions for HAQ multipliers

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(a)</th>
<th>(b)</th>
<th>Mean</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Adal) early RA</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>From PREMIER trial(^{102}) (DE 013); unpublished data (observed values) from trial report. MTX naïve patients.</td>
</tr>
<tr>
<td>Adalimumab (Adal) late RA</td>
<td>0.16</td>
<td>0.61</td>
<td>0.21</td>
<td>From van de Putte 2004(^{109}) (DE011), data with LOCF imputation, without concomitant MTX</td>
</tr>
<tr>
<td>Adal+MTX early RA</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>From PREMIER trial(^{102}) (DE 013); unpublished data (observed values) from trial report. MTX naïve patients.</td>
</tr>
<tr>
<td>Adal+MTX late RA</td>
<td>1.08</td>
<td>1.36</td>
<td>0.44</td>
<td>Combined results from ARMADA trial(^{108}) (DE009) and Keystone 2004(^{110}) (DE019)</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>0.20</td>
<td>0.80</td>
<td>0.20</td>
<td>Data assumed to be similar to anakinra using data from Bresnihan et al(^{171})</td>
</tr>
<tr>
<td>Ciclosporin (CyA)</td>
<td>0.13</td>
<td>0.26</td>
<td>0.33</td>
<td>RCT of injectable gold versus ciclosporin A in early RA(^{172}) Kvien TK, Zeidler HK, Hannonen P, Wollheim FA, Forre O, Hafstrom I, et al(^{173})</td>
</tr>
<tr>
<td>Etanercept (Etan) early RA</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>From ERA trial.(^{119}) Unpublished data with LOCF imputation from trial report. MTX naïve patients.</td>
</tr>
<tr>
<td>Etanercept (Etan) late RA</td>
<td>0.43</td>
<td>0.67</td>
<td>0.39</td>
<td>Combined results from Moreland 1999(^{118}), Codreanu 2003(^{103}), and TEMPO.(^{123}) Unpublished data with LOCF imputation from trial reports.</td>
</tr>
<tr>
<td>Etan + MTX early RA</td>
<td>0.72</td>
<td>0.50</td>
<td>0.59</td>
<td>From TEMPO(^{123}) (data from Wyeth submission)</td>
</tr>
<tr>
<td>Etan + MTX late RA</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>From Weinblatt 1999(^{121}) Unpublished data with LOCF imputation from trial report.</td>
</tr>
<tr>
<td>Gold (GST)</td>
<td>0.45</td>
<td>0.70</td>
<td>0.39</td>
<td>As for ciclosporin</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCQ)</td>
<td>0.15</td>
<td>0.40</td>
<td>0.27</td>
<td>Trial of HCQ in early RA(^{174})</td>
</tr>
<tr>
<td>Infliximab (+MTX) early RA</td>
<td>0.76</td>
<td>0.67</td>
<td>0.53</td>
<td>From St Clair 2004(^{151}) (ASPIRE trial). MTX naïve patients.</td>
</tr>
<tr>
<td>Infliximab (+MTX) late RA</td>
<td>****</td>
<td>****</td>
<td>****</td>
<td>From ATTRACT trial(^{128}) (unpublished data from trial report, observed values).</td>
</tr>
<tr>
<td>Leflunomide (LEF)</td>
<td>0.57</td>
<td>0.65</td>
<td>0.47</td>
<td>RCT of leflunomide versus methotrexate(^{170})</td>
</tr>
</tbody>
</table>
### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(a)</th>
<th>(b)</th>
<th>Mean</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (MTX)</td>
<td>0.98</td>
<td>0.82</td>
<td>0.54</td>
<td>As for leflunomide</td>
</tr>
<tr>
<td>Penicillamine (DPen)</td>
<td>0.20</td>
<td>0.80</td>
<td>0.20</td>
<td>Assumed same as azathioprine</td>
</tr>
<tr>
<td>Sulfasalazine (SSZ)</td>
<td>0.70</td>
<td>0.84</td>
<td>0.45</td>
<td>Follow-up observations of patients involved in an RCT(^{175}) Smolen JS, Kalden JR, Scott DL, Rozman B, Kvein TK, Larsen A, et al(^{176})</td>
</tr>
<tr>
<td>Combination CyA+MTX</td>
<td>0.80</td>
<td>0.45</td>
<td>0.64</td>
<td>Data from an RCT of ciclosporin A versus ciclosporin A combined with MTX in early RA.(^{177})</td>
</tr>
<tr>
<td>Combination MTX+SSZ</td>
<td>0.70</td>
<td>0.84</td>
<td>0.45</td>
<td>Assumed as for sulfasalazine</td>
</tr>
<tr>
<td>Combination MTX+SSZ+HCQ</td>
<td>0.15</td>
<td>0.40</td>
<td>0.27</td>
<td>Assumed as for hydroxychloroquine</td>
</tr>
</tbody>
</table>

### Time on treatments

The model allows for two stages of early quitting of treatment. Figure 48 shows the general shape for the survival curve assumed for a particular treatment.

**Figure 48 Illustrative curve for survival time on a treatment (based on leflunomide data)**

The first step represents cessation of treatment after 6 weeks, which is assumed to be for toxicity. The second step represents cessation between 6 and 24 weeks after starting treatment,
which could be for toxicity or ineffectiveness. Table 39 shows the data used for early cessation of DMARDs.
### Table 39 Early cessation of DMARDs: data, sources and comments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cessation ≤ 6weeks*</th>
<th>Ceasing between 6 &amp; 24 weeks</th>
<th>Comments &amp; Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (with or without MTX)</td>
<td>5%</td>
<td>10% (5% because of toxicity and 4% for inefficacy, 1% for other reasons)</td>
<td>No appropriate data found – assume same as infliximab</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>15%</td>
<td>25%.</td>
<td>Data estimated from Willkens et al. 178 Reasons for cessation due to toxicity, inefficacy or other reasons are not available.</td>
</tr>
<tr>
<td>Ciclosporin A</td>
<td>8%</td>
<td>24%. (12% because of inefficacy and 12% for toxicity).</td>
<td>Data are estimated from Yocum et al. 179 It is assumed that half of those ceasing between 6 and 24 weeks do so because of inefficacy and the other half because of toxicity; based on observations by Marra and colleagues. 180</td>
</tr>
<tr>
<td>Etanercept (with or without MTX)</td>
<td>4%</td>
<td>3% (1% because of toxicity and 2% for inefficacy)</td>
<td>Observational study Geborek et al 2002 168 (see leflunomide). 84% of all patients remained on treatment at 12 months.</td>
</tr>
<tr>
<td>Gold (GST)</td>
<td>14%</td>
<td>27%. (18% because of toxicity and 9% for inefficacy.</td>
<td>Figures are estimated from Hamilton et al. 181 Estimated figures from Zeider et al. 172 are 10% within 6 weeks and 34% at 24 weeks.</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>3%</td>
<td>18% (4% because of toxicity and 14% for inefficacy)</td>
<td>Data estimated from Furst et al 182 using a cohort treated with 800 mg per day as this group provided the most complete data set.</td>
</tr>
<tr>
<td>Infliximab + MTX</td>
<td>5%</td>
<td>10% (5% because of toxicity and 4% for inefficacy, 1% for other reasons)</td>
<td>Observational study Geborek et al 2002 (see leflunomide). 75% of all patient remained on treatment at 12 months.</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10% for drug toxicity and 3% for other reasons</td>
<td>30% (10% because of toxicity, 19% for inefficacy and 1% for other reasons).</td>
<td>Data estimated from Geborek et al (Figure 48). 168 This data is preferred to trial data because clinical experience indicates that continued drug use is less likely in practice compared with use in randomised trials. 183</td>
</tr>
<tr>
<td>Drug</td>
<td>Cessation ≤ 6weeks*</td>
<td>Ceasing between 6 &amp; 24 weeks</td>
<td>Comments &amp; Source</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8.5%</td>
<td>19.5% (8.5% because of toxicity and 11% for inefficacy).</td>
<td>Estimates from Hamilton et al(^{181})</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Assume same as azathioprine</td>
<td></td>
<td>No reliable data is available for use of penicillamine late in disease; late drug use data is required by our modelling strategy.</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>10%</td>
<td>28%. 9% because of toxicity, 10.5% for inefficacy, and 8.5% for other reasons.</td>
<td>No ideal source identified. Data estimated from two clinical trials (Proudman et al(^{184}) and Smolen et al(^{176}) that gave data from which inferences about early and late cessations were made.</td>
</tr>
<tr>
<td>Combination (CicA &amp; MTX)</td>
<td>0%</td>
<td>50%</td>
<td>No data source. Our model assumes that patients will have tried both MTX and CicA monotherapy prior to trying this combination. Therefore patients experiencing toxicity to either agent in past would not be eligible for this combination. The use of this combination after failed monotherapy with CicA and MTX assumes a synergistic effect for efficacy although there is no definitive evidence for this. In the absence of data but based on an educated guess, we assume that 50% of patients cease therapy after 24 weeks for lack of efficacy.</td>
</tr>
<tr>
<td>Combination (MTX &amp; SSZ)</td>
<td>As for sulfasalazine, above.</td>
<td></td>
<td>As our model does not propose combination therapy from the outset with this combination but proposes that SSZ is added when MTX is inefficacious (and not toxic), in a step-up strategy. We have assumed that patients respond, in terms of toxicity and drug continuation, as they would if SSZ alone had been used.</td>
</tr>
<tr>
<td>Drug</td>
<td>Cessation ≤ 6 weeks*</td>
<td>Ceasing between 6 &amp; 24 weeks</td>
<td>Comments &amp; Source</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Combination MTX, SSZ &amp; HCQ</td>
<td>As for hydroxychloroquine, above.</td>
<td></td>
<td>As above, our model does not propose combination therapy from the outset but drugs are added in a step-up strategy. Thus, toxicity and drug continuation rates for this combination are assumed to be similar to HCQ alone since patients only use HCQ in the combination if MTX and SSZ in combination have been inefficacious (and not toxic).</td>
</tr>
</tbody>
</table>

* It is assumed, unless stated otherwise, that patients ceasing by 6 weeks do so because of drug toxicity.

The implementation of this approach is illustrated in Figure 49. The variables $u_1$ and $u_2$ are drawn from a uniform distribution between 0 and 1. The value of $u_1$ is used primarily to determine the HAQ improvement on starting treatment using the Beta distribution with parameters as shown in Table 38, while $u_2$ determines the time on treatment. The four zones in Figure 49 represent the following:

A: Withdrawal within 6 weeks (assumed due to toxicity)
B: Withdrawal between 6 and 24 weeks for inefficacy
C: Withdrawal between 6 and 24 weeks for toxicity
D: Remaining on the treatment after 24 weeks
In implementation, the values of $u_1$ and $u_2$ are compared with critical values calculated so that zones A, B and C in Figure 49 have the appropriate areas to represent the probabilities given in Table 39. This method means that early withdrawal for inefficacy coincides with the minimum HAQ improvement.

For patients who remain on treatment after 24 weeks, the time on treatment is assumed to be independent of HAQ improvement. The value of $u_2$ is converted to a value from a Weibull distribution, represented in the curved part of Figure 48.

A random variable $X$ has a Weibull distribution with shape parameter $a$ and scale parameter $b$ if \( \left( \frac{X}{b} \right)^a \) has an exponential distribution with unit mean. The Weibull distribution is more general than the constant-risk exponential distribution in that it reduces to the exponential distribution when $a = 1$. If $a < 1$, then the risk decreases over time, while if $a > 1$, the risk increases over time. Parameters $a$ and $b$ are shown in Table 40. For convenience, the mean of the distribution is also shown.
### Table 40 Times to quitting DMARD

<table>
<thead>
<tr>
<th>DMARD</th>
<th>$a$</th>
<th>$b$ (yrs)</th>
<th>mean (yrs)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>0.73</td>
<td>5.96</td>
<td>7.26</td>
<td>Assumed same as infliximab</td>
</tr>
<tr>
<td>azathioprine</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>ciclosporin</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>etanercept</td>
<td>0.73</td>
<td>12.34</td>
<td>15.03</td>
<td>Geborek et al$^{168}$</td>
</tr>
<tr>
<td>gold</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>infliximab</td>
<td>0.73</td>
<td>5.96</td>
<td>7.26</td>
<td>Geborek et al$^{168}$</td>
</tr>
<tr>
<td>leflunomide</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>methotrexate</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>penicillamine</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td></td>
<td></td>
<td></td>
<td>GPRD database$^{185}$</td>
</tr>
<tr>
<td>combination</td>
<td>1</td>
<td>1.74</td>
<td>1.74</td>
<td>Tugwell et al$^{186}$</td>
</tr>
<tr>
<td>CyA+MTX</td>
<td></td>
<td></td>
<td></td>
<td>Gerards et al$^{187}$</td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td></td>
<td></td>
<td></td>
<td>As for SSZ alone</td>
</tr>
<tr>
<td>MTX+SSX+HCQ</td>
<td></td>
<td></td>
<td></td>
<td>As for HCQ alone</td>
</tr>
</tbody>
</table>

**HAQ changes on treatment**

The model assumes a constant risk of increase of HAQ score while on treatment and that an individual’s HAQ score increases gradually and in steps of 0.125, apart from the effects of starting and ending treatment. While HAQ can change at any stage of disease, and is known to be more labile in early disease, the assumption of a gradual increase in HAQ is reasonable for the parts of the model where comparisons are being made, as the model applies to the later stages of the disease. The rate of increase of HAQ was chosen to reflect the empirically observed increase reported by Scott et al.$^{188}$
Toxicity
Toxicity of treatments beyond 24 weeks was only an issue if it potentially affected later choices of treatment, as shown in Table 39 above. Thus it was only an issue for methotrexate, ciclosporin, and the combination MTX+SSZ. For other treatments, cessation because of toxicity or inefficacy has the same consequence in our model i.e. use of the treatment next in sequence. For ciclosporin it was assumed drug cessation was due to toxicity with a probability of 0.8 regardless of time spent on drug.\textsuperscript{189} For methotrexate, the probability $p$ was set to depend on the time $t$ years on the drug, by the formula $p = 0.362 + 0.115e^{-0.457t}$, which was derived from a comparison between the survival curves given in Maetzel \textit{et al.}\textsuperscript{190} For MTX+SSZ, we have assumed that the probability for methotrexate alone applies.

Costs
Costs are made up of drug costs plus monitoring costs. For all treatments, there are higher costs on starting than there are for continued use. The total cost for time on any treatment is modelled as a one-off starting cost followed by a steady annual usage cost. For completeness, all costs are shown. The price year is 2004 in each case. The unit costs of the various inputs are shown in Table 41 and Table 42. The monitoring assumptions are listed in Table 43.
### Table 41 Unit costs for tests and visits

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost (£)</th>
<th>Source</th>
</tr>
</thead>
</table>

### Visits

<table>
<thead>
<tr>
<th>Visits</th>
<th>Cost (£)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>24.00</td>
<td>Curtis L, Netten N. Unit Costs of Health and Social Care 2004, PSSRU, University of Kent, 2004191</td>
</tr>
<tr>
<td>Hospital OP</td>
<td>91.00</td>
<td>Curtis L, Netten N. Unit Costs of Health and Social Care 2004, PSSRU, University of Kent, 2004191</td>
</tr>
<tr>
<td>Hospital IP (per day)</td>
<td>202.00</td>
<td>Curtis L, Netten N. Unit Costs of Health and Social Care 2004, PSSRU, University of Kent, 2004191</td>
</tr>
<tr>
<td>Specialist nurse visit</td>
<td>45.50</td>
<td>Assumed half of OP visit</td>
</tr>
</tbody>
</table>

* inflated to 2004 prices using Hospital and Community Health Services (HCHS) inflation index191

### Table 42 Unit costs for drugs (sources: British National Formulary, BNF No. 49 (March 2005), accessed on line at www.bnf.org)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>£357.60 per dose</td>
<td>26 doses per year</td>
</tr>
<tr>
<td>azathioprine</td>
<td>53.4p per day</td>
<td>150 mg per day</td>
</tr>
<tr>
<td>ciclosporin</td>
<td>£3.73 per day</td>
<td>225 mg per day</td>
</tr>
<tr>
<td>etanercept</td>
<td>£89.38 per dose</td>
<td>102 doses per year</td>
</tr>
<tr>
<td>gold</td>
<td>£8.89 per dose</td>
<td>50 mg ampoule, administered at GP visit</td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td>11.4p per day</td>
<td>300 mg per day</td>
</tr>
<tr>
<td>infliximab</td>
<td>£451.20 per vial</td>
<td>70 kg patient, drug wastage if full vials not used, cost per administration £124</td>
</tr>
<tr>
<td>leflunomide</td>
<td>£1.70 per day</td>
<td>20 mg per day</td>
</tr>
<tr>
<td>methotrexate</td>
<td>11.7p per 2.5mg tablet</td>
<td>15 mg per week</td>
</tr>
<tr>
<td>penicillamine</td>
<td>49.2p per day</td>
<td>500 mg per day</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>32.9p per day</td>
<td>2.5 g per day</td>
</tr>
</tbody>
</table>
### Table 43 Monitoring assumptions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre-treatment</th>
<th>On treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>palliation</td>
<td>OP visit every 3 months</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>FBC, ESR, BCP, CXR</td>
<td>FBC, ESR, BCP at weeks 2, 4, 8, 12, then every 3 months</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>FBC, ESR, BCP</td>
<td>FBC and BCP weekly for 6 weeks, then every 2 weeks for 3 visits, then monthly</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>FBC, 2×BCP, ESR, urinalysis</td>
<td>FBC, BCP every 2 weeks for 4 months, then BCP monthly</td>
</tr>
<tr>
<td>Etanercept</td>
<td>FBC, ESR, BCP, CXR</td>
<td>FBC, ESR, BCP at weeks 2, 4, 8, 12, then every 3 months</td>
</tr>
<tr>
<td>Gold</td>
<td>FBC, ESR, BCP, urinalysis</td>
<td>FBC, BCP, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, then monthly. Treatment given by i.m. injections</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>FBC, ESR, BCP</td>
<td>FBC, ESR, BCP every 3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>FBC, ESR, BCP, CXR</td>
<td>FBC, ESR, BCP at weeks 2, 6 and every 8 weeks (at time of infusions)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>FBC, ESR, BCP, urinalysis</td>
<td>FBC every 2 weeks for 6 months, every 8 weeks thereafter. BCP monthly for 6 months, every 8 weeks thereafter</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>FBC, ESR, BCP, CXR</td>
<td>FBC, BCP every 2 weeks for 4 months then monthly</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>FBC, ESR, BCP</td>
<td>FBC every 2 weeks and BCP every 4 weeks for 12 weeks, then FBC and BCP every 3 months</td>
</tr>
</tbody>
</table>

(FBC = full blood count, ESR = erythrocyte sedimentation rate, BCP = biochemical profile, CXR = chest X-ray)

Combining the above information leads to the model inputs shown in Table 44. It should be noted that palliation does not include hospitalisation, although this may be higher for RA patients with no DMARD options, as we could not quantify this.
### Table 44 Treatment costs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Start-up (£)</th>
<th>Annual usage (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>palliation</td>
<td>0</td>
<td>364</td>
</tr>
<tr>
<td>adalimumab</td>
<td>515.88</td>
<td>9714.84</td>
</tr>
<tr>
<td>adalimumab+MTX</td>
<td>515.88</td>
<td>9751.34</td>
</tr>
<tr>
<td>azathioprine</td>
<td>694.81</td>
<td>1380.26</td>
</tr>
<tr>
<td>ciclosporin</td>
<td>350.37</td>
<td>2482.08</td>
</tr>
<tr>
<td>etanercept</td>
<td>515.88</td>
<td>9536.60</td>
</tr>
<tr>
<td>etanercept+MTX</td>
<td>515.88</td>
<td>9573.10</td>
</tr>
<tr>
<td>gold</td>
<td>2765.24</td>
<td>1581.48</td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td>101.89</td>
<td>448.97</td>
</tr>
<tr>
<td>infliximab</td>
<td>1770.88</td>
<td>9901.98</td>
</tr>
<tr>
<td>leflunomide</td>
<td>986.91</td>
<td>1211.72</td>
</tr>
<tr>
<td>methotrexate</td>
<td>512.76</td>
<td>1222.34</td>
</tr>
<tr>
<td>penicillamine</td>
<td>476.94</td>
<td>1401.77</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>584.47</td>
<td>514.88</td>
</tr>
<tr>
<td>Combination CyA+MTX</td>
<td>350.37</td>
<td>2566.34</td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>584.47</td>
<td>1341.97</td>
</tr>
<tr>
<td>MTX+SSZ+HCQ</td>
<td>101.89</td>
<td>1346.85</td>
</tr>
</tbody>
</table>

N.B. All costs discounted at 6% per annum from divergence point

The base model does not include costs for hospitalisation as a result of RA. This is because of wide variation in rates dictated by local facilities and practice. The ERAS study shows a large range of hospitalisation for RA and there are no data for the impact of DMARDs on this. The effect of DMARDs on joint replacement have also not been included in the base model. Again this is because of the absence of data on the effects of DMARDs on joint replacement rates. These uncertainties are explored later in a sensitivity analysis.

Basic mortality comes from standard life tables. A relative risk of 1.33 per unit HAQ is applied. More recently, Sokka and colleagues reported a risk of 2.73 per unit HAQ. We have maintained the relative risk 1.33 for the base case, but used the range from 1 to 2.73 for sensitivity analysis.
In the base case, it is assumed that there is a mean time of 4 years between each 0.125 unit increase in HAQ. This reflects a mean decline (increase) of 0.031/yr.\textsuperscript{188}

On quitting any treatment, it is assumed that the HAQ improvement (reduction) obtained on starting treatment is exactly reversed. For example, if HAQ score improves from 1.25 to 0.875 on starting treatment, and the HAQ score is 1 before quitting treatment, then the HAQ score will be 1.625 after quitting. If applying this rule would take the post-treatment HAQ score above 3, then the post-treatment HAQ score is set to 3.

\textit{Quality of Life Scores}

Conversion from HAQ to QALYs is by the formula $QoL = 0.862 - 0.327HAQ$ calculated from the data set supplied by Nigel Hurst, and reported in Hurst \textit{et al.}\textsuperscript{194} We have assumed that start and end effects can be modelled as one-off deductions equal to 0.2 years times the change in QoL score.

QALYs are discounted at 1.5\% per annum from the divergence point between strategies.

\textbf{4.2.3 Results}

The model was run for each of the strategy sets shown above. A fixed random number seed was used, and the model was run for at least 10,000 (virtual) patients. Comparisons between each pair of options can be found in the form of an incremental cost-effectiveness ratio (ICER) with a quasi confidence interval, reflecting the sampling in running the model, not parameter uncertainty. Fixed stopping rules were used to determine if the quasi confidence interval was sufficiently precise, or if the run-length needed to be increased. The definition of “sufficiently precise” used was as follows. In cases of dominance (NW or SE quadrants), 95\% quasi confidence intervals for cost difference and QALY difference each had to avoid zero. In other cases, a quasi confidence interval $(L, U)$ for the ICER had to satisfy the following properties, according to the values of $L$ and $U$:}
In cases where there were more than two options to compare, the more important comparisons are those between an option including a TNF inhibitor and the baseline without that TNF inhibitor. These are referred to as “major comparisons”. Comparisons between different strategies including TNF inhibitors are referred to as “minor comparisons”. We quote the results for the following minor comparisons:

- effect of adding methotrexate (Adal+MTX v Adal alone, Etan+MTX v Etan alone);
- comparison between monotherapies (Adal alone v Etan alone);
- comparison between combinations with MTX (Adal+MTX v Etan+MTX v Infl+MTX).

The model was first run with 10,000 patients. If any major comparison gave insufficiently precise results, then the number of patients was increased to 20,000, then to 40,000, then to 100,000, then to 200,000, and so on as necessary until all major comparisons gave sufficiently precise results. If any quoted minor comparison was insufficiently precise at this stage, the number of patients was increased once more. The actual number of patients modelled in each case is stated.

**Base Case Results**

Results were obtained with base-case parameters for each of the strategy sets described above.

*Single TNF inhibitor use*

The full individual results for each single TNF inhibitors, used alone or with methotrexate, for each strategy are given in Table 46 to Table 49 and the base-case ICERs are summarised in Table 45 below to allow easier comparison.
Table 45 Summary of base-case ICERs for each TNF inhibitor (alone and with MTX)

<table>
<thead>
<tr>
<th>TNF Inhibitor</th>
<th>Comparator</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usage consistent with 2002 NICE guidance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd line (late RA data)</td>
<td>Last in strategy</td>
</tr>
<tr>
<td>Adalimumab (no MTX)</td>
<td>Base dominates</td>
<td>67K</td>
</tr>
<tr>
<td>Etanercept (no MTX)</td>
<td>93K*</td>
<td>32K</td>
</tr>
<tr>
<td>Adalimumab (with MTX)</td>
<td>169K</td>
<td>45K</td>
</tr>
<tr>
<td>Etanercept (with MTX)</td>
<td>94K</td>
<td>33K</td>
</tr>
<tr>
<td>Infliximab (with MTX)</td>
<td>Base dominates*</td>
<td>69K</td>
</tr>
</tbody>
</table>

*Reflecting current practice

For the HAQ improvement on starting a TNF inhibitor, the “early RA” values were used for the strategy set involving TNF inhibitors at the start, both sets of values were used for single TNF inhibitors in third place, and the “late RA” values were used for all other cases. When interpreting these results, it should be borne in mind that the distinction between “early RA” and “late RA” is rather arbitrary and is not always practical. Of note, patients’ response to a drug or to a combination of drugs depends on their previous experience with these therapies. Patients’ previous experience with MTX is particularly relevant here: the “early RA” data used in our model represent the benefit that would be expected if the patients were naïve to MTX or had not previously failed MTX treatment. The analyses using “early RA” data in the strategies involving TNF inhibitors combined with MTX as third-line therapy are therefore better interpreted as sensitivity analyses that incorporated treatment benefit that is unlikely to be seen in current practice (as most patients, if not all, would have failed MTX before starting a TNF inhibitor as the third-line treatment according to current guidance). For TNF inhibitors used alone, the cost-effectiveness of current practice probably lies between the results in which “early RA” data and “late RA” data were used.
Table 46 TNF inhibitors in third place (200,000 patients) (late RA values)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47581</td>
<td>68</td>
<td>6.5016</td>
<td>0.0115</td>
</tr>
<tr>
<td>Etan</td>
<td>59467</td>
<td>82</td>
<td>7.0374</td>
<td>0.0118</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48011</td>
<td>69</td>
<td>6.7638</td>
<td>0.0115</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59671</td>
<td>83</td>
<td>7.0347</td>
<td>0.0119</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49708</td>
<td>70</td>
<td>6.5284</td>
<td>0.0115</td>
</tr>
<tr>
<td>Base</td>
<td>16565</td>
<td>16</td>
<td>6.5772</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31016</td>
<td>67</td>
<td>-0.0756</td>
<td>0.0105</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42902</td>
<td>80</td>
<td>0.4602</td>
<td>0.0109</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31445</td>
<td>67</td>
<td>0.1866</td>
<td>0.0105</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43106</td>
<td>80</td>
<td>0.4574</td>
<td>0.0110</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33143</td>
<td>69</td>
<td>-0.0489</td>
<td>0.0105</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>430</td>
<td>91</td>
<td>0.2622</td>
<td>0.0106</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>204</td>
<td>106</td>
<td>-0.0027</td>
<td>0.0114</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11886</td>
<td>99</td>
<td>0.5357</td>
<td>0.0109</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11660</td>
<td>100</td>
<td>0.2708</td>
<td>0.0111</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1698</td>
<td>92</td>
<td>-0.2355</td>
<td>0.0106</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9963</td>
<td>100</td>
<td>0.5063</td>
<td>0.0111</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>93,200</td>
<td>89,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>169,000</td>
<td>151,000</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>94,200</td>
<td>89,900</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates infliximab+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1,640</td>
<td>1,150</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>22,200</td>
<td>21,200</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>43,100</td>
<td>39,700</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>19,700</td>
<td>18,800</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Last amended: 11 October 2005
Table 47 TNF inhibitors in third place (100,000 patients) (early RA values)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48369</td>
<td>98</td>
<td>7.1718</td>
<td>0.0163</td>
</tr>
<tr>
<td>Etan</td>
<td>60092</td>
<td>117</td>
<td>7.5693</td>
<td>0.0170</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48611</td>
<td>99</td>
<td>7.3106</td>
<td>0.0163</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60408</td>
<td>117</td>
<td>7.6389</td>
<td>0.0170</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50516</td>
<td>100</td>
<td>7.2838</td>
<td>0.0162</td>
</tr>
<tr>
<td>Base</td>
<td>16591</td>
<td>23</td>
<td>6.5908</td>
<td>0.0158</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31777</td>
<td>96</td>
<td>0.5809</td>
<td>0.0153</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43501</td>
<td>113</td>
<td>0.9784</td>
<td>0.0159</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32020</td>
<td>96</td>
<td>0.7198</td>
<td>0.0153</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43817</td>
<td>114</td>
<td>1.0480</td>
<td>0.0160</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33925</td>
<td>98</td>
<td>0.6930</td>
<td>0.0152</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>242</td>
<td>131</td>
<td>0.1389</td>
<td>0.0157</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>317</td>
<td>152</td>
<td>0.0696</td>
<td>0.0169</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11723</td>
<td>142</td>
<td>0.3975</td>
<td>0.0163</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11797</td>
<td>142</td>
<td>0.3282</td>
<td>0.0163</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1904</td>
<td>132</td>
<td>-0.0268</td>
<td>0.0157</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9893</td>
<td>144</td>
<td>0.3551</td>
<td>0.0163</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>54,700</td>
<td>51,900  57,800</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44,500</td>
<td>43,000  46,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>44,500</td>
<td>42,700  46,500</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>41,800</td>
<td>40,600  43,100</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>49,000</td>
<td>46,900  51,200</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Ad+M more effective than Adal alone; Diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Et+M more effective than Etan alone; Diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>29,500</td>
<td>27,200  32,300</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>35,900</td>
<td>32,600  40,000</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>In+M more costly than Ad+M; Diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>27,900</td>
<td>25,400  30,800</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 48 TNF inhibitors at the start (400,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49538</td>
<td>51</td>
<td>9.7292</td>
<td>0.0093</td>
</tr>
<tr>
<td>Etan</td>
<td>62818</td>
<td>61</td>
<td>9.9067</td>
<td>0.0094</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49748</td>
<td>52</td>
<td>9.3278</td>
<td>0.0088</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63061</td>
<td>61</td>
<td>9.5491</td>
<td>0.0091</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51574</td>
<td>52</td>
<td>9.1631</td>
<td>0.0089</td>
</tr>
<tr>
<td>Base</td>
<td>15428</td>
<td>11</td>
<td>9.4712</td>
<td>0.0091</td>
</tr>
</tbody>
</table>

Comparison

<table>
<thead>
<tr>
<th>Option</th>
<th>Diff. Cost (£)</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34110</td>
<td>0.2580</td>
<td>0.0090</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47390</td>
<td>0.4355</td>
<td>0.0091</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34320</td>
<td>-0.1434</td>
<td>0.0087</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47633</td>
<td>0.0779</td>
<td>0.0090</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36146</td>
<td>-0.3081</td>
<td>0.0087</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>210</td>
<td>-0.4014</td>
<td>0.0088</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>243</td>
<td>-0.3576</td>
<td>0.0092</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13280</td>
<td>0.1775</td>
<td>0.0092</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13313</td>
<td>0.2213</td>
<td>0.0088</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1826</td>
<td>-0.1647</td>
<td>0.0085</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11487</td>
<td>0.3860</td>
<td>0.0088</td>
</tr>
</tbody>
</table>

Comparison ICER (£/QALY) Quasi confidence interval

<table>
<thead>
<tr>
<th>Option</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>132,000</td>
<td>124,000 142,000</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>109,000</td>
<td>104,000 114,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adalimumab alone dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etanercept alone dominates Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>74,800</td>
<td>67,800 83,500</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>60,200</td>
<td>55,700 65,400</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>29,800</td>
<td>28,400 31,200</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 49 TNF inhibitors in last place (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>36339</td>
<td>215</td>
<td>3.0771</td>
<td>0.0260</td>
</tr>
<tr>
<td>Etan</td>
<td>48251</td>
<td>258</td>
<td>3.9779</td>
<td>0.0288</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>36955</td>
<td>220</td>
<td>3.3384</td>
<td>0.0263</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>48218</td>
<td>258</td>
<td>3.9364</td>
<td>0.0292</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>38141</td>
<td>219</td>
<td>3.0938</td>
<td>0.0266</td>
</tr>
<tr>
<td>Base</td>
<td>2900</td>
<td>12</td>
<td>2.5802</td>
<td>0.0253</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>33439</td>
<td>213</td>
<td>0.4970</td>
<td>0.0187</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>45351</td>
<td>255</td>
<td>1.3978</td>
<td>0.0236</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34055</td>
<td>218</td>
<td>0.7582</td>
<td>0.0195</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>45319</td>
<td>255</td>
<td>1.3563</td>
<td>0.0239</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>35241</td>
<td>217</td>
<td>0.5137</td>
<td>0.0190</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>616</td>
<td>298</td>
<td>0.2612</td>
<td>0.0215</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>32</td>
<td>339</td>
<td>0.0415</td>
<td>0.0291</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11912</td>
<td>318</td>
<td>0.9008</td>
<td>0.0253</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11264</td>
<td>324</td>
<td>0.5981</td>
<td>0.0261</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1186</td>
<td>301</td>
<td>-0.2445</td>
<td>0.0218</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10077</td>
<td>322</td>
<td>0.8426</td>
<td>0.0258</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>67,300</td>
<td>62,500 - 72,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>32,400</td>
<td>31,300 - 33,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>44,900</td>
<td>42,600 - 47,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>33,400</td>
<td>32,200 - 34,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>68,600</td>
<td>63,800 - 74,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>2,360</td>
<td>1,190 - 123,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13,200</td>
<td>12,300 - 14,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>18,800</td>
<td>17,100 - 21,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>12,000</td>
<td>11,000 - 13,100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Sequential use of TNF inhibitors

The individual results for the sequential use of TNF inhibitors are given in Table 51 to Table 59, below and base case ICERs summarised in Table 50. It can be seen that the only TNF inhibitor that is clinically of use as a second-line TNF inhibitor when a first one fails is etanercept (mirroring the results of the single TNF inhibitors used in third-line with late RA data). The ICER for etanercept used as a second TNF inhibitor is around £90k/QALY Similarly using TNF inhibitor as the third sequential TNF inhibitor produced ICERs of over £90k/QALY for etanercept and adalimumab and infliximab were dominated.

Table 50 Summary ICERs for sequential use of two TNF inhibitors

<table>
<thead>
<tr>
<th>First TNF inhibitor used</th>
<th>Following TNF inhibitor</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (alone)</td>
<td>Etanercept</td>
<td>£88K/QALY</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>Base dominates</td>
</tr>
<tr>
<td>Etanercept (alone)</td>
<td>Adalimumab</td>
<td>Base dominates</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>Base dominates</td>
</tr>
<tr>
<td>Infliximab (with methotrexate)</td>
<td>Adalimumab</td>
<td>Base dominates</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>£94K/QALY</td>
</tr>
</tbody>
</table>
### Table 51 Second TNF inhibitor following adalimumab (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etan</td>
<td>57881</td>
<td>256</td>
<td>6.4119</td>
<td>0.0357</td>
</tr>
<tr>
<td>Infl</td>
<td>48183</td>
<td>217</td>
<td>5.8381</td>
<td>0.0344</td>
</tr>
<tr>
<td>Base</td>
<td>16002</td>
<td>51</td>
<td>5.9370</td>
<td>0.0332</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etan - Base</td>
<td>41879</td>
<td>2418</td>
<td>0.4749</td>
</tr>
<tr>
<td>Infl - Base</td>
<td>32181</td>
<td>212</td>
<td>-0.0989</td>
</tr>
<tr>
<td>Etan - Infl</td>
<td>9698</td>
<td>311</td>
<td>0.5738</td>
</tr>
</tbody>
</table>

**Comparison ICER (£/QALY) Quasi confidence interval**

<table>
<thead>
<tr>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etan - Base</td>
<td>88,200</td>
</tr>
<tr>
<td>Infl - Base</td>
<td>Base dominates infliximab</td>
</tr>
<tr>
<td>Etan - Infl</td>
<td>16,900</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

### Table 52 Second TNF inhibitor following etanercept (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>45642</td>
<td>212</td>
<td>5.5805</td>
<td>0.0339</td>
</tr>
<tr>
<td>Infl</td>
<td>48094</td>
<td>219</td>
<td>5.6170</td>
<td>0.0341</td>
</tr>
<tr>
<td>Base</td>
<td>15850</td>
<td>51</td>
<td>5.7234</td>
<td>0.0330</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>27973</td>
<td>206</td>
<td>-0.1429</td>
</tr>
<tr>
<td>Infl - Base</td>
<td>32244</td>
<td>213</td>
<td>-0.1065</td>
</tr>
<tr>
<td>Infl - Adal</td>
<td>2451</td>
<td>282</td>
<td>0.0364</td>
</tr>
</tbody>
</table>

**Comparison ICER (£/QALY) Quasi confidence interval**

<table>
<thead>
<tr>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
</tr>
<tr>
<td>Infl - Base</td>
<td>Base dominates infliximab</td>
</tr>
<tr>
<td>Infl - Adal</td>
<td>67,300</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 53 Second TNF inhibitor following infliximab (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>46511</td>
<td>152</td>
<td>5.8412</td>
<td>0.0243</td>
</tr>
<tr>
<td>Etan</td>
<td>57660</td>
<td>181</td>
<td>6.3892</td>
<td>0.0252</td>
</tr>
<tr>
<td>Base</td>
<td>16017</td>
<td>36</td>
<td>5.9476</td>
<td>0.0237</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>30494</td>
<td>148</td>
<td>-0.1063</td>
<td>0.0226</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>41643</td>
<td>175</td>
<td>0.4417</td>
<td>0.0238</td>
</tr>
<tr>
<td>Etan - Adal</td>
<td>11149</td>
<td>217</td>
<td>0.5480</td>
<td>0.0238</td>
</tr>
</tbody>
</table>

Comparison ICER (£/QALY) Quasi confidence interval

| Adal - Base | Base dominates adalimumab |
| Etan - Base | 94,300                        | 85,100                        | 106,000                        |
| Etan - Adal | 20,300                        | 18,600                        | 22,500 |

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 54 Third TNF inhibitor following Adal and Etan (10,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infl</td>
<td>46370</td>
<td>299</td>
<td>5.1254</td>
<td>0.0460</td>
</tr>
<tr>
<td>Base</td>
<td>15429</td>
<td>72</td>
<td>5.2350</td>
<td>0.0445</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infl - Base</td>
<td>30942</td>
<td>292</td>
<td>-0.1096</td>
<td>0.0445</td>
</tr>
</tbody>
</table>

Comparison ICER (£/QALY) Quasi confidence interval

| Infl - Base | Base dominates infliximab |

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 55 Third TNF inhibitor following Adal and Infl (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etan</td>
<td>55861</td>
<td>250</td>
<td>5.8130</td>
<td>0.0337</td>
</tr>
<tr>
<td>Base</td>
<td>15489</td>
<td>51</td>
<td>5.4062</td>
<td>0.0317</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Etan - Base</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff.QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>40373</td>
<td>242</td>
<td>0.4068</td>
<td>0.0328</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison ICER (£/QALY)**

<table>
<thead>
<tr>
<th>Etan - Base</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>99,200</td>
<td>85,400</td>
<td>118,000</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 56 Third TNF inhibitor following Etan and Adal (10,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infl</td>
<td>46190</td>
<td>298</td>
<td>5.0172</td>
<td>0.0457</td>
</tr>
<tr>
<td>Base</td>
<td>15279</td>
<td>72</td>
<td>5.1820</td>
<td>0.0442</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Infl - Base</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30911</td>
<td>291</td>
<td>-0.1648</td>
<td>0.0442</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison ICER (£/QALY)**

<table>
<thead>
<tr>
<th>Infl - Base</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base dominates infliximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 57 Third TNF inhibitor following Etan and Infl (10,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>44296</td>
<td>292</td>
<td>4.9918</td>
<td>0.0455</td>
</tr>
<tr>
<td>Base</td>
<td>15273</td>
<td>72</td>
<td>5.1834</td>
<td>0.0443</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Adal - Base</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>29023</td>
<td>284</td>
<td>-0.1916</td>
<td>0.0436</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison ICER (£/QALY)**

<table>
<thead>
<tr>
<th>Adal - Base</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 58 Third TNF inhibitor following Infl and Adal (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etan</td>
<td>55985</td>
<td>250</td>
<td>5.8304</td>
<td>0.0338</td>
</tr>
<tr>
<td>Base</td>
<td>15497</td>
<td>51</td>
<td>5.4224</td>
<td>0.0318</td>
</tr>
<tr>
<td>Comparison</td>
<td>40488</td>
<td>242</td>
<td>0.4080</td>
<td>0.0329</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>99,200</td>
<td>85,400</td>
<td>118,000</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 59 Third TNF inhibitor following Infl and Etan (10,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>44458</td>
<td>293</td>
<td>5.0896</td>
<td>0.0456</td>
</tr>
<tr>
<td>Base</td>
<td>15403</td>
<td>72</td>
<td>5.2178</td>
<td>0.0445</td>
</tr>
<tr>
<td>Comparison</td>
<td>29055</td>
<td>286</td>
<td>-0.1283</td>
<td>0.0439</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Sensitivity Analysis

Extensive sensitivity analysis has been carried out for two strategy sets: TNF inhibitors at the start, and TNF inhibitors in third place. As in the base case, for the HAQ improvement on starting a TNF inhibitor, the “early RA” values were used for the strategy set involving TNF inhibitors at the start, and both sets of values were used for single TNF inhibitors in third place. Full details of the sensitivity analysis are given in an Appendix 10. Summarised forms are given in Table 60, Table 61 and Table 62.
### Table 60 Sensitivity analyses - TNF inhibitors at the start

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Adal - Base</th>
<th>Etan - Base</th>
<th>Ad+MTX - Base</th>
<th>Et+MTX - Base</th>
<th>In+MTX - Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>132,000</td>
<td>109,000</td>
<td>Base</td>
<td>612,000</td>
<td>Base</td>
</tr>
<tr>
<td>No HAQ progression on TNF inhibitors</td>
<td>35,500</td>
<td>30,600</td>
<td>58,000</td>
<td>39,100</td>
<td>83,600</td>
</tr>
<tr>
<td>No HAQ progression on any DMARD</td>
<td>146,000</td>
<td>97,800</td>
<td>Base</td>
<td>1,310,000</td>
<td>Base</td>
</tr>
<tr>
<td>No effect of HAQ on mortality</td>
<td>105,000</td>
<td>101,000</td>
<td>Base</td>
<td>567,000</td>
<td>Base</td>
</tr>
<tr>
<td>Mortality ratio 2.73 per unit HAQ</td>
<td>143,000</td>
<td>118,000</td>
<td>Base</td>
<td>344,000</td>
<td>Base</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs down 50%</td>
<td>55,200</td>
<td>44,900</td>
<td>58,100</td>
<td>49,400</td>
<td>86,800</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs up 50%</td>
<td>Base</td>
<td>Base</td>
<td>Base</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>Survival times on conventional DMARDs down 50%</td>
<td>77,600</td>
<td>65,300</td>
<td>Base</td>
<td>154,000</td>
<td>Base</td>
</tr>
<tr>
<td>Survival times on conventional DMARDs up 50%</td>
<td>166,000</td>
<td>146,000</td>
<td>Base</td>
<td>1,900,000</td>
<td>Base</td>
</tr>
<tr>
<td>Survival times on TNF inhibitors down 50%</td>
<td>114,000</td>
<td>91,800</td>
<td>Base</td>
<td>Base</td>
<td>Base</td>
</tr>
<tr>
<td>Survival times on TNF inhibitors up 50%</td>
<td>134,000</td>
<td>114,000</td>
<td>1,530,000</td>
<td>232,000</td>
<td>Base</td>
</tr>
<tr>
<td>Review at 12 weeks</td>
<td>125,000</td>
<td>107,000</td>
<td>Base</td>
<td>641,000</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors down 50%</td>
<td>138,000</td>
<td>107,000</td>
<td>Base</td>
<td>673,000</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors up 50%</td>
<td>117,000</td>
<td>105,000</td>
<td>Base</td>
<td>539,000</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs down 50%</td>
<td>113,000</td>
<td>102,000</td>
<td>Base</td>
<td>403,000</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs up 50%</td>
<td>116,000</td>
<td>96,700</td>
<td>Base</td>
<td>540,000</td>
<td>Base</td>
</tr>
</tbody>
</table>

Base: baseline option dominates option with TNF inhibitor
Table 61 Sensitivity analyses - TNF inhibitors in third place – early RA values

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Adal - Base</th>
<th>Etan - Base</th>
<th>Ad+MTX - Base</th>
<th>Et+MTX - Base</th>
<th>In+MTX – Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>54,700</td>
<td>44,500</td>
<td>44,500</td>
<td>41,800</td>
<td>49,000</td>
</tr>
<tr>
<td>No HAQ progression on TNF inhibitors</td>
<td>26,600</td>
<td>23,200</td>
<td>24,900</td>
<td>22,100</td>
<td>26,500</td>
</tr>
<tr>
<td>No HAQ progression on any DMARD</td>
<td>49,200</td>
<td>38,500</td>
<td>41,000</td>
<td>36,700</td>
<td>43,500</td>
</tr>
<tr>
<td>No effect of HAQ on mortality</td>
<td>52,400</td>
<td>44,200</td>
<td>44,200</td>
<td>41,900</td>
<td>47,700</td>
</tr>
<tr>
<td>Mortality ratio 2.73 per unit HAQ</td>
<td>54,700</td>
<td>43,300</td>
<td>44,100</td>
<td>38,700</td>
<td>46,400</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs down 50%</td>
<td>38,300</td>
<td>31,800</td>
<td>32,600</td>
<td>30,000</td>
<td>35,200</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs up 50%</td>
<td>101,000</td>
<td>79,200</td>
<td>69,900</td>
<td>69,100</td>
<td>75,000</td>
</tr>
<tr>
<td>Survival times on conventional DMARDs down 50%</td>
<td>40,600</td>
<td>34,700</td>
<td>35,900</td>
<td>32,600</td>
<td>39,300</td>
</tr>
<tr>
<td>Survival times on conventional DMARDs up 50%</td>
<td>66,100</td>
<td>54,300</td>
<td>48,800</td>
<td>48,200</td>
<td>57,300</td>
</tr>
<tr>
<td>Survival times on TNF inhibitors down 50%</td>
<td>58,700</td>
<td>45,900</td>
<td>49,300</td>
<td>43,900</td>
<td>55,400</td>
</tr>
<tr>
<td>Survival times on TNF inhibitors up 50%</td>
<td>49,600</td>
<td>43,800</td>
<td>42,400</td>
<td>40,000</td>
<td>46,100</td>
</tr>
<tr>
<td>Review at 12 weeks</td>
<td>60,300</td>
<td>45,400</td>
<td>48,400</td>
<td>41,900</td>
<td>49,900</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors down 50%</td>
<td>61,200</td>
<td>47,000</td>
<td>46,500</td>
<td>42,600</td>
<td>53,100</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors up 50%</td>
<td>53,400</td>
<td>44,800</td>
<td>43,500</td>
<td>40,600</td>
<td>47,600</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs down 50%</td>
<td>52,700</td>
<td>44,200</td>
<td>43,600</td>
<td>39,900</td>
<td>49,900</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs up 50%</td>
<td>51,200</td>
<td>42,800</td>
<td>42,400</td>
<td>39,800</td>
<td>48,800</td>
</tr>
</tbody>
</table>
### Table 62 Sensitivity analyses - TNF inhibitors in third place – late RA values

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Adal - Base</th>
<th>Etan - Base</th>
<th>Ad+MTX - Base</th>
<th>Et+MTX - Base</th>
<th>In+MTX - Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>Base</td>
<td>93,200</td>
<td>169,000</td>
<td>94,200</td>
<td>Base</td>
</tr>
<tr>
<td>No HAQ progression on TNF inhibitors</td>
<td>56,500</td>
<td>30,200</td>
<td>40,400</td>
<td>30,500</td>
<td>60,900</td>
</tr>
<tr>
<td>No HAQ progression on any DMARD</td>
<td>489,000</td>
<td>66,700</td>
<td>108,000</td>
<td>69,000</td>
<td>405,000</td>
</tr>
<tr>
<td>No effect of HAQ on mortality</td>
<td>Base</td>
<td>86,700</td>
<td>143,000</td>
<td>89,100</td>
<td>Base*</td>
</tr>
<tr>
<td>Mortality ratio 2.73 per unit HAQ</td>
<td>Base</td>
<td>108,000</td>
<td>372,000</td>
<td>109,000</td>
<td>Base</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs down 50%</td>
<td>187,000</td>
<td>48,600</td>
<td>70,100</td>
<td>49,900</td>
<td>143,000</td>
</tr>
<tr>
<td>Effectiveness of conventional DMARDs up 50%</td>
<td>Base</td>
<td>505,000</td>
<td>Base</td>
<td>680,000</td>
<td>Base</td>
</tr>
<tr>
<td>Survival times on conventional DMARDs down 50%</td>
<td>271,000</td>
<td>59,400</td>
<td></td>
<td>282,000</td>
<td></td>
</tr>
<tr>
<td>Survival times on conventional DMARDs up 50%</td>
<td>Base</td>
<td>165,000</td>
<td></td>
<td>Base</td>
<td></td>
</tr>
<tr>
<td>Survival times on TNF inhibitors down 50%</td>
<td>250,000</td>
<td>58,400</td>
<td>84,900</td>
<td>58,600</td>
<td>228,000</td>
</tr>
<tr>
<td>Survival times on TNF inhibitors up 50%</td>
<td>Base</td>
<td>146,000</td>
<td>390,000</td>
<td>146,000</td>
<td>Base</td>
</tr>
<tr>
<td>Review at 12 weeks</td>
<td>Base</td>
<td>89,200</td>
<td>183,000</td>
<td>94,400</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors down 50%</td>
<td>Base</td>
<td>92,900</td>
<td>182,000</td>
<td>93,800</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on TNF inhibitors up 50%</td>
<td>Base</td>
<td>90,900</td>
<td>181,000</td>
<td>95,000</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs down 50%</td>
<td>Base</td>
<td>93,500</td>
<td>184,000</td>
<td>99,400</td>
<td>Base</td>
</tr>
<tr>
<td>Short-term quitters on conventional DMARDs up 50%</td>
<td>Base</td>
<td>89,200</td>
<td>165,000</td>
<td>91,800</td>
<td>Base</td>
</tr>
</tbody>
</table>

Base: baseline option dominates option with TNF inhibitor

Base*: baseline option definitely less costly than option involving TNF inhibitor. Difference in QALY not statistically significant even when large number of patients used.
Summary of model results

When the effectiveness values for early RA were used for TNF inhibitors in third place, the results for the three TNF inhibitors were broadly similar. They are sensitive to assumptions about HAQ progression while on treatment, and to assumptions about effectiveness and long-term survival on conventional DMARDs. When the effectiveness values for late RA were used instead, the results were considerably less favourable.

When the effectiveness values for early RA were used for TNF inhibitors at the start, the results were somewhat less favourable than the results obtained using “early RA” values for TNF inhibitors in third place. The results for combinations with methotrexate are much worse than for monotherapy. This reflects the definition of the strategy options in that starting with a TNF inhibitor in combination with methotrexate precludes the later use of methotrexate alone.

An important limitation of this work is the poor quality of the data on effectiveness of conventional DMARDs. It has not been possible to find data that would support quantification of a reduction in effectiveness with disease duration.
5 IMPLICATIONS FOR OTHER PARTIES

The substantial economic impact of rheumatoid arthritis in terms of direct and indirect costs has been highlighted elsewhere in this report. Studies indicate a great range of potential costs that cannot readily be explained by socioeconomic or clinical factors. However it is apparent that a minority of patients may account for a great proportion of the direct medical costs. Costs incurred by individuals, in a cohort of early arthritis patients, are similar to costs incurred by health care services. Costs incurred by family and friends in terms of forgone paid work, forgone leisure time and other factors greatly exceed costs incurred by individuals and health care services. Clearly this could have an impact on the quality of life of patients and carers. Further, physical disability resulting in difficulties in self-care, and work disability has implications for Personal and Social Services.

6 FACTORS RELEVANT TO NHS

Since the last NICE guidance the use of TNF inhibitors to treat RA has become established practice in rheumatology in the UK. Use of infliximab requires day-case facilities by rheumatology departments because it is given intravenously. Currently there is great variation in use of day-case facilities by rheumatologists, determined in part by local resources of inpatient and outpatient facilities. Widespread use of adalimumab and etanercept place a greater demand on outpatient facilities and requires greater involvement of outpatient nurses in order that patients and carers may be taught to self-administer injections and to provide back-up in case of difficulties and provide disease and drug monitoring services. Again there are great variations in use of nurse specialists in rheumatology and relatively few training opportunities for nurses wishing to specialise in this area. However increasing use of DMARDs has led to an increasing requirement for specialised nurses.

The long term impact of TNF inhibitors on joint failure and the likelihood of orthopaedic surgery cannot be demonstrated directly at present because the agents are still relatively new.
Surrogate endpoints such as radiographic change suggest potentially important benefits, and potentially a reduced demand for surgery, but the clinical relevance of reported radiographic changes is debated.

Finally, issues of equity have been highlighted by the wide variation in availability of TNF inhibitors across the country and these have continued despite NICE guidance.
## 7 DISCUSSION

### Summary

**Effectiveness - principle findings**
- All the TNF inhibitors were effective treatments for patients with RA
- For patients who were naïve to MTX, adalimumab monotherapy was marginally less effective and etanercept monotherapy was marginally more effective than MTX
- Combination of a TNF inhibitor with MTX was more effective than MTX alone in patients naïve to MTX
- An increased risk of serious infections cannot be ruled out for infliximab and adalimumab plus MTX

**Cost-effectiveness - principle findings**
- Last active therapy in sequence:
  - TNF inhibitors are most cost-effective when used last
  - The ICER for etanercept used last is £32k/QALY and substantially lower than the ICERs for adalimumab (£67k/QALY) or infliximab (£69k/QALY). Other things being equal etanercept should be the TNF inhibitor of choice
- Third-line use (as recommended in the 2002 NICE guidance):
  - Gives ICERs around £45k/QALY using early RA effectiveness data
  - Gives an ICER of £93k/QALY for etanercept using late RA data
  - Infliximab and adalimumab are dominated by the base strategy using late RA data
- First-line use:
  - Gives ICERs over £100k/QALY for etanercept and adalimumab
  - Infliximab is dominated by the base strategy
- Sequential use:
  - Only etanercept is clinically worth using as a second or third TNF inhibitor and gives ICERs of £88k/QALY or higher
  - Adalimumab and infliximab are dominated by base strategy when used as second or third TNF inhibitors
7.1 Principal findings

The key findings of this review were as follows:

Quality and quantity of evidence

- Twenty-nine RCTs (9 adalimumab, 11 etanercept, and 9 infliximab), including 10 trials reviewed in the previous assessment report\(^1\), are included in this review. The trials are generally of high quality and recruited a total of 9939 patients. Five of the trials\(^{102,119,131,136,137}\) recruited exclusively RA patients with short disease duration (\(\leq\) 3 years). In addition, the BeSt study is described and discussed in this review in view of its novel approach and clinical relevance although it does not strictly meet the inclusion criteria.

Head-to-head comparisons

- Only a small number of included RCTs looked at head-to-head comparisons of TNF inhibitors with MTX: ERA\(^{119}\) and TEMPO\(^{123}\) for etanercept and PREMIER\(^{102}\) for adalimumab. No identified RCT directly compared a TNF inhibitor with a conventional DMARD other than MTX. The BeSt study is the only RCT that compares different sets of sequential treatments in early RA patients.
- In the PREMIER trial\(^{102}\), adalimumab alone (at licensed dose) was marginally less effective than methotrexate in controlling the symptoms of RA in patients who are naïve to methotrexate, and was associated with slight, existing. The only advantage of adalimumab monotherapy over MTX was a reduction in radiographic joint damage and this may be a chance finding because of the multiple outcomes used. The results are reflected in the extension of marketing authorisation for adalimumab recently issued by the European Medicines Agency (EMEA)\(^{67}\), which recommended the use of adalimumab in combination with MTX, rather than adalimumab alone, in early RA patients.
- Etanercept alone (at licensed dose) was as effective or slightly more effective than MTX in controlling RA symptoms and retarding joint damage in patients who were naïve to or who had no treatment failure with MTX in the ERA\(^{119}\) and TEMPO\(^{123}\) trials. Although the mean disease duration for the patients was only one year in the ERA trial, compared with over six
years in the TEMPO trial, the results from these two studies are remarkably similar, with no statistical heterogeneity found between the studies in any of the outcomes being meta-analysed. Subgroup analyses within TEMPO trial also indicated that treatment effects do not vary substantially between early RA and late RA patients.

- TEMPO was unique in that it was the only trial that allowed head-to-head comparison between a TNF inhibitor and methotrexate, in a population that included both early RA and established RA. While it provides useful insight in many aspects, the generalisability of the results, at least in the UK, is not clear. In this trial half of the patients were reported as having previously received methotrexate without toxicity or lack of efficacy and yet these patients had not been treated with methotrexate for at least 6 months prior to the study. Such patients are uncommon in real practice. Consequently, the use of results from this trial in the economic model to give an estimate of improvement with the use of the combination of etanercept plus methotrexate in established RA, would exaggerate the treatment benefit as most real patients would have failed treatment with methotrexate at this stage.

**TNF inhibitors versus placebo**

- The majority of RCTs included in this review compared TNF inhibitors to placebo. Adalimumab, etanercept, and infliximab are all effective treatments, compared with placebo, in terms of improving symptoms of the disease and preventing radiographic damage due to disease. In the analysis of etanercept versus placebo, we found a pattern of decreasing effect size for ACR20 in terms of relative risk in trials in which patients: (1) were not receiving any concurrent DMARDs; (2) were receiving concurrent DMARDs which had failed to provide adequate disease control; and (3) were receiving concurrent, newly initiated methotrexate (see Figure 24, page 98). Statistically significant differences were found in most of the efficacy outcomes (but not necessarily safety outcomes) between (3) and the other two analyses, confirmed the importance of separating comparisons in which newly initiated MTX were involved. The difference between (1) and (2), however, was only marginal (test for heterogeneity p=0.10). This is consistent with the suggestion that the presence or absence of concurrent DMARDs that had failed to provide adequate control of disease activity does not have a significant influence on the treatment effect of adalimumab or etanercept. Further observations from direct comparison within etanercept
trials, namely Codreanu 2003\textsuperscript{103} (replacing ongoing sulfasalazine with etanercept or adding etanercept to ongoing sulfasalazine) and ADORE\textsuperscript{107} (replacing ongoing MTX with etanercept or adding etanercept to ongoing MTX) are also consistent with this interpretation: there was generally no significant differences between etanercept alone arms and ‘combination’ arms in efficacy and safety outcomes in these two trials. No adalimumab trial allowed such observation, and the current licence stipulates that adalimumab should be given in combination with MTX unless it is not tolerated, possibly on the basis that the absolute improvement observed in adalimumab trials was larger when adalimumab was given with MTX.

- The pooled risk of malignancies for adalimumab compared to placebo approaches statistical significance in our meta-analysis. Malignancies were also observed more frequently in infliximab treated patients in placebo controlled trials. While these findings were based on small number of cases and do not appear to be supported by observational studies, continuous vigilance regarding this potential adverse effect is warranted. Observational studies published to date have compared the incidence of malignancies for TNF inhibitor treated patients to either the incidence observed in general population or that observed in cohorts of RA patients. Comparisons have ignored the well known “healthy patient” effect of trials and, indeed, patients who entered trials of TNF inhibitors or who received TNF treatment in practice were a subgroup of RA patients of whom patients with risk factors associated with malignancies (such as past history of malignancy; chronic obstructive pulmonary diseases; viral hepatitis and HIV infection) were excluded. The patients who received TNF inhibitors in observational studies were therefore likely to have lower risk of malignancies (with the exception of lymphoma) compared with general population or general RA population. Future observational studies should attempt to adjust for such potential confounding.

\textit{TNF inhibitor} + \textit{MTX} versus \textit{MTX}

- Four trials\textsuperscript{102,123,131,137} compared the combination of a TNF inhibitor plus methotrexate to methotrexate alone in patients naïve to methotrexate or patients who did not have a history of treatment failure with methotrexate. The combinations are significantly more effective than MTX alone for all the three TNF inhibitors, although the incremental benefits are significantly smaller (with the exception of joint damage) than those observed in
comparisons between TNF inhibitors and placebo. Combination of infliximab and methotrexate in this context was associated with increased risk of serious infection, and a similar, non-significant trend (which may be due to insufficient statistical power) was observed for adalimumab. No trials have compared a combination of methotrexate with a conventional DMARD to the combination of methotrexate with a TNF inhibitor.

**Overall effectiveness and safety**

- At the licensed dose the NNTs (95% CI) required to produce an improvement in ACR20 response in comparison with placebo are: adalimumab 3.6 (3.1, 4.2), etanercept 2.1 (1.9, 2.4), infliximab ***. While these are favourable NNTs for medical interventions, they also emphasise the importance of direct comparisons between DMARDs in estimating the incremental cost-effectiveness ratio of new treatments for RA.
- The NNT figures appear to slightly favour of etanercept. Indirect comparisons of agents should be interpreted with caution however given the potential differences in patient populations, study design and method of analysis across trials. Moreover, this is particularly the case when using NNTs with a metric like the ACR response. Not only do ACR responses have a ceiling effect but the also the absolute health gain obtained from achieving a positive ACR response is a function of the baseline health status of patients. Truly fair and unbiased comparisons can only be made through a direct comparisons of TNF inhibitors in trials and these are urgently needed.
- An important clinical difference between the included trials is whether patients recruited were concurrently receiving newly initiated methotrexate in both intervention and control arms. In those trials where patients have not previously received methotrexate or had no treatment failure associated with methotrexate the relative risk of clinical improvement compared to the comparator arm was between half and a third less than in the trials where people have previously received methotrexate. However, this is to a large extent due to the fact that the response rates were much higher in the control arm where patients were being given methotrexate either which they had previously responded to or for the first time. This is shown by the fact that the absolute risk differences, and thus NNTs, do not systematically differ between these two scenarios, consistent with similar health gains from the use of TNF inhibitors being experienced in both groups.
Methodology

- In this systematic review, we have chosen to pool results from the end of trials irrespective of the duration of follow-up to maximise the number of studies in and, therefore the statistical power of, the meta-analyses. We acknowledge that it may, on occasion, be preferable to pool results with similar duration of follow-up when there is evidence that the effect size of the treatment varies over time. Nevertheless, statistical heterogeneity was not found between the end of trial results in the majority of cases. Where heterogeneity was observed, the differences in the duration of follow-up does not usually explain the heterogeneity, except for the single case of Keystone 2004b in the ACR70 analysis of etanercept versus placebo.

- As the duration of trial increases, the influence of imputation methods (for example, last-observation-carry-forward or assuming all withdrawal non-responders) used to deal with missing data becomes greater. The impact is difficult to assess, however, as results obtained using different analytical methods are rarely reported together.

- The differential withdrawal and follow-up between treatment groups, particularly in placebo-controlled trials, makes the assessment of adverse events difficult. The quality of reporting adverse events in published papers needs to be improved but, commonly, cause-effect relationships are difficult to determine. Skin carcinomas, for example, were omitted from the reporting of malignancy in several trials. Trials lack power to identify potentially important toxicities and although post-marketing surveillance through databases such as the BSRBR can be useful in detecting rarer adverse events such large scale studies are resource intensive, depend on the good-will of many specialists and raise important concerns about data quality and ownership.

Results of modelling

- The results of our economic evaluation using BRAM generally reflect the patterns observed in the review of clinical effectiveness. The estimated ICER for etanercept used as third-line treatment compared with base case, is consistent our previous estimate (£93k/QALY and £83k/QALY, respectively). The additional evidence available and improvements in the economic model mean that the ICER for infliximab as a third-line agent has changed from £115k/QALY to infliximab being dominated by the base DMARD strategy. In particular, an estimated mean HAQ improvement of 0.6 (derived from a
personal communication) was used in the first evaluation, whereas a mean improvement of 
[redacted], based on empirical data from the ATTRACT trial, is used in this evaluation.

- When used alone as third-line treatment, the modelling results for adalimumab and etanercept using “early RA” data are much more favourable than the results using “late RA” data. The evidence about whether HAQ improvements tend to be smaller in patients with longer disease duration was inconsistent in the trials. Nevertheless, given equal change in absolute HAQ score on treatment, the improvement in early RA patients (who tend to have better HAQ scores to start with) will give a larger relative improvement. This effect is reflected in the current version of the BRAM, which modelled HAQ improvement using a multiplier for each treatment and the individual patient’s baseline HAQ score, rather than using a fixed average HAQ change for all patients.

- Compared to etanercept alone, concurrent use of MTX makes little difference in cost-effectiveness when etanercept is used as third-line treatment. Concurrent use of MTX improved the cost-effectiveness of adalimumab as third-line treatment.

- The modelling results for TNF inhibitors combined with MTX as third-line therapy using “early RA” data demonstrate that use of inappropriate estimate of treatment effect (assuming the HAQ improvement for combination therapy in patients who were naïve to MTX or who had not failed MTX can be applied to patients who had failed MTX treatment) can produce ICERs that are misleadingly low.

- The BRAM produces ICERs in the region of £100,000/QALY for monotherapy with a TNF inhibitor as first-line treatment. Combination with methotrexate makes the results even less favourable to TNF inhibitors in cost-effectiveness terms. This appears to be because, although the combination has better effectiveness than monotherapy in itself, the use of the combination precludes subsequent use of methotrexate (which is cheap).

- The more favourable ICERs for TNF inhibitors used as last active therapy (compared with palliation) and less favourable ICERs for TNF inhibitors used as first-line treatment (compared with MTX) highlight the importance of using appropriate comparators in economic evaluation. Such comparators should reflect treatment options relevant to a patient’s disease stage.

7.2 Assumptions, limitations and uncertainties

Strengths of this review included:
A comprehensive search strategy to identify all relevant evidence already within the public domain was undertaken.

Additional information, not previously available, was provided by industry and lead researchers.

There were a substantial number of trials for each agent which generally showed consistent results.

Trials were mainly well conducted.

Clinical expert input at an early stage ensured that a clinically relevant perspective was maintained throughout.

The availability of data from the BSR biologics register and GPRD that was not available in our first review.

The BRAM has been in the public domain for some time and subject to scrutiny and a number of improvements. A meeting was held with all three manufacturers prior to undertaking the report to ensure that there were no concerns about fundamental errors within the model and general agreement about the direction of proposed further development.

**Limitations and uncertainties include:**

- There is a potential for bias through unblinding in TNF inhibitor studies, as infusion and injection-related adverse events are more frequent with active therapy. Unblinding of physician or patient has been demonstrated to introduce bias which generally exaggerates the treatment effect.

- This review primarily focuses on evidence from randomised controlled trials, which, so far, have insufficient number of patients and follow-up time to detect rare but potentially serious adverse events. Some of the non-statistically significant trends in adverse events identified in this review therefore warrant close monitoring when new trial evidence becomes available. For example, for all three TNF inhibitors, a similar non-significant trend for increased serious adverse events was found for TNF inhibitors combined with MTX compared to MTX alone in patients who were naïve to MTX. Pooling the data for all three agents showed that serious adverse events just approached statistical significance.
Assumptions relating to the economic analyses are described in detail in section 4.2, page 171. However, key limitations include:

- The BRAM assumes that if patients continue on a DMARD it remains effective. Patients and clinicians are aware of the limitations and flaws of such an assumption.\(^{195}\)
- The evidence concerning how long patients remain on treatment is uncertain and we have used data from observational cohorts studying drug-survival with particular DMARDs to determine when lack of effectiveness or toxicity causes a change in treatment.
- The evidence about how long patients remain on TNF inhibitors is also uncertain. We did not use data from the BSRBR about drug-survival for the different TNF inhibitors because of uncertainty about its validity: constraints imposed by national guidance on the use of TNF inhibitors means that data may not be accurately recorded and there has been no audit or validation of the registry data.
- The drug survival curves for six, twelve and eighteen months in the BSRBR show different patterns of patients remaining on each TNF inhibitor during the first six months of treatment suggesting a cohort effect, possibly caused by changing use of these drugs, that needs to be investigated and explained and which adds to the uncertainty about how long patients will remain on treatment.
- We have explored the strategies of using either TNF inhibitor alone or combination therapy (TNF inhibitor + MTX) as the first-line treatment for early RA patients and incorporated data of HAQ improvement from relevant clinical trials. There was insufficient data to distinguish survival on treatment between these two strategies and thus a common dataset for withdrawal is used. This may potentially underestimate the treatment benefit of combination therapy, if the combination therapy is better than monotherapy. The impact is probably greater for adalimumab than for etanercept: in the PREMIER trial the combination therapy was better than adalimumab alone whereas in TEMPO trial continuation on the drug appeared to be similar between these two strategies.
- We only modelled adalimumab at 40 mg every other week using associated costs. In the PREMIER trial the dose could be increased (dosing interval reduced) to 40 mg weekly. Since the data from PREMIER are used in the “early RA” scenario in our model, the treatment benefit may have been overestimated and the costs underestimated.
• By using an NHS and PSS perspective, as required by NICE, the BRAM significantly underestimates the potential economic advantages of effective disease control since costs incurred by families and carers are substantial.

• Strategies for treating RA are potentially very complex. For reasons of feasibility we only modelled the most common. Our model is based on the saw-tooth strategy in which there is continued or serial use of one or multiple DMARDs. While this approach appears to reflect and be effective in clinical practice, there are limited long-term data on optimum strategies for treating RA although recent data, from example from the BeSt study, described in this report, suggests that alternative approaches may be more effective.

7.3 Implications for Research

• Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs are needed.

• Trials of different anti-TNFs in patients who have failed a previous TNF inhibitor are also needed.

• Longer term studies of the quality of life (QoL) in patients with RA and the impact of DMARDs and other interventions on QoL are needed.

• Longer term studies or follow up, directly assessing the impact of DMARDs including TNF inhibitors on joint replacement, other disease and drug-related morbidity, and mortality, are required.

• Continued vigilance about the potential harms of TNF inhibitors is necessary and work is needed to improve assessment of cause-effect relationships in patients who experience adverse effects especially as RA itself can cause multi-system disease.

8 CONCLUSIONS

Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, physical function and slowing radiographic changes in joints. When used alone, adalimumab is marginally less effective and etanercept is marginally more effective than
methotrexate, in methotrexate naïve patients. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in this population, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well established effectiveness of MTX alone. In addition, an increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab and infliximab.

Results of published economic evaluations vary: some analyses suggest that use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, others report very high ICERs. Although most are of high quality, none of them use all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. The societal perspective generates more favourable ICERs. All economic evaluations submitted by the manufacturers report ICERs that fall within the currently accepted thresholds of cost-effectiveness. However these models make assumptions and use data that favour the TNF inhibitor being evaluated, the appropriateness of which can be questioned.

The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (32k/QALY) being significantly lower than the ICERs for adalimumab (67k/QALY) or infliximab (69k/QALY). Other things being equal etanercept would be, therefore, the TNF inhibitor of choice. However the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The next most cost-effective use of TNF inhibitors is third-line, as recommended in the 2002 NICE guidance, which gives ICERs around 45K/QALY using early RA effectiveness data. Using data for late RA, however, gives and ICER of is £93k/QALY for etanercept while infliximab and adalimumab are dominated by the base strategy. First-line use gives ICERs over £100k/QALY for etanercept and adalimumab while infliximab is dominated by the base strategy and should not be used as a first-line agent.

Modelling the sequential use of TNF inhibitors (when the first TNF inhibitor was used third-line) only supports the use of etanercept. Adalimumab and infliximab are both dominated when
used in both second and third in the sequence of TNF inhibitors. The ICER for etanercept as a second agent is around £90k/QALY and is over £90k/QALY for use as the third TNF inhibitor.

Direct head-to-head trials of DMARDs and the TNF inhibitors are needed to establish more certainly the relative values of the different agents. Longer term follow up and post-marketing surveillance are needed to ascertain the true risk of adverse events.
9 APPENDICES

Appendix 1 Details of key outcomes used in RA trials

The Health Assessment Questionnaire (HAQ)

The HAQ now comprises a family of questionnaires designed to assess the functional capacity of patients with musculoskeletal complaints and specifically RA. The most widely used HAQ is derived from the Stanford Health Assessment Questionnaire\textsuperscript{196} and consists of 2 or 3 questions in 8 categories:

- Dressing and grooming: dress yourself, including doing shoelaces, and shampooing your hair
- Rising: from an armless chair and in and out of bed
- Eating: being able to cut meat, lift a full cup or glass to mouth, and open a new carton of milk
- Walking: outdoors on flat ground and climb 5 steps
- Hygiene: wash and dry entire body, take a bath, get on and off the toilet
- Reaching: reach and get down a 5lb object, bend down and pick up clothing
- Grip: open car doors, open previously unopened jars, turn taps on and off
- Activities: run errands and shop, get in and out of car, do chores

The score from the most limited activity in each category is obtained. Each category is scored 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), or 3 (unable to do). Use of aids or devices to help with function is taken into account so that need for such assistance automatically scores 2 (unless 3 has been ticked). The maximum score in each of the 8 categories is added to give a maximum possible score of 24. This total score may be divided by 8 to give an average value in the range 0 to 3.
HAQ has several modifications\(^{197}\):

- **Modified HAQ (MHAQ):** is a shortened version of HAQ which uses only one question in each of the 8 categories and does not consider the use of aids and devices to assist function. It is simpler to score and has the same range as HAQ (0 to 3).
- **RA-HAQ:** is another shortened version of HAQ designed to overcome some of the metric limitations of MHAQ.
- **DHAQ:** This uses the original 8 categories of HAQ but is based on the most difficult items in each of the categories. Neither the RA-HAQ nor DHAQ have been widely used, unlike MHAQ.

**American College for Rheumatology Response Criteria\(^ {198}\)**

In order to achieve an ACR20 response a 20% improvement in the score for tender joints and a 20% improvement in swollen joints is necessary and 20% improvement in at least 3 of the following:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score (e.g. HAQ)
- acute phase response (e.g. ESR or CRP)

Responses may also be defined as ACR50 (50%) or ACR70 (70%) depending on degree of benefit.

ACR-N is an extension of the ACR response criteria, and is defined as the lowest of the following three values:

- Percentage change in the number of swollen joints
- Percentage change in the number of tender joints
- The median of the percentage change in the other five measures listed above

It is thus a continuous variable. For example, a patient with an ACR-N of 38 means an improvement of at least 38% in tender and swollen joint counts and an improvement of at least 38% in three of the five other parameters.\(^ {199}\) The ACR-N has been adopted in some clinical
trials such as the ERA study\textsuperscript{119} without prior validation; its advantages and disadvantages have recently been debated.\textsuperscript{199,200}

**Disease Activity Score (DAS)**

**Original DAS**

\[
\text{DAS} = 0.54(\sqrt{\text{RAI}^*}) + 0.065(\text{total number of swollen joints out of 44}) + 0.33(\ln \text{ESR}) + 0.0072(\text{patient general health score where } 0=\text{best}, \ 100=\text{worst})
\]

*RAI refers to a graded score of joint tenderness for 53 joints known as the Ritchie Articular Index.

**Disease activity score based on 28 joint evaluations**

\[
\text{DAS 28-4} = 0.56(\sqrt{\text{TJC28}}) + 0.28(\sqrt{\text{SJC28}}) + 0.7\ln(\text{ESR}) + 0.014(\text{patient general health score where } 0=\text{best}, \ 100=\text{worst})
\]

Where scores for general health are not available, or not measured, the following formula is used:

\[
\text{DAS 28-3} = (0.56(\sqrt{\text{TJC28}}) + 0.28(\sqrt{\text{SJC28}}) + 0.7\ln(\text{ESR}))^{1.08} + 0.16
\]

**Radiographic Assessment Methods\textsuperscript{201}**

**Sharp Score**

The simplified Sharp system\textsuperscript{202}, that evaluates hand and wrist images, assesses 17 areas for erosions and 18 areas for joint space narrowing. Each joint is scored on a 6-point scale as follows: 0 = no erosion; 1 = discrete erosion; 2 = two separate quadrants with erosions or 20-
40% joint involvement; 3 = 3 separate quadrants with erosions or 41-60% joint involvement; 4 = all four quadrants with joint erosion or 61-80% joint involvement; and 5 = extensive destruction with >80% joint involvement. The range of erosion scores for a patient with two hands and wrists is 0 to 170. For joint space narrowing each joint is scored using a 5-point scale as follows: 0 = no narrowing; 1 = up to 25% narrowing; 2 = 26-65% narrowing; 3 = 66-99% narrowing; 4 = complete narrowing. The range for joint space narrowing is therefore 0 to 144. This gives a total joint score in the range 0 to 314.

**Van der Heijde modified Sharp score**

In this case 16 joints are assessed in each hand and wrist and 6 joints in each foot. Erosions are scored 0 to 5 and depending on the affected surface area and 0 to 10 in the feet yielding possible erosion scores of 0 to 160 for hands/wrists and 0 to 120 for feet (total 0 to 280). Joint space narrowing is assessed in 15 joints for each hand/wrist and 6 joints in each foot on a scale of 0 to 4. The range of possible JSN scores is in the range 0 to 168. This yields a possible total score in the range 0 to 448.

**The Larsen Score**

In this method standard films are used to classify each joint into one of 6 possible categories (0 = normal, 5 = severely damaged). Any joint may be scored but the focus is on hands and feet. In the hands each proximal interphalangeal joint and each metacarpophalangeal joint scores 0 to 5; each wrist joint scores 0 to 25 (the basic score is multiplied by 5): this gives a maximum score of 150 for two hands and wrists. In the feet each metatarsophalangeal joint is scored 0 to 5, giving a total score of 50 for two feet. This yields a possible total score in the range 0 to 200.

**Scott modified Larsen**

Scott and colleagues suggested minor modifications to the scale in order to improve correlation between scorers. It was proposed that grade 1 included erosions and cysts of <1 mm diameter and grade included one or more erosions of >1mm diameter.
Appendix 2 Searches - clinical Effectiveness

Source – Cochrane Library (CENTRAL) 2005 Issue 1

#1 rheumatoid NEXt arthritis in All Fields in all products
#2 MeSH descriptor Arthritis, Rheumatoid, this term only in MeSH products
#3 (#1 OR #2)
#4 "tumor necrosis factor*" in All Fields in all products
#5 "tumour necrosis factor*" in All Fields in all products
#6 MeSH descriptor Receptors, Tumor Necrosis Factor, this term only in MeSH products
#7 "anti tnf" in All Fields in all products
#8 antitnf in All Fields in all products
#9 infliximab in All Fields in all products
#10 remicade in All Fields in all products
#11 enbrel in All Fields in all products
#12 etanercept in All Fields in all products
#13 adalimumab in All Fields in all products
#14 humira in All Fields in all products
#15 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 (#3 AND #15)

Source - Ovid MEDLINE(R) 1966 to February Week 2 2005

1 arthritis rheumatoid/
2 tumo?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti TNF.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8

Last amended: 11 October 2005
10 rheumatoid arthritis.mp.
11 1 or 10
12 9 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized controlled trials.sh.
16 random allocation.sh.
17 double blind method.sh.
18 single blind method.sh.
19 or/13-18
20 (animals not human).sh.
21 19 not 20
22 clinical trial.pt.
23 exp clinical trials/
24 (clin$ adj25 trial$).ti,ab.
25 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
26 placebo$.ti,ab.
27 random$.ti,ab.
28 placebos.sh.
29 research design.sh.
30 or/22-29
31 30 not 20
32 31 not 21
33 21 or 32
34 12 and 33
35 limit 34 to yr=2001 - 2005
36 adalimumab.mp.
37 humira.mp.
38 or/36-37
39 1 and 38 and 33
40 35 or 39
Source - EMBASE (Ovid) 1980 to 2005 Week 08

1  arthritis rheumatoid/
2  tumor necrosis factor.mp.
3  exp receptors tumor necrosis factor/
4  anti TNF.mp.
5  infliximab.mp.
6  remicade.mp.
7  enbrel.mp.
8  etanercept.mp.
9  or/2-8
10  rheumatoid arthritis.mp.
11  1 or 10
12  9 and 11
13  adalimumab.mp.
14  humira.mp.
15  or/13-14
16  randomized controlled trial/
17  exp clinical trial/
18  exp controlled study/
19  double blind procedure/
20  randomization/
21  placebo/
22  single blind procedure/
23  (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
24  ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
25  (placebo$ or matched communities or matched schools or matched populations).mp.
26  (comparison group$ or control group$).mp.
27  (clinical trial$ or random$).mp.
28  (quasiexperimental or quasi experimental or pseudo experimental).mp.
29  matched pairs.mp.
30  or/16-29
31  12 and 30
32  limit 31 to yr=2001 - 2005
33  15 and 11 and 30
34  32 or 33

Source – Science Citation Index (Web of Science) 1981-2005

#1 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept OR tumor necrosis factor OR tumour necrosis factor OR tnf))

#2 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept))

#3 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept) AND (trial* OR random* OR control*))

#4 TS=(rheumatoid arthritis AND (adalimumab OR humira) AND (trial* OR random* OR control*))

#5 TS=(rheumatoid arthritis AND (adalimumab OR humira) AND (trial* OR random* OR control*))

#6 #3 OR #4

#7 #3 OR #5
Appendix 3 Additional tables and figures for clinical effectiveness review

Adalimumab

*Adalimumab vs placebo sensitivity analyses*
### Table 63 Meta-analyses - Adalimumab licensed dose and above vs placebo (with or without ongoing conventional DMARDs), end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RR (fixed)</td>
<td>2.23 [1.94, 2.56]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RR (fixed)</td>
<td>3.73 [2.91, 4.77]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RR (fixed)</td>
<td>5.28 [3.49, 8.00]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RD (fixed)</td>
<td>0.30 [0.26, 0.34]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RD (fixed)</td>
<td>0.24 [0.21, 0.27]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>5 [108-111,115]</td>
<td>2172</td>
<td>RD (fixed)</td>
<td>0.14 [0.11, 0.16]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>5 [108-111,115]</td>
<td>2169</td>
<td>WMD (fixed)</td>
<td>-5.52 [-6.39, -4.64]</td>
</tr>
<tr>
<td>Patient's global assessment, mean change from baseline</td>
<td>5 [108-111,115]</td>
<td>2168</td>
<td>WMD (fixed)</td>
<td>-1.76 [-2.01, -1.50]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>5 [108-111,115]</td>
<td>2168</td>
<td>WMD (fixed)</td>
<td>-0.33 [-0.38, -0.28]</td>
</tr>
<tr>
<td>DAS28, mean change from baseline</td>
<td>2 [109,115]</td>
<td>721</td>
<td>WMD (random)</td>
<td>-1.30 [-1.69, -0.92]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1 [110]</td>
<td>551</td>
<td>WMD (fixed)</td>
<td>-2.20 [-3.33, -1.07]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (random)</td>
<td>0.60 [0.40, 0.88]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>0.35 [0.28, 0.43]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>1.41 [0.90, 2.21]</td>
</tr>
<tr>
<td>Death</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>1.76 [0.45, 6.86]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>1.08 [0.81, 1.44]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>2.99 [0.93, 9.66]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>1.97 [0.53, 7.27]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>2.52 [0.56, 11.47]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>5 [108-111,115]</td>
<td>2179</td>
<td>RR (fixed)</td>
<td>2.35 [1.03, 5.34]</td>
</tr>
<tr>
<td>Any infection</td>
<td>4 [108-111]</td>
<td>1895</td>
<td>RR (fixed)</td>
<td>1.19 [1.08, 1.31]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
Table 64 Meta-analyses - Adalimumab (s.c. or i.v. all doses) vs placebo (with or without ongoing conventional DMARDs), end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>8 108-115</td>
<td>2581</td>
<td>RR (fixed)</td>
<td>2.27 [1.99, 2.60]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>8 108-115</td>
<td>2581</td>
<td>RR (fixed)</td>
<td>3.78 [2.96, 4.83]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>5 108-111,115</td>
<td>2347</td>
<td>RR (fixed)</td>
<td>5.09 [3.36, 7.71]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>8 108-115</td>
<td>2581</td>
<td>RD (fixed)</td>
<td>0.30 [0.27, 0.34]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>8 108-115</td>
<td>2581</td>
<td>RD (random)</td>
<td>0.23 [0.18, 0.28]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>5 108-111,115</td>
<td>2347</td>
<td>RD (fixed)</td>
<td>0.13 [0.11, 0.15]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>8 108-115</td>
<td>2578</td>
<td>WMD (fixed)</td>
<td>-5.37 [-6.11, -4.64]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>8 108-115</td>
<td>2577</td>
<td>WMD (fixed)</td>
<td>-1.74 [-1.97, -1.51]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>8 108-115</td>
<td>2577</td>
<td>WMD (fixed)</td>
<td>-0.31 [-0.35, -0.27]</td>
</tr>
<tr>
<td>DAS28, mean change from baseline</td>
<td>2 109,115</td>
<td>827</td>
<td>WMD (fixed)</td>
<td>-1.23 [-1.44, -1.02]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1 110</td>
<td>551</td>
<td>WMD (fixed)</td>
<td>-2.20 [-3.33, -1.07]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>8 108-115</td>
<td>2588</td>
<td>RR (random)</td>
<td>0.62 [0.46, 0.84]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>8 108-115</td>
<td>2588</td>
<td>RR (fixed)</td>
<td>0.39 [0.32, 0.47]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>8 108-115</td>
<td>2588</td>
<td>RR (fixed)</td>
<td>1.44 [0.93, 2.24]</td>
</tr>
<tr>
<td>Death</td>
<td>8 108-115</td>
<td>2588</td>
<td>RR (fixed)</td>
<td>1.53 [0.44, 5.26]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>8 108-115</td>
<td>2588</td>
<td>RR (fixed)</td>
<td>1.06 [0.80, 1.40]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>6 108-111,114,115</td>
<td>2414</td>
<td>RR (fixed)</td>
<td>2.84 [0.90, 8.97]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>6 108-111,114,115</td>
<td>2414</td>
<td>RR (fixed)</td>
<td>2.00 [0.55, 7.24]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>6 108-111,114,115</td>
<td>2414</td>
<td>RR (fixed)</td>
<td>2.23 [0.50, 9.91]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>7 108-111,113-115</td>
<td>2468</td>
<td>RR (fixed)</td>
<td>2.27 [1.00, 5.18]</td>
</tr>
</tbody>
</table>
### Etanercept

#### Etanercept versus sulfasalazine in sulfasalazine partial responders/non-responders

Table 65 Summary of 24-week results from Codreanu 2003 - Etanercept vs sulfasalazine in sulfasalazine partial responders/non-responders

<table>
<thead>
<tr>
<th>Any infection</th>
<th>$4_{108-111}$</th>
<th>2070</th>
<th>RR (fixed)</th>
<th>$1.19 [1.08, 1.31]$</th>
</tr>
</thead>
</table>

Shaded cells indicate statistically significant result at $P<0.05$
<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td>2.64 [1.67, 4.17]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>1</td>
<td>153</td>
<td>RD (fixed)</td>
<td>0.46 [0.31, 0.61]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>1</td>
<td>153</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>1</td>
<td>153</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>1</td>
<td>153</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>1</td>
<td>153</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>1</td>
<td>153</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1</td>
<td>153</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td>0.26 [0.12, 0.54]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>1</td>
<td>153</td>
<td>RR (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
**Etanercept versus placebo**

**Table 66 Meta-analyses – Etanercept s.c. all doses vs placebo (with or without ongoing conventional DMARDs), end of trial**

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1672</td>
<td>RR (fixed)</td>
<td>3.48 [2.78, 4.35]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1672</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>6 103,118,121,122,125,126</td>
<td>1492</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1672</td>
<td>RD (fixed)</td>
<td>0.43 [0.38, 0.47]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1672</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>6 103,118,121,122,125,126</td>
<td>1492</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1689</td>
<td>WMD (random)</td>
<td>-5.78 [-8.12, -3.43]</td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>7 103,117,118,121,122,125,126</td>
<td>1689</td>
<td>WMD (fixed)</td>
<td>-2.33 [-2.56, -2.10]</td>
</tr>
<tr>
<td>HAQ, end of study result</td>
<td>6 103,118,121,122,125,126</td>
<td>1440</td>
<td>WMD (fixed)</td>
<td>-0.49 [-0.57, -0.40]</td>
</tr>
<tr>
<td>DAS, end of study result</td>
<td>1 103</td>
<td>150</td>
<td>WMD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>No data available</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>7 103,104,117,118,121,122,125</td>
<td>2168</td>
<td>RR (fixed)</td>
<td>0.43 [0.36, 0.51]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>6 103,104,117,118,121,122</td>
<td>1748</td>
<td>RR (fixed)</td>
<td>0.28 [0.21, 0.36]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>7 103,104,117,118,121,122,125</td>
<td>2168</td>
<td>RR (fixed)</td>
<td>0.87 [0.54, 1.38]</td>
</tr>
<tr>
<td>Death</td>
<td>7 103,104,117,118,121,122,125</td>
<td>2168</td>
<td>RR (fixed)</td>
<td>1.44 [0.44, 4.69]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5 103,104,118,121,125</td>
<td>1429</td>
<td>RR (fixed)</td>
<td>1.25 [0.76, 2.06]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>6 103,104,118,121,122,125</td>
<td>1988</td>
<td>RR (fixed)</td>
<td>0.47 [0.13, 1.67]</td>
</tr>
<tr>
<td>Comparison or outcome</td>
<td>Studies</td>
<td>Participants</td>
<td>Statistical method</td>
<td>Effect size [95% CI]</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------------------</td>
<td>--------------</td>
<td>--------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>6¹⁰³,¹⁰⁴,¹¹⁸,¹²¹,¹²²,¹²⁵</td>
<td>1988</td>
<td>RR (fixed)</td>
<td>0.64 [0.15, 2.77]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>6¹⁰³,¹⁰⁴,¹¹⁸,¹²¹,¹²²,¹²⁵</td>
<td>1988</td>
<td>RR (fixed)</td>
<td>0.34 [0.07, 1.74]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>7¹⁰³,¹⁰⁴,¹¹⁸,¹²¹,¹²²,¹²⁵,¹²⁶</td>
<td>2046</td>
<td>RR (fixed)</td>
<td>0.75 [0.37, 1.48]</td>
</tr>
<tr>
<td>Any infection</td>
<td>6¹⁰³,¹⁰⁴,¹¹⁸,¹²¹,¹²²,¹²⁵</td>
<td>1988</td>
<td>RR (random)</td>
<td>1.01 [0.83, 1.24]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
Infliximab

Infliximab alone vs placebo or MTX

Table 67 Meta-analyses - Infliximab i.v. (all doses) without MTX vs control (placebo or MTX) in MTX partial responders/non-responders, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Comparator</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paulus 20 responder</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>RR (fixed)</td>
<td>7.35 [1.91, 28.21]</td>
</tr>
<tr>
<td></td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RR (fixed)</td>
<td>2.86 [0.40, 20.67]</td>
</tr>
<tr>
<td>Paulus 50 responder</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>RR (fixed)</td>
<td>5.14 [1.31, 20.15]</td>
</tr>
<tr>
<td></td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RR (fixed)</td>
<td>4.33 [0.26, 72.44]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>RD Paulus 20 responder</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>RD (fixed)</td>
<td>0.53 [0.35, 0.70]</td>
</tr>
<tr>
<td></td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RD (fixed)</td>
<td>0.13 [-0.05, 0.31]</td>
</tr>
<tr>
<td>RD Paulus 50 responder</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>RD (fixed)</td>
<td>0.35 [0.17, 0.52]</td>
</tr>
<tr>
<td></td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RD (fixed)</td>
<td>0.14 [0.00, 0.27]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>WMD (fixed)</td>
<td>-12.20 [-17.17, -7.23]</td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>WMD (fixed)</td>
<td>-1.00 [-1.39, -0.61]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RR (fixed)</td>
<td>0.48 [0.25, 0.93]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RR (fixed)</td>
<td>0.32 [0.15, 0.69]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>RR (fixed)</td>
<td>3.00 [0.17, 52.53]</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Data not available</td>
</tr>
<tr>
<td>Malignancy</td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>Not estimable</td>
<td>No events</td>
</tr>
<tr>
<td>Serious infection</td>
<td>vs MTX</td>
<td>1^133</td>
<td>58</td>
<td>Not estimable</td>
<td>No events</td>
</tr>
<tr>
<td>Any infection</td>
<td>vs placebo</td>
<td>1^132</td>
<td>73</td>
<td>RR (fixed)</td>
<td>2.94 [0.37, 23.06]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
### Infliximab vs placebo (with concomitant, ongoing MTX)

Table 68 Meta-analyses – Infliximab i.v. licensed dose and above vs placebo with ongoing MTX in MTX partial responders/non-responders, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>4105,129,133,136</td>
<td>1513</td>
<td>RR (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>4105,129,133,136</td>
<td>1513</td>
<td>RR (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>2105,129</td>
<td>1448</td>
<td>RR (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>4105,129,133,136</td>
<td>1513</td>
<td>RD (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>4105,129,133,136</td>
<td>1513</td>
<td>RD (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>2105,129</td>
<td>1448</td>
<td>RD (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>2105,129</td>
<td>1401</td>
<td>WMD (fixed)</td>
<td>-5.28 [-6.27, -4.29]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>2105,129</td>
<td>1400</td>
<td>WMD (fixed)</td>
<td>-1.60 [-1.91, -1.29]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>2105,129</td>
<td>1381</td>
<td>WMD (fixed)</td>
<td>-0.29 [-0.36, -0.23]</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>1136</td>
<td>24</td>
<td>WMD (fixed)</td>
<td>-1.80 [-2.68, -0.92]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>2129,136</td>
<td>373</td>
<td>WMD (fixed)</td>
<td>-6.79 [-9.19, -4.39]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>2129,133</td>
<td>471</td>
<td>RR (fixed)</td>
<td>0.38 [0.28, 0.50]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>2129,133</td>
<td>471</td>
<td>RR (fixed)</td>
<td>0.28 [0.19, 0.41]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>3129,133,136</td>
<td>495</td>
<td>RR (fixed)</td>
<td>0.99 [0.46, 2.15]</td>
</tr>
<tr>
<td>Death</td>
<td>2105,129</td>
<td>1510</td>
<td>RR (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2105,129</td>
<td>1510</td>
<td>RR (fixed)</td>
<td>*******</td>
</tr>
<tr>
<td>Condition</td>
<td>N</td>
<td>Cases</td>
<td>RR (fixed)</td>
<td>95% CI</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------</td>
<td>-------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>3,105,129,133</td>
<td>1553</td>
<td>RR (fixed)</td>
<td>2.64 [0.62, 11.26]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>3,105,129,133</td>
<td>1553</td>
<td>RR (fixed)</td>
<td>1.68 [0.31, 9.04]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>3,105,129,133</td>
<td>1553</td>
<td>RR (fixed)</td>
<td>2.30 [0.40, 13.17]</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3,105,129,133</td>
<td>1553</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>2,105,128</td>
<td>1510</td>
<td>RR (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
### Table 69 Meta-analyses – Infliximab i.v. all doses vs placebo with ongoing MTX in MTX partial responders/non-responders, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>5</td>
<td>1555</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>5</td>
<td>1555</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>2</td>
<td>1448</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>5</td>
<td>1555</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>5</td>
<td>1555</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>2</td>
<td>1448</td>
<td>RD (fixed)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count, end of study result</td>
<td>2</td>
<td>1401</td>
<td>WMD (fixed)</td>
<td>-5.28 [-6.27, -4.29]</td>
</tr>
<tr>
<td>Patient’s global assessment, end of study result</td>
<td>2</td>
<td>1400</td>
<td>WMD (fixed)</td>
<td>-1.60 [-1.91, -1.29]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>2</td>
<td>1381</td>
<td>WMD (fixed)</td>
<td>-0.29 [-0.36, -0.23]</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>1</td>
<td>24</td>
<td>WMD (fixed)</td>
<td>-1.80 [-2.68, -0.92]</td>
</tr>
<tr>
<td>Modfied van de Heijde-Sharp score, mean change from baseline</td>
<td>2</td>
<td>373</td>
<td>WMD (fixed)</td>
<td>-6.79 [-9.19, -4.39]</td>
</tr>
<tr>
<td>Withdrawal for any reasons</td>
<td>3</td>
<td>513</td>
<td>RR (fixed)</td>
<td>0.37 [0.28, 0.50]</td>
</tr>
<tr>
<td>Withdrawal due to lack of efficacy</td>
<td>3</td>
<td>513</td>
<td>RR (fixed)</td>
<td>0.27 [0.18, 0.40]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>4</td>
<td>537</td>
<td>RR (fixed)</td>
<td>1.01 [0.47, 2.18]</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1510</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>2</td>
<td>1510</td>
<td>RR (fixed)</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>3</td>
<td>1567</td>
<td>RR (fixed)</td>
<td>2.64 [0.62, 11.26]</td>
</tr>
<tr>
<td>Malignancy – skin cancer</td>
<td>3</td>
<td>1567</td>
<td>RR (fixed)</td>
<td>1.68 [0.31, 9.04]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>RR (fixed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>-------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>3105,129,133</td>
<td>1567</td>
<td>2.30 [0.40, 13.17]</td>
<td></td>
</tr>
<tr>
<td>Serious infection</td>
<td>4105,129,133,134</td>
<td>1595</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>2105,129</td>
<td>1510</td>
<td>**</td>
<td></td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
### Table 70 Meta-analyses – Combination of infliximab (i.v. all doses) + MTX vs MTX alone in MTX naïve patients, end of trial

<table>
<thead>
<tr>
<th>Comparison or outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical method</th>
<th>Effect size [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RR (fixed)</td>
<td>1.20 [1.07, 1.36]</td>
</tr>
<tr>
<td>ACR50 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RR (fixed)</td>
<td>1.51 [1.26, 1.82]</td>
</tr>
<tr>
<td>ACR70 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RR (fixed)</td>
<td>1.67 [1.31, 2.13]</td>
</tr>
<tr>
<td>RD ACR20 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RD (fixed)</td>
<td>0.11 [0.04, 0.18]</td>
</tr>
<tr>
<td>RD ACR50 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RD (fixed)</td>
<td>0.16 [0.10, 0.23]</td>
</tr>
<tr>
<td>RD ACR70 responder</td>
<td>2,131,137</td>
<td>1000</td>
<td>RD (fixed)</td>
<td>0.14 [0.08, 0.20]</td>
</tr>
<tr>
<td>Swollen joint count, mean change from baseline</td>
<td>1,131</td>
<td>846</td>
<td>WMD (fixed)</td>
<td>-3.23 [-4.43, -2.03]</td>
</tr>
<tr>
<td>Patient’s global assessment, mean change from baseline</td>
<td>1,131</td>
<td>842</td>
<td>WMD (fixed)</td>
<td>-0.89 [-1.15, -0.63]</td>
</tr>
<tr>
<td>HAQ, mean change from baseline</td>
<td>2,131,137</td>
<td>1016</td>
<td>WMD (fixed)</td>
<td>0.11 [0.04, 0.18]</td>
</tr>
<tr>
<td>DAS28, end of study result</td>
<td>2,131,137</td>
<td>838</td>
<td>WMD (fixed)</td>
<td>0.39 [0.05, 2.75]</td>
</tr>
<tr>
<td>Modified van de Heijde-Sharp score, mean change from baseline</td>
<td>1,131</td>
<td>1004</td>
<td>WMD (fixed)</td>
<td>1.25 [0.86, 1.82]</td>
</tr>
<tr>
<td>Withdrawal due to adverse events</td>
<td>2,131,137</td>
<td>1060</td>
<td>RR (fixed)</td>
<td>3.02 [1.55, 5.88]</td>
</tr>
<tr>
<td>Death</td>
<td>1,131</td>
<td>1040</td>
<td>RR (fixed)</td>
<td>0.39 [0.05, 2.75]</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1,131</td>
<td>1040</td>
<td>RR (fixed)</td>
<td>1.25 [0.86, 1.82]</td>
</tr>
<tr>
<td>Malignancy – all</td>
<td>1,131</td>
<td>1040</td>
<td>RR (fixed)</td>
<td>3.50 [0.19, 64.88]</td>
</tr>
<tr>
<td>Malignancy – skin cancer excluding melanoma</td>
<td>1,131</td>
<td>1040</td>
<td>RR (fixed)</td>
<td>2.59 [1.11, 6.04]</td>
</tr>
<tr>
<td>Malignancy – all cancer excluding non-melanoma skin cancer</td>
<td>1,131</td>
<td>1040</td>
<td>RR (fixed)</td>
<td>1.25 [0.86, 1.82]</td>
</tr>
</tbody>
</table>

Shaded cells indicate statistically significant result at P<0.05
Appendix 4 Searches – economic evaluations

Source – Ovid MEDLINE(R) 1966 to February Week 3 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 economics/
12 exp "costs and cost analysis"/
13 cost of illness/
14 exp health care costs/
15 economic value of life/
16 exp economics medical/
17 exp economics hospital/
18 economics pharmaceutical/
19 exp "fees and charges"/
20 (economic$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
21 (expenditure$ not energy).tw.
22 (value adj1 money).tw.
23 budget$.tw.
24 or/11-23
25 10 and 24
26 limit 25 to yr=2001-2005
27 adalimumab.mp.

Last amended: 11 October 2005
28 humira.mp.
29 or/27-28
30 29 and 24
31 26 or 30
32 quality of life/
33 life style/
34 health status/
35 health status indicators/
36 value of life/
37 quality of wellbeing.tw.
38 or/32-37
39 1 and 38
40 limit 39 to yr=2001-2005
41 31 or 40

Source - EMBASE (Ovid) 1980 to 2005 Week 09

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 cost benefit analysis/
12 cost effectiveness analysis/
13 cost minimization analysis/
14 cost utility analysis/
15 economic evaluation/
(cost or costs or costed or costly or costing).tw.
(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
(technology adj assessment$).tw.
or/11-18
10 and 19
limit 20 to yr=2001-2005
adalimumab.mp.
humira.mp.
or/22-23
24 and 19
26 21 or 25
exp quality of life/
health status/
27 or 28
1 and 29
limit 30 to yr=2001 - 2005

Source – Cochrane Library (NHSEED) 2005 Issue 1

See search strategy for Cochrane Library under Clinical Effectiveness

Source – HEED Feb 2005

A series of searches were done using the following terms: anti tnf; infliximab; remicade, enbrel, etanercept, adalimumab, humira and references which included rheumatoid arthritis were selected.
Appendix 5 Searches – decision analytic models

Source - Ovid MEDLINE(R) 1966 to February Week 2 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 decision support techniques/
12 markov.mp.
13 exp models economic/
14 decision analysis.mp.
15 cost benefit analysis/
16 or/11-15
17 10 and 16
18 limit 17 to yr=2001 - 2005
19 adalimumab.mp.
20 humira.mp.
21 or/19-20
22 1 and 21 and 16
23 18 or 22

Source - EMBASE (Ovid) 1980 to 2005 Week 08

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
exp receptors tumor necrosis factor/
anti tnf.mp.
infliximab.mp.
remicade.mp.
enbrel.mp.
etanercept.mp.
or/2-8
1 and 9
decision support techniques/
markov.mp.
exp models economic/
decision analysis.mp.
cost benefit analysis/
or/11-15
10 and 16
limit 17 to yr=2001-2005
adalimumab.mp.
humira.mp.
or/19-20
1 and 21 and 16
18 or 22
Appendix 6 Searches – systematic reviews of DMARDs

Source – Ovid MEDLINE(R) 1999 to March Week 4 2005

1 arthritis rheumatoid/
2 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 dmar.mp.
4 1 and (2 or 3)
5 (systematic adj review$).mp.
6 (data adj synthesis).mp.
7 (published adj studies).ab.
8 (data adj extraction).ab.
9 meta-analysis/
10 meta-analysis.ti.
11 comment.pt.
12 letter.pt.
13 editorial.pt.
14 animals/
15 human/
16 14 not (14 and 15)
17 4 not (11 or 12 or 13 or 16)
18 or/5-10
19 17 and 18
20 limit 19 to yr=2001 - 2005
21 from 20 keep 5-6,9,12

Source - EMBASE (Ovid) 1996 to 2005 Week 14

1 (systematic adj review$).mp.
2 meta-analysis.ti.
3 meta-analysis/
4 arthritis rheumatoid/
5 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6 dmard$.mp.
7 or/1-3
8 4 and (5 or 6)
9 7 and 8
10 limit 9 to yr=2001 - 2005
11 from 10 keep 1,3,6,13,22,32,59

Source – Cochrane Library 2005 Issue 1

#1 dmard* in All Fields in all products
#2 hydroxychloroquine OR ciclosporine OR gold OR methotrexate in All Fields in all products
#3 leflunomide OR penicillamine OR sulfasalazine OR azathioprine in All Fields in all products
#4 "rheumatoid arthritis" in All Fields in all products
#5 MeSH descriptor Arthritis, Rheumatoid, this term only in MeSH products
#6 (#1 OR #2 OR #3)
#7 (#4 OR #5)
#8 (#6 AND #7)
## Appendix 7 List of excluded studies for clinical effectiveness review

<table>
<thead>
<tr>
<th>Citation</th>
<th>Reason for exclusion/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. No appropriate comparison between TNF inhibitors and other active comparators or placebo</strong></td>
<td></td>
</tr>
<tr>
<td>Fleischmann et al 2003&lt;sup&gt;205&lt;/sup&gt;</td>
<td>This was a retrospective analysis which compared the efficacy and safety of etanercept between age ≥65 group and age &lt;65 group using data from etanercept trials. No data from placebo groups or other active comparator groups were included.</td>
</tr>
<tr>
<td>Genovese et al 2004&lt;sup&gt;454&lt;/sup&gt;</td>
<td>This study compared the combination of anakinra and etanercept with etanercept alone. It was thus an assessment of the efficacy and safety of anakinra vs placebo. The results indicated that adding anakinra to etanercept provided no treatment benefit but was associated with increased risk of adverse events.</td>
</tr>
<tr>
<td>Goekoop-Ruiterman et al 2004, BeSt study&lt;sup&gt;40&lt;/sup&gt;</td>
<td>This is an ongoing RCT which compares four treatment strategies for RA. As all strategies included infliximab treatment at some point and thus the effectiveness and safety of infliximab compared with other agents cannot be appropriately assessed. Although not meeting inclusion criteria, because of its importance, we have described this study in detail in Section 3.2.4 of this report.</td>
</tr>
<tr>
<td>Van Riel et al EULAR 2005, ADORE study&lt;sup&gt;107&lt;/sup&gt;</td>
<td>This was an open-label RCT which compared two treatment strategies in RA patients inadequately controlled by methotrexate therapy: adding etanercept to methotrexate or replacing methotrexate with etanercept. No comparison of etanercept with placebo or other active treatment can be made.</td>
</tr>
<tr>
<td><strong>2. Neither full paper nor trial report available</strong></td>
<td></td>
</tr>
<tr>
<td>Schattenkirchner 1998&lt;sup&gt;106&lt;/sup&gt;</td>
<td>This was a small (n=24), double-blind, phase I RCT which compared adalimumab s.c. 0.5 mg/kg weekly to placebo with follow-up of 8 to 12 weeks.</td>
</tr>
<tr>
<td><strong>3. Not including outcomes of interest (clinically important outcomes)</strong></td>
<td></td>
</tr>
<tr>
<td>Smeets et al 2003&lt;sup&gt;206&lt;/sup&gt;</td>
<td>This was a RCT which studied the effect of single dose of infliximab compared with placebo on cell infiltration in synovial tissues in 24 patients.</td>
</tr>
<tr>
<td>St Clair et al 2002&lt;sup&gt;205&lt;/sup&gt;</td>
<td>This is a pharmacokinetic study of infliximab using data from ATTRACT trial.</td>
</tr>
<tr>
<td>Schotte et al 2001&lt;sup&gt;208&lt;/sup&gt;</td>
<td>This appears to be a study of the effect of etanercept on the production of pro-inflammatory cytokine mono-nuclear cells in the blood. Unable to obtain the paper (citation may be incorrect).</td>
</tr>
<tr>
<td><strong>4. Interventions do not include adalimumab, etanercept, or infliximab</strong></td>
<td></td>
</tr>
<tr>
<td>Grigor et al 2004&lt;sup&gt;209&lt;/sup&gt; TICORA study</td>
<td>This was a single-blind RCT which compared two treatment strategies (intensive outpatient management and routine care) in RA patients. Neither strategy included TNF inhibitors as part of the treatment.</td>
</tr>
<tr>
<td>Lukina et al 2001&lt;sup&gt;210&lt;/sup&gt;</td>
<td>This was a RCT which compares intramuscular injections of anti-IFN-gamma, anti-TNF-alpha, and placebo in 30 RA patients. The identity of the anti-TNF-alpha is not clear and it does not appear to be one of the three TNF inhibitors of interest.</td>
</tr>
<tr>
<td>Sigidin et al 2001&lt;sup&gt;211&lt;/sup&gt;</td>
<td>This appears to be a duplicate publication of Lukina et al 2001 listed above. The identity of the anti-TNF-alpha is not clear and it does not appear to be one of the three TNF inhibitors of interest.</td>
</tr>
<tr>
<td><strong>5. Not RCTs</strong></td>
<td></td>
</tr>
<tr>
<td>Brocq et al 2002&lt;sup&gt;212&lt;/sup&gt;</td>
<td>Non-randomised study describing outcomes from consecutive use of etanercept and infliximab and vice versa.</td>
</tr>
<tr>
<td>Buch et al 2004&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Observational study of ceasing and restarting TNF inhibitors with no control group.</td>
</tr>
<tr>
<td>Capria et al 2004&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Non-randomised study investigating TNF inhibition and endothelial dysfunction.</td>
</tr>
<tr>
<td>Cohen et al 2004&lt;sup&gt;214&lt;/sup&gt;</td>
<td>Observational study of adding methotrexate to partial responders to etanercept monotherapy with no control group.</td>
</tr>
<tr>
<td>Ferraro-Peyret et al 2004&lt;sup&gt;215&lt;/sup&gt;</td>
<td>Non-randomised study investigating infliximab treatment and autoantibodies in RA and ankylosing spondylitis patients.</td>
</tr>
<tr>
<td>Citation</td>
<td>Reason for exclusion/comment</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Genovese et al 2001&lt;sup&gt;216&lt;/sup&gt;</td>
<td>Three-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract.</td>
</tr>
<tr>
<td>Genovese et al 2002&lt;sup&gt;217&lt;/sup&gt;</td>
<td>Four-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract.</td>
</tr>
<tr>
<td>Genovese et al 2003&lt;sup&gt;218&lt;/sup&gt;</td>
<td>Five-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract.</td>
</tr>
<tr>
<td>Gomez-Puerta et al 2004&lt;sup&gt;219&lt;/sup&gt;</td>
<td>Observational study of using etanercept after treatment failure with infliximab with no control group.</td>
</tr>
<tr>
<td>Korczowska et al 2003&lt;sup&gt;220&lt;/sup&gt;</td>
<td>Non-randomised study investigating infliximab treatment and bone turnover.</td>
</tr>
<tr>
<td>Kucharz et al 2003&lt;sup&gt;221&lt;/sup&gt;</td>
<td>Non-randomised study investigating infliximab treatment and serum endostatin level.</td>
</tr>
<tr>
<td>Saadeh et al 2002&lt;sup&gt;223&lt;/sup&gt;</td>
<td>Non-randomised study investigating infliximab treatment and asthma control in RA patients. Abstract.</td>
</tr>
<tr>
<td>Smith et al 2004&lt;sup&gt;224&lt;/sup&gt;</td>
<td>Case report of treating renal amyloidosis complicating rheumatoid arthritis with etanercept.</td>
</tr>
<tr>
<td>Yazici et al 2001&lt;sup&gt;225&lt;/sup&gt;</td>
<td>Non-randomised study comparing the efficacy of etanercept with infliximab. Abstract.</td>
</tr>
</tbody>
</table>

6. Review articles

<table>
<thead>
<tr>
<th>Citation</th>
<th>Reason for exclusion/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breedveld 2001&lt;sup&gt;226&lt;/sup&gt;</td>
<td>Review of TNF blockade in RA.</td>
</tr>
<tr>
<td>Calin 2003&lt;sup&gt;227&lt;/sup&gt;</td>
<td>Review of infliximab.</td>
</tr>
<tr>
<td>Muhlhauser 2003&lt;sup&gt;228&lt;/sup&gt;</td>
<td>Review of etanercept (German).</td>
</tr>
<tr>
<td>Pugsley 2001&lt;sup&gt;229&lt;/sup&gt;</td>
<td>Review of etanercept.</td>
</tr>
<tr>
<td>Rashmi and Ujala 2004&lt;sup&gt;230&lt;/sup&gt;</td>
<td>Review of novel therapeutic approach for RA.</td>
</tr>
<tr>
<td>Rao 2002&lt;sup&gt;231&lt;/sup&gt;</td>
<td>Review of adalimumab treatment in RA.</td>
</tr>
<tr>
<td>Saatner 2005&lt;sup&gt;232&lt;/sup&gt;</td>
<td>Review of adalimumab (German).</td>
</tr>
<tr>
<td>Vervaeren 2002&lt;sup&gt;233&lt;/sup&gt;</td>
<td>Review of new treatment in RA (French).</td>
</tr>
<tr>
<td>Winning 2001&lt;sup&gt;234&lt;/sup&gt;</td>
<td>Review of infliximab treatment in RA.</td>
</tr>
<tr>
<td>Yung 2001&lt;sup&gt;235&lt;/sup&gt;</td>
<td>Review of etanercept.</td>
</tr>
</tbody>
</table>

7. News articles/commentaries/editorials

<table>
<thead>
<tr>
<th>Citation</th>
<th>Reason for exclusion/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous 2003&lt;sup&gt;236&lt;/sup&gt;</td>
<td>Summary of adalimumab DE019 (German).</td>
</tr>
<tr>
<td>Anonymous 2004&lt;sup&gt;237&lt;/sup&gt;</td>
<td>News on Genovese et al 2004 listed above which compared the combination of anakinra and etanercept and etanercept alone.</td>
</tr>
<tr>
<td>Bain and Brazil 2003&lt;sup&gt;238&lt;/sup&gt;</td>
<td>Commentary on adalimumab.</td>
</tr>
<tr>
<td>Becker 2004&lt;sup&gt;239&lt;/sup&gt;</td>
<td>News article on adalimumab (German).</td>
</tr>
<tr>
<td>Boers 2001&lt;sup&gt;240&lt;/sup&gt;</td>
<td>Letter. Commentary on ATTRACT trial.</td>
</tr>
<tr>
<td>Bruhn 2002&lt;sup&gt;241&lt;/sup&gt;</td>
<td>Commentary on adalimumab (German).</td>
</tr>
<tr>
<td>Bruhn 2004&lt;sup&gt;242&lt;/sup&gt;</td>
<td>News article on TEMPO trial (German).</td>
</tr>
<tr>
<td>Choy 2004&lt;sup&gt;243&lt;/sup&gt;</td>
<td>Editorial on combination therapy.</td>
</tr>
<tr>
<td>Cutolo 2001&lt;sup&gt;244&lt;/sup&gt;</td>
<td>Commentary on an etanercept RCT.</td>
</tr>
<tr>
<td>Czajka 2001&lt;sup&gt;245&lt;/sup&gt;</td>
<td>News article on ATTRACT trial (German).</td>
</tr>
<tr>
<td>Hanveyld 2004&lt;sup&gt;246&lt;/sup&gt;</td>
<td>News article on TEMPO trial (Dutch).</td>
</tr>
<tr>
<td>Hellwig 2003&lt;sup&gt;247&lt;/sup&gt;</td>
<td>Commentary on adalimumab (German).</td>
</tr>
<tr>
<td>Masche 2003&lt;sup&gt;248&lt;/sup&gt;</td>
<td>Commentary on adalimumab (German).</td>
</tr>
<tr>
<td>Matucci-Cerinic 2004&lt;sup&gt;249&lt;/sup&gt;</td>
<td>Commentary on ARMADA trial.</td>
</tr>
<tr>
<td>Moreland 2004&lt;sup&gt;250&lt;/sup&gt;</td>
<td>Commentary on an infliximab RCT.</td>
</tr>
<tr>
<td>Moreland 2004&lt;sup&gt;251&lt;/sup&gt;</td>
<td>Commentary on an adalimumab RCT.</td>
</tr>
<tr>
<td>Rothschild 2002&lt;sup&gt;252&lt;/sup&gt;</td>
<td>Conference news report regarding TNF therapies.</td>
</tr>
</tbody>
</table>

8. Irrelevant (conference news reports; cost studies)
<table>
<thead>
<tr>
<th>Citation</th>
<th>Reason for exclusion/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braddock 2004</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Croasdell 2003</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Evans 2003</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Levy 2004</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Oelke 2002</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Trepman et al 2003</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>Yung 2002</td>
<td>Conference news report.</td>
</tr>
<tr>
<td>van de Putte et al</td>
<td>Cost study for an adalimumab trial. Abstract.</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
### Appendix 8 Details of strategy sets used in BRAM

#### Table 71 Strategy set with etanercept followed by another TNF inhibitor

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
</tr>
<tr>
<td>SSZ</td>
<td>ETAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>ETAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETAN</td>
<td>DIVERGENCE</td>
<td>POINT</td>
<td></td>
</tr>
<tr>
<td>OPTION 1</td>
<td>ADAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAL</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTION 2</td>
<td>INFL+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFL+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTION 3</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>Dpen</td>
<td>CyA+MTX</td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dpen</td>
<td>PALL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Always move to</td>
<td>Relevant toxicity</td>
<td>Moves dependent on toxicity If toxic, move to</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>MTX</td>
<td></td>
<td>MTX</td>
<td>SSZ</td>
</tr>
<tr>
<td>SSZ</td>
<td>INFL+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>INFL+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFL+MTX</td>
<td>DIVERGENCE</td>
<td>POINT</td>
<td></td>
</tr>
<tr>
<td>OPTION 1</td>
<td>ADAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAL</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTION 2</td>
<td>ETAN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETAN</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPTION 3</td>
<td>LEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td></td>
<td>CyA or MTX</td>
<td>DPEN</td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dpen</td>
<td>PALL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 73 Strategy set: adalimumab and infliximab possibly followed by etanercept

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 74 Strategy set: etanercept and adalimumab possibly followed by infliximab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Always move to</td>
<td>Relevant toxicity</td>
<td>Moves dependent on toxicity If toxic, move to</td>
<td>Otherwise, move to</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 76 Strategy set: infliximab and adalimumab possibly followed by etanercept

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>If toxic, move to</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 77 Strategy set: infliximab and etanercept possibly followed by adalimumab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Always move to</th>
<th>Relevant toxicity</th>
<th>Moves dependent on toxicity</th>
<th>Otherwise, move to</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX</td>
<td>MTX</td>
<td>SSZ</td>
<td>MTX+SSZ</td>
<td></td>
</tr>
<tr>
<td>SSZ</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+SSZ</td>
<td>Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>Etan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan</td>
<td>Divergence pt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 1</td>
<td>Adal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Option 2</td>
<td>LEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEF</td>
<td>GST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GST</td>
<td>AZA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA</td>
<td>CyA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>CyA or MTX</td>
<td>DPen</td>
<td>CyA+MTX</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX</td>
<td>DPen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPen</td>
<td>Pall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 9 Existing economic evaluations: appraisal and data extraction

<table>
<thead>
<tr>
<th>Authors</th>
<th>Choi HK, Seeger JD, Kuntz KM*15b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>2002</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td>Cost effectiveness analysis</td>
</tr>
<tr>
<td>Country of origin</td>
<td>USA</td>
</tr>
<tr>
<td>Currency used</td>
<td>US Dollars</td>
</tr>
<tr>
<td>Years to which costs apply</td>
<td>1999</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
</tr>
<tr>
<td>Study population</td>
<td>Patients with methotrexate (MTX) naïve rheumatoid arthritis (RA)</td>
</tr>
<tr>
<td>Intervention 1</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Intervention 2</td>
<td>Leflunomide</td>
</tr>
<tr>
<td>Intervention 3</td>
<td>MTX (up to 15 mg weekly)</td>
</tr>
<tr>
<td>Intervention 4</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Intervention 5</td>
<td>No second line agent</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Clinical trial data used: ACR20 response criteria and a weighted outcome measure of ACR responses relative to a full weight of ACR70 responses (ACR70 response: ACR70 WR) by calculating a weighted average of proportions achieving ACR70, ACR50 and ACR20. A weight of 1 was assigned to ACR70, a weight of 50/70 and a weight of 20/70 to ACR20.</td>
</tr>
<tr>
<td>Cost data handled appropriately</td>
<td>Yes.</td>
</tr>
</tbody>
</table>

Direct and indirect costs were considered. Medication costs were averaged wholesale prices and monitoring costs were based on published estimates where available. If unavailable, costs were derived from the cost of the components recommended by ACR for each DMARD were summed, or by monitoring guidelines in the package insert of leflunomide.

The cost of no second-line treatment was calculated by subtracting ophthalmologic monitoring cost (once over the 6 month period) from the monitoring cost of the least expensive DMARD costs. Monitoring costs of etanercept were assumed to be the same as the monitoring costs of the no second-line treatment. Toxicity cost associated with MTX therapy was estimated to be $259 (1999 prices). Toxicity cost of SSZ was assumed to be...
Inpatient surgical costs were included to capture potential savings associated with improvement of RA from each option. An exponential relationship between HAQ score and inpatient surgery costs for each treatment strategy was developed. Medical admission costs were assumed to be largely due to toxicity of DMARDs.

Indirect costs were included to capture the potential savings associated with improvement of RA for each treatment. An HAQ indirect cost assignment was used, using the same HAQ efficacy estimates used for the surgical costs. A linear relationship was assumed to between work capacity and HAQ score to infer indirect cost savings associated with HAQ improvement. This was based on a published CEA in a Swedish RA population. The average wage was multiplied by work capacity achieved in each option to estimate the cost of lost work capacity.

**Modelling summary**
A decision analytic model was constructed and analysed using Data software (version 3.5, TreeAge Software Inc, Williamstown MA, USA). The decision tree had a time horizon of 6 months was used in the model (this was considered to represent the usual duration of clinical trials of RA).

**Outcome measures used in economic evaluations**
The occurrence of toxicity related to each therapy and ACR response criteria (ACR20 or ACR70). ICERs were for per patient achieving ACR20 or ACR70WR.

**Direction of result with appropriate quadrant location**
In the base case analysis using either ACR20 or ACR70WR for MTX naïve RA, MTX and SSZ both cost less and were more effective (SE quadrant: cost saving) when compared to no second-line therapy. SSZ compared to MTX at ACR20 was in the NE quadrant (more costly but also more effective). Using ACR70, SSZ compared to MTX cost more but was less effective (NW quadrant). Leflunomide was also ruled out by simple dominance when compared to MTX (i.e. NW Quadrant). Compared to MTX and SSZ, etanercept was both more expensive and more effective (i.e. NE quadrant).

Etanercept vs sulfasalazine: $41,900 per ACR20
Etanercept vs methotrexate: $40,800 per ACR70WR

**Statistical analysis for**
Not undertaken
<table>
<thead>
<tr>
<th>Authors</th>
<th>Choi HK, Seeger JD, Kuntz KM</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient-level stochastic data</td>
<td></td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Yes: sensitivity analyses were performed to determine the robustness of the base-case results to variations of baseline estimates. Three way sensitivity analyses were also done to determine robustness of base-case results to variations of more than one key variable, including the main variable of triple therapy efficacy.</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>MTX is cost effective (cost savings vs the no second line treatment option) for MTX-naïve RA in achieving ACR20 or ACR70WR over a 6 month period. The relative cost effectiveness between SSZ and MTX cannot be determined with reasonable certainty, but SSZ therapy appears to be as cost effective as MTX (cost saving) in achieving ACR outcomes over a 6 month period. The most efficacious option, etanercept, incurs higher incremental costs per ACR20 or ACR70WR than other options analysed. Whether etanercept compared with MTX is cost effective depends upon whether &gt;$40,000 per ACR20 or ACR70WR over a 6 month period is considered acceptable.</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td>Wong JB, Singh G, Kavanaugh A&lt;sup&gt;158&lt;/sup&gt;</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>2002</td>
</tr>
<tr>
<td><strong>Type of economic evaluation</strong></td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td><strong>Country of origin</strong></td>
<td>USA</td>
</tr>
<tr>
<td><strong>Currency used</strong></td>
<td>US Dollars</td>
</tr>
<tr>
<td><strong>Years to which costs apply</strong></td>
<td>1998</td>
</tr>
<tr>
<td><strong>Perspective</strong></td>
<td>Societal</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Patients with active, refractory rheumatoid arthritis</td>
</tr>
<tr>
<td><strong>Intervention 1</strong></td>
<td>Placebo + Methotrexate (MTX)</td>
</tr>
<tr>
<td><strong>Intervention 2</strong></td>
<td>Infliximab + MTX</td>
</tr>
<tr>
<td><strong>Source of effectiveness data</strong></td>
<td>Data were extrapolated from the ATTRACT trial and from ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System). Quality of life (QoL) data was assessed as self-reported global health using a visual analogue scale: for the first year data from ATTRACT were used and after the first year estimates were based on ARAMIS.</td>
</tr>
<tr>
<td><strong>Cost data handled appropriately</strong></td>
<td>Yes.</td>
</tr>
<tr>
<td>Drug costs were based on the average wholesale price of infliximab, infusion administration costs, and pre-treatment evaluation. Direct costs were taken from ATTRACT and included all non-protocol related medical care costs. For a societal perspective, indirect cost estimates from ATTRACT were also used for the first year for the subset of patients who were employed at the time of enrolment. Indirect costs beyond the first year were estimated to be between one to three times the costs in year one. Costs from ARAMIS included self-reported hospitalisation, emergency room visits, outpatient surgeries, home care and non-traditional treatments as well as those for physicians, therapists, and nurse practitioners, laboratory tests, radiological studies, drugs and nursing home or rehabilitations hospitalisations.</td>
<td></td>
</tr>
<tr>
<td><strong>Modelling summary</strong></td>
<td>Markov model consisting of 21 health states to project the 54 week results of RCTs to lifetime economic and clinical outcomes. A cycle length of 6 months was used.</td>
</tr>
<tr>
<td><strong>Outcome measures used in economic evaluations</strong></td>
<td>Life expectancy and quality-adjusted life years (QALY) (based on VAS) in order to calculate cost per QALY.</td>
</tr>
<tr>
<td><strong>Direction of result with appropriate quadrant location</strong></td>
<td>NE Quadrant. $30,500 per QALY.</td>
</tr>
<tr>
<td><strong>Statistical analysis for</strong></td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Author</td>
<td>Wong JB, Singh G, Kavanaugh A&lt;sup&gt;158&lt;/sup&gt;</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>patient-level stochastic data</td>
<td></td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Yes.</td>
</tr>
<tr>
<td></td>
<td>Sensitivity analyses were conducted to examine the impact of varying the values used, with and without indirect costs related to productivity losses from disability.</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>Infliximab plus MTX for 54 weeks for RA should be cost-effective with its clinical benefit providing good value for the drug cost, especially when including productivity losses. Although infliximab beyond 54 weeks will likely be cost effective, the economics and clinical benefit remain uncertain and will depend upon long-term results of clinical trials.</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td>Kobelt G, Jonsson L, Young A, Eberhardt K.</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Date</td>
<td>2003</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Country of origin</td>
<td>France, Sweden, UK</td>
</tr>
<tr>
<td>Currency used</td>
<td>Euros (€), Swedish Kronor (SEK), Pounds sterling (GBP)</td>
</tr>
<tr>
<td>Years to which costs apply</td>
<td>Not stated</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
</tr>
<tr>
<td>Study population</td>
<td>Patients with rheumatoid arthritis not responding to at least two DMARDs (including methotrexate)</td>
</tr>
<tr>
<td>Intervention 1</td>
<td>Infliximab + MTX</td>
</tr>
<tr>
<td>Intervention 2</td>
<td>MTX alone</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Clinical data from two RA cohorts, followed for up to 15 years, in Sweden and the UK (Early RA Study (ERAS)), in which average Health Assessment Questionnaire (HAQ) scores were calculated and used to inform the effectiveness data and the transition probabilities within the model.</td>
</tr>
<tr>
<td>Cost data handled appropriately</td>
<td>Direct costs included hospitalisation, surgical interventions, ambulatory and community care and RA medication. Non-medical direct costs and informal care costs were excluded. The cost of hospitalisation was based on the number of inpatient days in different wards and ward-specific costs, the cost of surgical interventions was based on the type of intervention and its duration multiplied by the cost per minute of operating theatre use. Outpatient costs were based on the number of visits to different health care professionals. The cost of RA drugs was calculated from the number of months of use and the cost associated with standard drug monitoring protocols in place in the rheumatology departments of participating study centres. Unit cost data was taken from hospital accounting data and official price lists. Indirect costs were calculated as the loss of work capacity of patients in the more advanced disease states. For patients in disease state 1 (i.e. a HAQ &lt; 0.6) only short term sick leave was considered. The human capital approach was used in which an individual’s productivity is valued at market price. The total number of productive years lost at each stage (of the model) was compared with the number in state 1, and the difference multiplied by the average gross annual income. The cost of infliximab was calculated using the official list price and the doses prescribed in clinical practice (in Sweden and in the UK, respectively).</td>
</tr>
<tr>
<td>Author</td>
<td>Kobelt G, Jonsson L, Young A, Eberhardt K. ¹⁵⁹</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Modelling summary</td>
<td>Markov model with a cycle length of 1 year (in line with the annual follow-up of epidemiological studies). A time horizon of 10 years was used.</td>
</tr>
<tr>
<td>Outcome measures used in economic evaluations</td>
<td>Incremental quality adjusted life years (QALYs) (based on EQ-5D), and incremental cost effectiveness ratios (ICERs)</td>
</tr>
<tr>
<td>Direction of result with appropriate quadrant location</td>
<td>NE quadrant. For 1 year of treatment, €3440 per QALY in Sweden and €34800 per QALY in UK. The only exception is with the ‘Alternative model’ comparing total costs at 1 year (unadjusted) and total costs at 1 year (adjusted for the effect loss at discontinuation) for Sweden. The direction of results in these two cases is the SE quadrant (cost saving).</td>
</tr>
<tr>
<td>Statistical analysis for patient-level stochastic data</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>A sensitivity analysis was undertaken by way of an ‘alternative model’ in which a loss of treatment effect was assumed in the year after discontinuation, expressed as a faster disease progression than that reported in the cohorts. Differences in HAQ scores between infliximab and MTX groups in the clinical trials were applied to the cohorts for the treatment arm for the first year. Thus, treatment was compared directly with that of the cohorts. A sensitivity analysis was also undertaken on the price of infliximab.</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>One or two years of treatment with infliximab reduced direct and indirect resource consumption in Sweden and the UK, thereby partly offsetting the treatment costs. In the base-case analysis, including direct and indirect costs, the cost per QALY gained was 32,000 SEK in Sweden (€3,440) and 21,600 GBP in the UK (€34,800) for 1 year of treatment. The respective QALY gains were 0.248 and 0.298. With 2 years of treatment, the cost per QALY gained was 150,000 SEK in Sweden (€16,100) and 29,900 GBP in the UK (€48,200). The results suggest that 1-2 years of treatment with infliximab and MTX,</td>
</tr>
</tbody>
</table>
## Author
Kobelt G, Jonsson L, Young A, Eberhardt K.¹⁵⁹

Compared to MTX alone, will lead to savings in both direct and indirect costs. Savings in direct costs are €1500-2000 in Sweden and up to €800 in the UK. These savings will not offset the cost of infliximab. The majority of savings will come from maintaining the patients’ ability to work. However, when only direct costs are included, the cost-effectiveness ratios remain within the usual range for treatments to be recommended for use.
| Author                                                                 | Welsing PMJ, Severens JL, Hartman M, van Riel PLCM, Laan RFJM. 
|-----------------------------------------------------------------------|-------------------------------------------------------------
| Date                                                                  | 2004                                                        |
| Type of economic evaluation                                           | Cost-utility analysis                                       |
| Country of origin                                                     | Netherlands                                                 |
| Currency used                                                         | Euros                                                       |
| Years to which costs apply                                            | Not stated                                                  |
| Perspective                                                           | Societal                                                    |
| Study population                                                      | Patients with rheumatoid arthritis who satisfy the indication for TNF inhibitors in the Netherlands. |
| Intervention 1                                                        | Usual treatment                                             |
| Intervention 2                                                        | Treatment with leflunomide, in the case of non response after 3 months switch to usual treatment |
| Intervention 3                                                        | Treatment with etanercept, in the case of non response after 3 months switch to usual treatment |
| Intervention 4                                                        | Treatment with leflunomide, in the case of non response after 3 months switch to etanercept, in the case of non response switch to TNF-blocking agent switch to usual treatment |
| Intervention 5                                                        | Treatment with etanercept, in the case of non response after 3 months switch to leflunomide, in the case of non response switch to leflunomide switch to usual treatment |
| Source of effectiveness data                                          | The following sources of effectiveness data were used:      |
|                                                                      | 1. QoL data from a 48 week multi-centred trial involving 411 patients were assigned to the health states within the Markov model; |
|                                                                      | 2. Follow-up data of patients from an open longitudinal study of early RA (disease duration <1 year with no prior use of DMARDs), underway since 1985 at the University Medical Centre Nijmegen, in the Netherlands. These patients stopped treatment with sulfasalazine and methotrexate due to insufficient effect or toxicity and who had high disease activity. This data was used to calculate transition probabilities for usual treatment. |
|                                                                      | 3. Effectiveness data from a dataset, made available by Wyeth Pharmaceuticals (Madison, NJ), from clinical trials of monotherapy with etanercept in patient who failed DMARD treatment (1-4 DMARDs) and of combination therapy with MTX in patients with insufficient response to MTX alone. Patients with high disease activity at baseline and a good or moderate |

Last amended: 11 October 2005
Author | Welsing PMJ, Severens JL, Hartman M, van Riel PLCM, Laan RFJM, 162
---|---
**response to etanercept (EULAR criteria) after 3 months were selected. These data were used to calculate transition probabilities.** Published ACR20, ACR50 and ACR70 response criteria after 1 and 2 years of treatment were used to represent Markov states for moderate disease activity, low disease activity and remission, respectively. Expected patient years are calculated in each of the different Markov states.

<p>| Cost data handled appropriately | Yes. Costs were assigned from a 48 week multi-centred trial with MTX that included 411 patients. Medical and non-medical (absence from paid work, travel expenses) costs were collected. |
| Modelling summary | A Markov model consisting of health states defined by the DAS score. A cycle length of 3 months was used. Markov states from remission (DAS &lt;1.6), low disease activity (1.6&lt; DAS &gt;2.4), moderate disease activity (2.4&lt; DAS &gt;3.7), and high disease activity (DAS28&gt;3.7) were used. A time limit of 5 years (20 cycles) was applied. A specific Markov model was used with the same structure and the same costs and utility values of the Markov states for each treatment strategy. The models used specific transition probabilities and costs for the respective drug treatments. Using these models, the expected costs and effects were compared between the different treatment strategies. |
| Outcome measures used in economic evaluations | QALYs were compared between the different treatment strategies to calculate cost per QALY and ICERs. EQ-5D was used to calculate utilities. Also considered is cost per patient year in the three DAS28 states. |
| Direction of result with appropriate quadrant location | NE quadrant; except for a small number of studies in the NW quadrant, relating to comparisons between Interventions 4 and 5. Etanercept alone was dominated by leflunomide/etanercept combinations. Versus usual treatment the ICERs were €163,556 per QALY for Lef-Etan and €297,151 per QALY for Etan-Lef. Versus leflunomide the ICERs were €317,627 per QALY for Lef-Etan and €517,061 per QALY for Etan-Lef. |
| Statistical analysis for patient-level stochastic data | Not undertaken |
| Appropriateness of statistical analysis | Not applicable |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Welsing PMJ, Severens JL, Hartman M, van Riel PLCM, Laan RFJM.162</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Yes. Model uncertainty was explored using probabilistic sensitivity analyses (PSA). Distributions were specified for the transition probabilities, the costs and the utility values of the Markov states and for the response of etanercept (EULAR good/moderate) and Leflunomide treatment (ACR20) after 3 months. 2.5-97.5 percentile were reported from PSA for costs and QALYs, but no ICERs were given.</td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Yes. One way sensitivity analysis was applied to determine the relative importance of different parameters for the primary outcome. Correlations between the parameters and outcomes were calculated. Important model parameter values as defined by the correlation were also varied in a one-way sensitivity analysis</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>Treatment strategies that include TNF inhibitors are probably the most effective for patients in whom two DMARDs have previously failed, of which one is MTX. From these strategies, treatment starting with leflunomide, and in the case of non response switching to TNF inhibitor, probably results in the most favourable ratio between the extra costs and effects.</td>
</tr>
</tbody>
</table>
Author | Brennan A, Bansback N, Reynolds A, Conway P.157
Date | 2004
Type of economic evaluation | Cost utility analysis
Country of origin | UK
Currency used | Pounds sterling (GBP)
Years to which costs apply | 2000
Perspective | National Health Service in the UK
Study population | Patients with rheumatoid arthritis who failed to previously respond to at least two DMARDs (MTX as first line and sulfasalazine as second line).
Intervention 1 | Treatment pathway I: 3rd option - etanercept monotherapy; 4th - intramuscular gold; and 5th - ciclosporin and MTX.
Intervention 2 | Treatment pathway II: 3rd option - intramuscular gold; 4th - ciclosporin and MTX; and 5th - leflunomide
Source of effectiveness data | DAS28 scores were used. Comparative data on the DAS28 for etanercept was unavailable therefore data from a phase III study of etanercept vs placebo was used, alongside published data for other DMARDs. Patient characteristics of published data were compared with those of the Phase III study in to identify studies that enrolled similar patients. Where comparable studies were unavailable, ACR20 response was assumed to be 35%, using published meta-analysis of patient with >10 yrs disease duration. These sources were used to inform model parameter values relating to initial response to therapy and initial HAQ response.
Long term HAQ response was estimated from published sources and data from a long-term open label study of etanercept. ERAS was used as a source of data for HAQ improvements during periods of non-response. Long term withdrawal was estimated using data from a study based on clinical practice in Sweden – showing an annual withdrawal of 8.3%.
Evidence presented in 4 separate studies was used as a basis for the relationship between HAQ and utility to inform QoL data. Variation in the results was small and the median relationship was used in the primary analysis. Trial data was used to inform response rates of treatment and HAQ improvements.
Author: Brennan A, Bansback N, Reynolds A, Conway P

Cost data handled appropriately: Yes.

Drug and monitoring costs and other direct were examined for each treatment. Drug costs derived from current list prices and monitoring costs were estimated using BSR guidelines. Evidence from studies in the US and Sweden suggests a strong correlation between HAQ score and direct costs. Costs reported in these studies were used to inform parameter values (converted to 2000 UK currency using the purchaser parity index and inflation). Both gave an almost identical linear relationship of £860 p.a. increase in direct costs. In the model the difference in the two comparators HAQ score trends is converted into a difference in direct health care costs, i.e. worse HAQ scores generate higher direct costs, pro rata.

Sensitivity analyses were used: firstly, to examine the impact of the additional costs associated with home help, residential and nursing home care and, secondly, to examine the impact of economic productivity to society through maintained employment. Data from a Swedish study was used to inform the latter.

Modelling summary: A decision analytic model was developed in Excel. Patients following each treatment pathway (etanercept vs DMARD sequence) were simulated. A cycle length of 6 months was used. A patient population of 10,000 was simulated over the lifetime and a Monte Carlo approach taken. Discounting was applied to costs (6% p.a.) and benefits (1.5% p.a.) in line with guidance from the National Institute for Clinical Excellence (NICE).

Outcome measures used in economic evaluations: QALY through the use of etanercept compared with current UK clinical practice. HAQ and EQ-5D data were used to calculate QALYs through regression.

Direction of result with appropriate quadrant location: NE Quadrant. £16,330 per QALY.

Statistical analysis for patient-level stochastic data: Yes – patient level data was used taken from model simulation.

Appropriateness of statistical analysis: Yes

Uncertainty around cost-effectiveness expressed: Uncertainty in the results was expressed in terms of conducting scenario-based one way sensitivity analyses in order to investigate the impact of alternative scenarios for the key model parameter values.
<table>
<thead>
<tr>
<th>Author</th>
<th>Brennan A, Bansback N, Reynolds A, Conway P. 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Yes.</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>One way sensitivity analysis (‘scenario-based) was undertaken: analyses as described above was performed, in addition to analyses of changes to the response rate of etanercept, changes to HAQ scores and changes to mortality estimates.</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes.</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>Etanercept is cost effective when compared to non-biological agents. NICE recognised it as cost effective and recommended its availability for use in patients who have failed at least two DMARDs previously. This model was used to inform the decision taken by NICE.</td>
</tr>
</tbody>
</table>
### Authors

<table>
<thead>
<tr>
<th>Date</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-utility analyses</td>
</tr>
<tr>
<td>Country of origin</td>
<td>Sweden, France</td>
</tr>
<tr>
<td>Currency used</td>
<td>Euros</td>
</tr>
<tr>
<td>Years to which costs apply</td>
<td>2002</td>
</tr>
<tr>
<td>Perspective</td>
<td>Societal</td>
</tr>
<tr>
<td>Study population</td>
<td>Patients with rheumatoid arthritis who failed to respond to at least two DMARDs, including methotrexate (MTX) in Sweden</td>
</tr>
<tr>
<td>Intervention 1</td>
<td>Etanercept or infliximab</td>
</tr>
<tr>
<td>Intervention 2</td>
<td>Baseline level (failed at least 2 DMARDs, including methotrexate).</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Follow up of patients from a cohort treated with etanercept or infliximab.</td>
</tr>
<tr>
<td>Clinical outcomes measured &amp; methods of valuation used</td>
<td>The Swedish version of the HAQ, DAS28 and the EQ-5D. were used during the first year of follow-up.</td>
</tr>
<tr>
<td>Cost data handled appropriately</td>
<td>Yes. Direct costs were based on unit cost data from Lund (the largest centre used in the trial), and a Swedish Pharmaceutical lexicon. Indirect costs were estimated by the human capital method using the average annual gross salary. Short term sick leave was based on the number of days of absence and the loss of productivity was based on the proportion of full time work of patients aged &gt;65 years.</td>
</tr>
<tr>
<td>Modelling summary</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Outcome measures used in economic evaluations</td>
<td>Mean utilities per year and QALY gained with 1 year of treatment – based on EQ-5D data.</td>
</tr>
<tr>
<td>Direction of result with appropriate quadrant location</td>
<td>NE Quadrant. After 3 months treatment: €43,500 per QALY. After 6 weeks treatment: €36,900 per QALY.</td>
</tr>
<tr>
<td>Statistical analysis for patient-level stochastic data</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Yes – means and standard deviations reported. No bootstrapping was undertaken, and this may have been appropriate given the small dataset.</td>
</tr>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Authors</td>
<td>Kobelt G, Eberhardt K, Geborek P.(^{160})</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Sensitivity analysis is undertaken on all 160 patients: all patients who began one of the treatments. The main economic evaluation is based on those patients who continued to receive TNF inhibitor treatment for at least 12 months and had complete data (116 patients)</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>Cost effectiveness ratios are within the generally accepted threshold of €50,000, but need to be confirmed with larger samples. Assuming that the improvements occurred within 3 months after treatment, the cost per QALY is €36,900. Sensitivity analysis, including all 160 patients, gave an estimated cost per QALY of €53,600. The cost per QALY increases for patient groups with less severe disease.</td>
</tr>
<tr>
<td>Authors</td>
<td>Chiou C, Choi J, Reyes CM(^{167})</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Date</td>
<td>2004</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>Country of origin</td>
<td>USA</td>
</tr>
<tr>
<td>Currency used</td>
<td>Dollars (US$)</td>
</tr>
<tr>
<td>Years to which costs apply</td>
<td>2003</td>
</tr>
<tr>
<td>Perspective</td>
<td>Health care (payers)</td>
</tr>
<tr>
<td>Study population</td>
<td>Patients with moderate to severe rheumatoid arthritis (RA) who were deemed candidates for the following biologic monotherapies and combination therapies.</td>
</tr>
<tr>
<td>Intervention 1</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Intervention 2</td>
<td>Anakinra (reference case for monotherapy)</td>
</tr>
<tr>
<td>Intervention 3</td>
<td>Etanercept</td>
</tr>
<tr>
<td>Intervention 4</td>
<td>Adalimumab + MTX</td>
</tr>
<tr>
<td>Intervention 5</td>
<td>Anakinra + MTX</td>
</tr>
<tr>
<td>Intervention 6</td>
<td>Etanercept + MTX</td>
</tr>
<tr>
<td>Intervention 7</td>
<td>Infliximab + MTX</td>
</tr>
<tr>
<td>Source of effectiveness data</td>
<td>Effectiveness data was sourced from a review of previously published randomised clinical trials (RCT). The results of the review were presented to an expert panel of rheumatologists who selected the relevant clinical trials based on similar patient inclusion criteria and baseline characteristics. American College of Rheumatology (ACR) response criteria: ACR20, ACR50, and ACR70 were used within the model. Probabilities for achieving ACR20, ACR50 and ACR70 for each treatment strategy were sourced from published literature. The absolute response rates from the clinical trial data with the most comparable patient population characteristics and study design were used as input data for the model. Serious adverse event (SAE) rates were also sourced from clinical trial data. The same expert panel classified the adverse events, associated with each treatment strategy, into severity levels and estimated the corresponding medical resource utilisation associated with each. SAEs were categorised as either mild, moderate, or severe. The highest frequency reported in a study was used to assign the probability within each severity classification. Probabilities for being in each health state were determined by the product of the probability of achieving each ACR response criteria and for developing different levels of SAEs,</td>
</tr>
<tr>
<td>Authors</td>
<td>Chiou C, Choi J, Reyes CM¹⁶⁷</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>assuming that the probability for achieving each were independent.</td>
</tr>
<tr>
<td>Cost data handled appropriately</td>
<td>Yes. Drug costs were based on US average wholesale prices. Health care resource costs for medication, injection and infusion, monitoring and management of SAEs were obtained from the 2003 American Medical Association Current Procedural Terminology (CPT codes) codebook, the 2003 Medicare Reimbursement Fee Schedule and the Medstat Diagnosis Related Group (DRG) Guide. The costs of complications were estimated as follows: a mild complication included the cost of one visit every 6 months and associated laboratory tests, the cost of a moderate complication included that of a mild complication plus the cost of antibiotics, and the cost of a severe complication included the cost of hospitalisation for pneumonia or sepsis.</td>
</tr>
<tr>
<td>Modelling summary</td>
<td>A decision tree was developed in DATA 4.0 (TreeAge software) to compare the costs and outcomes of a hypothetical cohort of patients. The time horizon was 1 year, effectiveness was measured at 6 and 12 months. The structure of the model is flexible, allowing for data that may be available over a longer follow-up period. If effectiveness data was not available at 12 months, 6 and 12 month effectiveness data were assumed to be equivalent. Within the model 16 health states were used: these were the product of the severity of SAE and the ACR response criteria, e.g. a patient could have no ACR, ACR20, ACR50, or ACR70 and could be experiencing no SAE, mild SAEs, moderate SAEs, or severe SAEs.</td>
</tr>
<tr>
<td>Outcome measures used in economic evaluations</td>
<td>Effectiveness was measured in quality-adjusted life years (QALYs). It was assumed that patients would live with one of the 16 health states at any given time. Preference weights for each health state, used to calculate the QALYs, were measured using a visual analogue scale (VAS) (Health Assessment Questionnaire (HAQ)) obtained from a survey of 748 patients with RA.</td>
</tr>
<tr>
<td>Statistical analysis for patient-level stochastic data</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Uncertainty around cost-</td>
<td>Not undertaken</td>
</tr>
<tr>
<td>Authors</td>
<td>Chiou C, Choi J, Reyes CM¹⁶⁷</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>effectiveness expressed</td>
<td></td>
</tr>
<tr>
<td>Appropriateness of method dealing with uncertainty around cost effectiveness</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Yes: one way sensitivity analyses were performed on all input variables. Cost variables were varied from 50 to 200% of baseline and probability values increased and decreased by 50% baseline. Cost of treatment and the probability of achieving ACR response criteria were the main drivers of incremental cost effectiveness ratios (ICERs). Costs of SAEs, probabilities of developing SAEs, health care resource costs and the cost of MTX did not affect the ICERs.</td>
</tr>
<tr>
<td>Modelling inputs &amp; techniques appropriate</td>
<td>Yes</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>Anakinra was the least expensive option and etanercept dominated other treatments. Cost of drugs and probability for achieving response were the main drivers of ICERs.</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td>Bansback NJ, Brennan A, Ghatnekar O.(^{163})</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>2005</td>
</tr>
<tr>
<td><strong>Type of economic evaluation</strong></td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td><strong>Country of origin</strong></td>
<td>UK, Sweden</td>
</tr>
<tr>
<td><strong>Currency used</strong></td>
<td>Euros (€)</td>
</tr>
<tr>
<td><strong>Years to which costs apply</strong></td>
<td>2001</td>
</tr>
<tr>
<td><strong>Perspective</strong></td>
<td>Health Care</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Patients with moderate to severe rheumatoid arthritis for whom at least two traditional DMARDs had failed (simulation of 10,000 patients)</td>
</tr>
<tr>
<td><strong>Intervention 1</strong></td>
<td>Adalimumab monotherapy</td>
</tr>
<tr>
<td><strong>Intervention 2</strong></td>
<td>Adalimumab + methotrexate (MTX) (study no. DE009 &amp; DE019)</td>
</tr>
<tr>
<td><strong>Intervention 3</strong></td>
<td>Adalimumab + MTX (study no. DE009)</td>
</tr>
<tr>
<td><strong>Intervention 4</strong></td>
<td>Etanercept monotherapy</td>
</tr>
<tr>
<td><strong>Intervention 5</strong></td>
<td>Etanercept + MTX</td>
</tr>
<tr>
<td><strong>Intervention 6</strong></td>
<td>Infliximab + MTX</td>
</tr>
<tr>
<td><strong>Intervention 7</strong></td>
<td>Traditional drug treatment (DMARDs)</td>
</tr>
<tr>
<td><strong>Source of effectiveness data</strong></td>
<td>Treatment response data from a published review and conference abstracts. Two combination RCTs were available for adalimumab. The first, ARMADA, was similar to the etanercept and infliximab trials in design and patient numbers. The second, a larger more comprehensive study, also included radiographic evaluations. In Sweden, decisions to continue treatment are made using the DAS response criteria. This study presents results for two definitions of classifying successful response: ACR20 and ACR50. Comparison of trials suggests similarities between the results of ACR and DAS responses. This model assumes that the ACR20 corresponds to a moderate DAS28 score and ACR50 corresponds to a good DAS score. In addition HAQ was mapped to a health utility measure (HUI 3). Analysis of patient level adalimumab data was used to calculate HAQ improvement in ACR20 and ACR50 responders. The model assumed that HAQ worsened after withdrawal from treatment; immediately at the point of withdrawal and equal the initial HAQ improvement for all treatments.</td>
</tr>
<tr>
<td><strong>Cost data handled</strong></td>
<td>Yes</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Author</th>
<th>Bansback NJ, Brennan A, Ghatnkar O.</th>
</tr>
</thead>
<tbody>
<tr>
<td>appropriately</td>
<td></td>
</tr>
<tr>
<td>Modelling summary</td>
<td>A decision analytic model building on two previously described models. Patient based transition state model, simulating a population of 10,000 patients. A cycle length of 6 months was used, within which the risks of withdrawal, adverse events and mortality were determined, based on experiences of an average patient. Patients were simulated for their lifetime. Model parameter values were derived from patient level data analysis of adalimumab RCTs or published sources.</td>
</tr>
<tr>
<td>Outcome measures used in economic evaluations</td>
<td>At each 6 month cycle in the model the patients’ health related quality of life (HRQoL) scores were evaluated by simple linear transformation from the HAQ-DI score. From this a cost utility analysis was possible.</td>
</tr>
<tr>
<td>Direction of result with appropriate quadrant location</td>
<td>North East quadrant. For the group ACR50/DAS28 good: €34,167 per QALY (Adalimumab+MTX) €34,922 per QALY (Adalimumab+MTX 1) €35,760 per QALY (Etanercept + MTX) €48,333 per QALY (Infliximab + MTX) €41,561 per QALY (Adalimumab) €36,927 per QALY (Etanercept) For the group ACR20/DAS28 moderate: €40,875 per QALY (Adalimumab+MTX) €44,018 per QALY (Adalimumab+MTX 1) €51,976 per QALY (Etanercept + MTX) €64,935 per QALY (Infliximab + MTX) €65,499 per QALY (Adalimumab) €42,480 per QALY (Etanercept)</td>
</tr>
<tr>
<td>Statistical analysis for patient-level stochastic data</td>
<td>Patient level data was used to calculate HAQ improvement in patients who were ACR20 and ACR50 responders.</td>
</tr>
<tr>
<td>Appropriateness of statistical analysis</td>
<td>Yes</td>
</tr>
<tr>
<td>Uncertainty around cost-effectiveness expressed</td>
<td>Yes. Cost effectiveness acceptability curve &amp; cost effectiveness plane</td>
</tr>
<tr>
<td>Appropriateness of method</td>
<td>Yes.</td>
</tr>
</tbody>
</table>
dealing with uncertainty around cost effectiveness

Appropriate methods were used: both central values and probability density functions were used to describe the distribution of uncertainty.

Sensitivity analysis

Yes.
Univariate sensitivity analysis and multivariate sensitivity analysis employed. Uncertainty in assumptions around model structure were also explored.

Modelling inputs & techniques appropriate

Yes

Author’s conclusions

Adalimumab appears to be cost-effective for the treatment of moderate to severe RA. Results suggest that adalimumab is at least cost effective as other TNF inhibitors. with the exception of infliximab; the costs results were between €35,000 and €42,000 per QALY, a range normally considered cost effective in European countries.

1 Including additional information from a larger adalimumab trial in a pooled analysis
<table>
<thead>
<tr>
<th><strong>Author</strong></th>
<th>Kobelt G, Lindgren P, Singh A, Klareskog L&lt;sup&gt;164&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
<td>2005</td>
</tr>
<tr>
<td><strong>Type of economic evaluation</strong></td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td><strong>Country of origin</strong></td>
<td>Sweden, France, USA</td>
</tr>
<tr>
<td><strong>Currency used</strong></td>
<td>Euros (€)</td>
</tr>
<tr>
<td><strong>Years to which costs apply</strong></td>
<td>2004</td>
</tr>
<tr>
<td><strong>Perspective</strong></td>
<td>Societal</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Patients with active rheumatoid arthritis (RA), who failed to respond to at least two disease modifying antirheumatic drugs (DMARDs), other than methotrexate (MTX). Patients who had been previously exposed to MTX were included provided they were deemed to be appropriate candidates for MTX treatment at the time of enrolment to the study.</td>
</tr>
<tr>
<td><strong>Intervention 1</strong></td>
<td>Etanercept</td>
</tr>
<tr>
<td><strong>Intervention 2</strong></td>
<td>MTX</td>
</tr>
<tr>
<td><strong>Intervention 3</strong></td>
<td>Etanercept &amp; MTX</td>
</tr>
<tr>
<td><strong>Source of effectiveness data</strong></td>
<td>A double blind randomised clinical trial of 682 patients (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes TEMPO). Disease progression is based on observed transitions in the clinical trial for patients with a Health Assessment Questionnaire (HAQ) measurement used at both the start and the end of each year for the first 2 years. Transition probabilities for the model beyond the trial data are based on the average reported annual progression of HAQ (0.03). Disease activity and severity has been measured, in the TEMPO trial, by correlating the patient global visual analogue scale (global VAS) with the DAS28. As a result, it was found that a DAS28 of 3.2 corresponds to a score of 41 on the global VAS</td>
</tr>
<tr>
<td><strong>Cost data handled appropriately</strong></td>
<td>Yes – direct resource utilisation included all health care and community services as well as investments, devices, transportation, and informal help. Indirect costs included early retirement due to RA, long and short term sick leave, loss of leisure time. Costs and benefits were discounted at 3%. Cost data came from a survey of 616 Swedish patients, related to function and disease activity, plus 1810 patients early retirement data.</td>
</tr>
<tr>
<td><strong>Modelling summary</strong></td>
<td>A Markov model was developed with five main functional states and cut off points at HAQ 0.6, 1.1, 1.6, 2.1. Each state is further separated into two substrates representing high and low disease activity. All resulting 10 states</td>
</tr>
</tbody>
</table>
are further sub-divided according to those receiving study treatments or not. Changes in disease status are modelled as transitions between the states at intervals of 1 year (cycles). Costs and utility are assigned to each of the 20 states and the model estimates expected costs and QALYs for defined cohorts of patients over given periods of time. A Monte Carol simulation was run and bootstrapping was used to estimate uncertainty around input values. Model run for 10 years of treatment, or for treatment in trial only for 2 years and extrapolation to 10 years.

<p>| Outcome measures used in economic evaluations | Data related to function and disease activity (EQ-5D) obtained from a survey of 1016 patients with confirmed RA, carried out in 1997, and a more recent follow-up survey, conducted in 2002, of 616 patients. EQ-5D was related to HAQ scores and disease activity using multiple regression. |
| Direction of result with appropriate quadrant location | North-east quadrant Treatment for 2 years, extrapolation to 10 years: Etanercept alone dominated. Etanercept/methotrexate vs methotrexate €37331 per QALY. Treatment for 2 years, extrapolation to 5 years: Etanercept alone dominated. Etanercept/methotrexate vs methotrexate €54548 per QALY. Treatment for 10 years: Etanercept/methotrexate vs methotrexate €46494 per QALY. Treatment for 5 years, extrapolation to 10 years. Etanercept/methotrexate vs methotrexate €47316 per QALY. |
| Statistical analysis for patient-level stochastic data | Not undertaken |
| Appropriateness of statistical analysis | Not applicable |
| Uncertainty around cost-effectiveness expressed | Yes. |
| Appropriateness of method dealing with uncertainty around cost effectiveness | Yes – the methods used were appropriate. A Monte Carlo simulation was run and bootstrapping was used to estimate the uncertainty around the model parameter values. Cost effectiveness acceptability curves (CEAC) were also used. |
| Sensitivity analysis | Yes – sensitivity analyses was conducted and the results were found to be most sensitive to assumptions about the costs of treatment and the difference in utility between the treatment groups. |
| Modelling inputs &amp; techniques appropriate | Yes |</p>
<table>
<thead>
<tr>
<th>Author’s conclusions</th>
<th>Kobelt G, Lindgren P, Singh A, Klareskog L\textsuperscript{164}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporating the influence of disease activity allows better assessment of the effects of anti TNF treatment on patients’ general wellbeing. The cost per QALY gained with combination treatment with etanercept with methotrexate compared with methotrexate alone falls within the acceptable range and the probability that the cost effectiveness ratio is below a threshold of €50,000 is 88%.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 10 Sensitivity Analysis

Extensive sensitivity analysis has been carried out for two strategy sets: TNF inhibitors at the start, and TNF inhibitors in third place. As in the base case, for the HAQ improvement on starting a TNF inhibitor, the “early RA” values were used for the strategy set involving TNF inhibitors at the start, and both sets of values were used for single TNF inhibitors in third place. Unless otherwise stated, we ran the model for a sufficient number of replications to ensure sufficient precision in the results for major comparisons, but did not increase the number to allow for minor comparisons.

For the first set of sensitivity analysis, we have considered the assumption that HAQ increases at the same rate on all DMARDs. We have effectively removed HAQ increases while on TNF inhibitors by setting mean time between such increases to 4000 years. The results are shown in Table 78, Table 79 and Table 80.

Table 78 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>50010</td>
<td>163</td>
<td>10.4513</td>
<td>0.0312</td>
</tr>
<tr>
<td>Etan</td>
<td>63267</td>
<td>194</td>
<td>11.0386</td>
<td>0.0335</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49975</td>
<td>164</td>
<td>10.0744</td>
<td>0.0303</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63276</td>
<td>195</td>
<td>10.7012</td>
<td>0.0329</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>52146</td>
<td>168</td>
<td>9.9181</td>
<td>0.0303</td>
</tr>
<tr>
<td>Base</td>
<td>15494</td>
<td>33</td>
<td>9.4796</td>
<td>0.0286</td>
</tr>
</tbody>
</table>
### Comparison of TNF inhibitors in adults with RA

**Unit:** West Midlands Health Technology Assessment Collaboration

**Last amended:** 11 October 2005

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34516</td>
<td>160</td>
<td>0.9717</td>
<td>0.0293</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47773</td>
<td>189</td>
<td>1.5590</td>
<td>0.0308</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34480</td>
<td>162</td>
<td>0.5948</td>
<td>0.0288</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47782</td>
<td>191</td>
<td>1.2216</td>
<td>0.0309</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36652</td>
<td>166</td>
<td>0.4385</td>
<td>0.0287</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>36</td>
<td>222</td>
<td>0.3768</td>
<td>0.0299</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>9</td>
<td>259</td>
<td>-0.3374</td>
<td>0.0330</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13257</td>
<td>242</td>
<td>0.5873</td>
<td>0.0317</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13302</td>
<td>244</td>
<td>0.6268</td>
<td>0.0312</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2171</td>
<td>227</td>
<td>-0.1563</td>
<td>0.0294</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11130</td>
<td>245</td>
<td>0.7831</td>
<td>0.0312</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>35,500</td>
<td>33,500 – 37,800</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>30,600</td>
<td>29,500 – 31,900</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>58,000</td>
<td>52,800 – 64,200</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>39,100</td>
<td>37,200 – 41,200</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>83,600</td>
<td>73,900 – 96,200</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal more effective than Adal+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan more effective than Etan+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>22,600</td>
<td>20,300 – 25,500</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>21,200</td>
<td>19,200 – 23,700</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>14,200</td>
<td>13,000 – 15,600</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 79 TNF inhibitors in third place – early RA values (10,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48434</td>
<td>311</td>
<td>7.7130</td>
<td>0.0557</td>
</tr>
<tr>
<td>Etan</td>
<td>60513</td>
<td>373</td>
<td>8.4145</td>
<td>0.0612</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48582</td>
<td>313</td>
<td>7.8008</td>
<td>0.0558</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60773</td>
<td>370</td>
<td>8.5175</td>
<td>0.0605</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50828</td>
<td>324</td>
<td>7.9163</td>
<td>0.0563</td>
</tr>
<tr>
<td>Base</td>
<td>16527</td>
<td>72</td>
<td>6.5148</td>
<td>0.0495</td>
</tr>
</tbody>
</table>

Comparison

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31907</td>
<td>305</td>
<td>1.1982</td>
<td>0.0510</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43987</td>
<td>361</td>
<td>1.8997</td>
<td>0.0546</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32056</td>
<td>307</td>
<td>1.2859</td>
<td>0.0504</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44247</td>
<td>361</td>
<td>2.0027</td>
<td>0.0556</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34301</td>
<td>318</td>
<td>1.4014</td>
<td>0.0513</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>149</td>
<td>419</td>
<td>0.0877</td>
<td>0.0538</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>260</td>
<td>482</td>
<td>0.1030</td>
<td>0.0608</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12079</td>
<td>452</td>
<td>0.7015</td>
<td>0.0573</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12191</td>
<td>451</td>
<td>0.7167</td>
<td>0.0578</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2246</td>
<td>424</td>
<td>0.1155</td>
<td>0.0548</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9945</td>
<td>460</td>
<td>0.6012</td>
<td>0.0583</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>26,600</td>
<td>24,500 – 29,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>23,200</td>
<td>21,800 – 24,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>24,900</td>
<td>23,100 – 27,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>22,100</td>
<td>20,900 – 23,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>24,500</td>
<td>22,800 – 26,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>17,200</td>
<td>14,600 – 21,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>17,000</td>
<td>14,400 – 20,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>19,400</td>
<td>9,620 – Dominated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>16,500</td>
<td>13,600 – 21,100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 80 TNF inhibitors in third place – late RA values (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47957</td>
<td>156</td>
<td>7.1140</td>
<td>0.0276</td>
</tr>
<tr>
<td>Etan</td>
<td>59974</td>
<td>186</td>
<td>7.9947</td>
<td>0.0301</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48359</td>
<td>156</td>
<td>7.3452</td>
<td>0.0276</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60143</td>
<td>186</td>
<td>7.9866</td>
<td>0.0303</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49938</td>
<td>159</td>
<td>7.1057</td>
<td>0.0276</td>
</tr>
<tr>
<td>Base</td>
<td>16534</td>
<td>36</td>
<td>6.5575</td>
<td>0.0249</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>31423</td>
<td>152</td>
<td>0.5565</td>
<td>0.0241</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43440</td>
<td>180</td>
<td>1.4372</td>
<td>0.0264</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31825</td>
<td>152</td>
<td>0.7877</td>
<td>0.0244</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43608</td>
<td>180</td>
<td>1.4291</td>
<td>0.0269</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33404</td>
<td>155</td>
<td>0.5482</td>
<td>0.0243</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>402</td>
<td>207</td>
<td>0.2312</td>
<td>0.0251</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>168</td>
<td>241</td>
<td>-0.0081</td>
<td>0.0291</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12017</td>
<td>226</td>
<td>0.8807</td>
<td>0.0269</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11784</td>
<td>225</td>
<td>0.6414</td>
<td>0.0273</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1579</td>
<td>208</td>
<td>-0.2395</td>
<td>0.0250</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10205</td>
<td>227</td>
<td>0.8809</td>
<td>0.0274</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>56,500</td>
<td>51,900</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>30,200</td>
<td>29,100</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>40,400</td>
<td>38,000</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>30,500</td>
<td>29,400</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>60,900</td>
<td>55,900</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal; Diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13,600</td>
<td>12,700</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>18,400</td>
<td>16,800</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11,600</td>
<td>10,800</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

For the next sensitivity analysis, we applied the same principle (mean time to HAQ increase 4000 years) to all DMARDs. The results are shown in Table 81, Table 82 and Table 83.
Table 81 TNF inhibitors at the start (1,000,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49989</td>
<td>33</td>
<td>12.0586</td>
<td>0.0075</td>
</tr>
<tr>
<td>Etan</td>
<td>63506</td>
<td>39</td>
<td>12.3130</td>
<td>0.0077</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>50100</td>
<td>33</td>
<td>11.4872</td>
<td>0.0071</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63750</td>
<td>39</td>
<td>11.8605</td>
<td>0.0074</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51854</td>
<td>33</td>
<td>11.3239</td>
<td>0.0071</td>
</tr>
<tr>
<td>Base</td>
<td>15649</td>
<td>7</td>
<td>11.8238</td>
<td>0.0074</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34340</td>
<td>32</td>
<td>0.2348</td>
<td>0.0069</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47857</td>
<td>38</td>
<td>0.4892</td>
<td>0.0070</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34451</td>
<td>32</td>
<td>-0.3367</td>
<td>0.0067</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>48101</td>
<td>38</td>
<td>0.0367</td>
<td>0.0069</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36206</td>
<td>33</td>
<td>-0.4999</td>
<td>0.0067</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>111</td>
<td>44</td>
<td>-0.5715</td>
<td>0.0067</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>244</td>
<td>52</td>
<td>-0.4525</td>
<td>0.0070</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13517</td>
<td>48</td>
<td>0.2544</td>
<td>0.0070</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13650</td>
<td>49</td>
<td>0.3734</td>
<td>0.0067</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1754</td>
<td>45</td>
<td>-0.1633</td>
<td>0.0065</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11895</td>
<td>49</td>
<td>0.5366</td>
<td>0.0067</td>
</tr>
</tbody>
</table>
### Table 82 TNF inhibitors in third place (early RA data) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48924</td>
<td>157</td>
<td>9.5376</td>
<td>0.0327</td>
</tr>
<tr>
<td>Etan</td>
<td>61048</td>
<td>188</td>
<td>10.0343</td>
<td>0.0342</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48788</td>
<td>157</td>
<td>9.6644</td>
<td>0.0329</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60796</td>
<td>187</td>
<td>10.0839</td>
<td>0.0343</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50868</td>
<td>160</td>
<td>9.6680</td>
<td>0.0328</td>
</tr>
<tr>
<td>Base</td>
<td>16822</td>
<td>37</td>
<td>8.8857</td>
<td>0.0315</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>32102</td>
<td>154</td>
<td>0.6519</td>
<td>0.0293</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44226</td>
<td>183</td>
<td>1.1486</td>
<td>0.0306</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31966</td>
<td>155</td>
<td>0.7787</td>
<td>0.0295</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43974</td>
<td>182</td>
<td>1.1982</td>
<td>0.0307</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34046</td>
<td>157</td>
<td>0.7824</td>
<td>0.0293</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>136</td>
<td>210</td>
<td>-0.1268</td>
<td>0.0300</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>252</td>
<td>243</td>
<td>-0.0496</td>
<td>0.0318</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12124</td>
<td>229</td>
<td>0.4967</td>
<td>0.0309</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12008</td>
<td>227</td>
<td>0.4194</td>
<td>0.0311</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2080</td>
<td>212</td>
<td>0.0036</td>
<td>0.0300</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9928</td>
<td>229</td>
<td>0.4158</td>
<td>0.0310</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>49,200</td>
<td>45,200 54,100</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>38,500</td>
<td>36,500 40,700</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>41,000</td>
<td>38,100 44,400</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>36,700</td>
<td>34,900 38,700</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>43,500</td>
<td>40,500 47,100</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>24,400</td>
<td>21,600 28,100</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>28,600</td>
<td>24,800 33,800</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Inf+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>23,900</td>
<td>20,700 28,300</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 83 TNF inhibitors in third place (late RA data) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48257</td>
<td>70</td>
<td>8.9428</td>
<td>0.0146</td>
</tr>
<tr>
<td>Etan</td>
<td>60184</td>
<td>83</td>
<td>9.5288</td>
<td>0.0151</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48581</td>
<td>70</td>
<td>9.1718</td>
<td>0.0146</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60325</td>
<td>84</td>
<td>9.5095</td>
<td>0.0151</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50288</td>
<td>71</td>
<td>8.9613</td>
<td>0.0146</td>
</tr>
<tr>
<td>Base</td>
<td>16800</td>
<td>16</td>
<td>8.8786</td>
<td>0.0141</td>
</tr>
</tbody>
</table>

Comparison

<table>
<thead>
<tr>
<th></th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31457</td>
<td>68</td>
<td>0.0643</td>
<td>0.0128</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43384</td>
<td>81</td>
<td>0.6503</td>
<td>0.0133</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31781</td>
<td>69</td>
<td>0.2932</td>
<td>0.0129</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43525</td>
<td>81</td>
<td>0.6310</td>
<td>0.0134</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33488</td>
<td>69</td>
<td>0.0828</td>
<td>0.0128</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>324</td>
<td>93</td>
<td>0.2289</td>
<td>0.0129</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>141</td>
<td>108</td>
<td>-0.0193</td>
<td>0.0137</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11928</td>
<td>101</td>
<td>0.5860</td>
<td>0.0133</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11744</td>
<td>101</td>
<td>0.3378</td>
<td>0.0135</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1707</td>
<td>94</td>
<td>-0.2104</td>
<td>0.0129</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10037</td>
<td>102</td>
<td>0.5482</td>
<td>0.0134</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>489,000</td>
<td>350,000 - 812,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>66,700</td>
<td>64,100 - 69,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>108,000</td>
<td>99,600 - 119,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>69,000</td>
<td>66,200 - 72,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>405,000</td>
<td>309,000 - 586,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1,420</td>
<td>895 - 3,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>20,400</td>
<td>19,400 - 21,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>34,800</td>
<td>32,100 - 37,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>18,300</td>
<td>17,400 - 19,300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mortality**

For the next set of sensitivity analysis, we considered the effect of HAQ on mortality. Compared to the base case of a mortality ratio of 1.33 per unit HAQ, we considered the possibility of no effect, and of a mortality ratio of 2.73 per unit HAQ, as reported by Sokka and colleagues\(^{193}\). The results are shown in Table 84 to Table 84.

**No effect of HAQ on mortality**

### Table 84 TNF inhibitors at the start (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>50976</td>
<td>103</td>
<td>10.1796</td>
<td>0.0189</td>
</tr>
<tr>
<td>Etan</td>
<td>64670</td>
<td>123</td>
<td>10.3258</td>
<td>0.0191</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>50943</td>
<td>104</td>
<td>9.6881</td>
<td>0.0180</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>64962</td>
<td>124</td>
<td>9.9331</td>
<td>0.0184</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>53012</td>
<td>106</td>
<td>9.5434</td>
<td>0.0180</td>
</tr>
<tr>
<td>Base</td>
<td>16122</td>
<td>21</td>
<td>9.8471</td>
<td>0.0184</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>34853</td>
<td>102</td>
<td>0.3326</td>
<td>0.0183</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>48548</td>
<td>121</td>
<td>0.4787</td>
<td>0.0186</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34820</td>
<td>103</td>
<td>-0.1590</td>
<td>0.0180</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>48840</td>
<td>122</td>
<td>0.0861</td>
<td>0.0184</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36890</td>
<td>105</td>
<td>-0.3037</td>
<td>0.0178</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>33</td>
<td>142</td>
<td>0.4915</td>
<td>0.0181</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>292</td>
<td>165</td>
<td>-0.3927</td>
<td>0.0187</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13695</td>
<td>154</td>
<td>0.1462</td>
<td>0.0187</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>14020</td>
<td>156</td>
<td>0.2451</td>
<td>0.0181</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2069</td>
<td>144</td>
<td>-0.1447</td>
<td>0.0175</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11950</td>
<td>156</td>
<td>0.3897</td>
<td>0.0180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>105,000</td>
<td>94,400 118,000</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>101,000</td>
<td>94,100 110,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>567,000</td>
<td>398,000 990,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>93,700</td>
<td>74,500 126,000</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>57,200</td>
<td>49,800 67,200</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>30,700</td>
<td>28,000 33,900</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 85 TNF inhibitors in third place (early RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49705</td>
<td>159</td>
<td>7.4034</td>
<td>0.0266</td>
</tr>
<tr>
<td>Etan</td>
<td>61944</td>
<td>187</td>
<td>7.7953</td>
<td>0.0274</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49726</td>
<td>158</td>
<td>7.5188</td>
<td>0.0267</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62090</td>
<td>189</td>
<td>7.8556</td>
<td>0.0276</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51737</td>
<td>161</td>
<td>7.5071</td>
<td>0.0265</td>
</tr>
<tr>
<td>Base</td>
<td>17246</td>
<td>37</td>
<td>6.7843</td>
<td>0.0259</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>32460</td>
<td>156</td>
<td>0.6192</td>
<td>0.0247</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44698</td>
<td>183</td>
<td>1.0111</td>
<td>0.0256</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32480</td>
<td>155</td>
<td>0.7346</td>
<td>0.0248</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44845</td>
<td>184</td>
<td>1.0714</td>
<td>0.0258</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34492</td>
<td>158</td>
<td>0.7229</td>
<td>0.0246</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>21</td>
<td>212</td>
<td>0.1154</td>
<td>0.0255</td>
</tr>
<tr>
<td>Et+M – Étan</td>
<td>147</td>
<td>245</td>
<td>0.0603</td>
<td>0.0271</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12238</td>
<td>230</td>
<td>0.3919</td>
<td>0.0262</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12364</td>
<td>230</td>
<td>0.3368</td>
<td>0.0263</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2011</td>
<td>213</td>
<td>-0.0117</td>
<td>0.0254</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10353</td>
<td>233</td>
<td>0.3485</td>
<td>0.0264</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>52,400</td>
<td>48,500 - 57,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44,200</td>
<td>42,100 - 46,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>44,200</td>
<td>41,400 - 47,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>41,900</td>
<td>39,900 - 44,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>47,700</td>
<td>44,600 - 51,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>31,200</td>
<td>27,400 - 36,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>36,700</td>
<td>31,600 - 43,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>29,700</td>
<td>25,700 - 35,300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 86 TNF inhibitors in third place (late RA values) (1,000,000 patients*)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49710</td>
<td>32</td>
<td>6.7368</td>
<td>0.0053</td>
</tr>
<tr>
<td>Etan</td>
<td>61875</td>
<td>38</td>
<td>7.2691</td>
<td>0.0054</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49830</td>
<td>32</td>
<td>6.9818</td>
<td>0.0053</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>61968</td>
<td>38</td>
<td>7.2562</td>
<td>0.0054</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51711</td>
<td>32</td>
<td>6.7518</td>
<td>0.0053</td>
</tr>
<tr>
<td>Base</td>
<td>17271</td>
<td>7</td>
<td>6.7548</td>
<td>0.0052</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>32439</td>
<td>31</td>
<td>-0.0180</td>
<td>0.0048</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44604</td>
<td>37</td>
<td>0.5143</td>
<td>0.0050</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32559</td>
<td>31</td>
<td>0.2270</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44697</td>
<td>37</td>
<td>0.5014</td>
<td>0.0050</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34440</td>
<td>32</td>
<td>-0.0030</td>
<td>0.0048</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>120</td>
<td>42</td>
<td>0.2450</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>93</td>
<td>49</td>
<td>-0.0129</td>
<td>0.0052</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12165</td>
<td>46</td>
<td>0.5323</td>
<td>0.0050</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12138</td>
<td>46</td>
<td>0.2744</td>
<td>0.0051</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1881</td>
<td>43</td>
<td>-0.2300</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10257</td>
<td>46</td>
<td>0.5044</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>86,700</td>
<td>85,100 - 88,500</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>143,000</td>
<td>138,000 - 150,000</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>89,100</td>
<td>87,400 - 91,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Infl+MTX more costly than Base; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>490</td>
<td>287 - 1,670</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>22,900</td>
<td>22,400 - 23,300</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>44,200</td>
<td>42,600 - 46,000</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>20,300</td>
<td>19,900 - 20,800</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
* This simulation run was extended to 1,000,000 patients in the hope of obtaining a significant difference in QALY outcomes between the Infliximab option and the baseline option. Satisfactory precision in all other major comparisons was obtained with smaller numbers.
**Mortality Ratio 2.73 per unit HAQ**

Table 87 TNF inhibitors at the start (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>45701</td>
<td>98</td>
<td>8.5818</td>
<td>0.0181</td>
</tr>
<tr>
<td>Etan</td>
<td>57376</td>
<td>116</td>
<td>8.7290</td>
<td>0.0183</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>46340</td>
<td>100</td>
<td>8.2757</td>
<td>0.0169</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>57902</td>
<td>118</td>
<td>8.4855</td>
<td>0.0175</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>47718</td>
<td>101</td>
<td>8.0807</td>
<td>0.0170</td>
</tr>
<tr>
<td>Base</td>
<td>13620</td>
<td>21</td>
<td>8.3567</td>
<td>0.0173</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>32080</td>
<td>95</td>
<td>0.2251</td>
<td>0.0172</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43756</td>
<td>112</td>
<td>0.3723</td>
<td>0.0174</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32720</td>
<td>98</td>
<td>-0.0810</td>
<td>0.0166</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44282</td>
<td>114</td>
<td>0.1288</td>
<td>0.0171</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34098</td>
<td>98</td>
<td>-0.2760</td>
<td>0.0166</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>640</td>
<td>132</td>
<td>-0.3061</td>
<td>0.0169</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>526</td>
<td>151</td>
<td>-0.2435</td>
<td>0.0176</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11676</td>
<td>141</td>
<td>0.1472</td>
<td>0.0177</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11562</td>
<td>144</td>
<td>0.2098</td>
<td>0.0167</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1378</td>
<td>134</td>
<td>-0.1950</td>
<td>0.0162</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10184</td>
<td>145</td>
<td>0.4048</td>
<td>0.0167</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>143,000</td>
<td>124,000 168,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>118,000</td>
<td>107,000 130,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td></td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>344,000</td>
<td>272,000 468,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal alone dominates Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan alone dominates Etan+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>79,300</td>
<td>63,900 105,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>55,100</td>
<td>47,400 65,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>25,200</td>
<td>23,100 27,600</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

Table 88 TNF inhibitors in third place (early RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>44923</td>
<td>151</td>
<td>6.5889</td>
<td>0.0244</td>
</tr>
<tr>
<td>Etan</td>
<td>55324</td>
<td>177</td>
<td>6.9735</td>
<td>0.0254</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>45091</td>
<td>150</td>
<td>6.7247</td>
<td>0.0243</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>55583</td>
<td>178</td>
<td>7.0934</td>
<td>0.0255</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>47200</td>
<td>155</td>
<td>6.7366</td>
<td>0.0245</td>
</tr>
<tr>
<td>Base</td>
<td>14749</td>
<td>35</td>
<td>6.0374</td>
<td>0.0233</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>30174</td>
<td>147</td>
<td>0.5516</td>
<td>0.0235</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>40574</td>
<td>171</td>
<td>0.9362</td>
<td>0.0241</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>30341</td>
<td>146</td>
<td>0.6874</td>
<td>0.0233</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>40834</td>
<td>171</td>
<td>1.0561</td>
<td>0.0244</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32451</td>
<td>150</td>
<td>0.6993</td>
<td>0.0234</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>168</td>
<td>198</td>
<td>0.1358</td>
<td>0.0241</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>260</td>
<td>226</td>
<td>0.1199</td>
<td>0.0258</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>10401</td>
<td>212</td>
<td>0.3846</td>
<td>0.0249</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>10493</td>
<td>214</td>
<td>0.3687</td>
<td>0.0250</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2110</td>
<td>200</td>
<td>0.0119</td>
<td>0.0240</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>8383</td>
<td>216</td>
<td>0.3568</td>
<td>0.0251</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>54,700</td>
<td>50,400 – 59,800</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43,300</td>
<td>41,200 – 45,700</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>44,100</td>
<td>41,300 – 47,400</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>38,700</td>
<td>36,900 – 40,600</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>46,400</td>
<td>43,500 – 49,800</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>27,000</td>
<td>23,800 – 31,300</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>28,500</td>
<td>24,900 – 33,100</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>23,500</td>
<td>20,400 – 27,600</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 89 TNF inhibitors in third place (late RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>42280</td>
<td>92</td>
<td>5.8368</td>
<td>0.0155</td>
</tr>
<tr>
<td>Etan</td>
<td>53512</td>
<td>111</td>
<td>6.4045</td>
<td>0.0159</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>43349</td>
<td>93</td>
<td>6.1226</td>
<td>0.0153</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>53344</td>
<td>111</td>
<td>6.4004</td>
<td>0.0160</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>44265</td>
<td>94</td>
<td>5.8897</td>
<td>0.0156</td>
</tr>
<tr>
<td>Base</td>
<td>14771</td>
<td>22</td>
<td>6.0458</td>
<td>0.0148</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>27508</td>
<td>89</td>
<td>-0.2090</td>
<td>0.0143</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>38741</td>
<td>106</td>
<td>0.3586</td>
<td>0.0149</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>28577</td>
<td>90</td>
<td>0.0767</td>
<td>0.0144</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>38573</td>
<td>107</td>
<td>0.3545</td>
<td>0.0151</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>29493</td>
<td>91</td>
<td>-0.1562</td>
<td>0.0144</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1069</td>
<td>119</td>
<td>0.2858</td>
<td>0.0145</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>168</td>
<td>139</td>
<td>0.0041</td>
<td>0.0157</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11232</td>
<td>129</td>
<td>0.5677</td>
<td>0.0151</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>9996</td>
<td>131</td>
<td>0.2778</td>
<td>0.0153</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>916</td>
<td>120</td>
<td>-0.2329</td>
<td>0.0146</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9080</td>
<td>130</td>
<td>0.5107</td>
<td>0.0153</td>
</tr>
</tbody>
</table>
Comparisons:

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>108,000</td>
<td>99,700 - 118,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>372,000</td>
<td>271,000 - 595,000</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>109,000</td>
<td>100,000 - 119,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>3,740</td>
<td>3,010 - 4,950</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>19,800</td>
<td>18,700 - 21,000</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>36,000</td>
<td>32,300 - 40,600</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>17,800</td>
<td>16,700 - 19,000</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

**Effectiveness of conventional DMARDs**

For this sensitivity analysis, we considered varying the effectiveness of conventional DMARDs. This was done by reducing or increasing the $a$ parameter for HAQ multiplier by 50%, keeping the value of $a+b$ fixed. For example, for leflunomide we have $a = 0.57$, $b = 0.65$. This was changed to $a = 0.285$, $b = 0.935$ in the first set, and to $a = 0.855$, $b = 0.365$ in the second set.

**Reduced effectiveness of conventional DMARDs**

**Table 90 TNF inhibitors at the start (40,000 patients)**
<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49117</td>
<td>160</td>
<td>8.281</td>
<td>0.0274</td>
</tr>
<tr>
<td>Etan</td>
<td>62395</td>
<td>192</td>
<td>8.717</td>
<td>0.0280</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49498</td>
<td>163</td>
<td>8.256</td>
<td>0.0267</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62714</td>
<td>193</td>
<td>8.628</td>
<td>0.0277</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51370</td>
<td>167</td>
<td>8.082</td>
<td>0.0267</td>
</tr>
<tr>
<td>Base</td>
<td>15137</td>
<td>34</td>
<td>7.665</td>
<td>0.0270</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td><strong>Diff. Cost (£)</strong></td>
<td><strong>Q.S.E.</strong></td>
<td><strong>Diff. QALY</strong></td>
<td><strong>Q.S.E.</strong></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>33981</td>
<td>157</td>
<td>0.616</td>
<td>0.0247</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47259</td>
<td>187</td>
<td>1.052</td>
<td>0.0258</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34361</td>
<td>160</td>
<td>0.591</td>
<td>0.0242</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47577</td>
<td>188</td>
<td>0.963</td>
<td>0.0255</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36233</td>
<td>164</td>
<td>0.417</td>
<td>0.0241</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>381</td>
<td>219</td>
<td>-0.0249</td>
<td>0.0251</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>318</td>
<td>254</td>
<td>-0.0890</td>
<td>0.0260</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13278</td>
<td>237</td>
<td>0.4360</td>
<td>0.0263</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13216</td>
<td>240</td>
<td>0.3720</td>
<td>0.0257</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1872</td>
<td>225</td>
<td>-0.1734</td>
<td>0.0245</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11344</td>
<td>242</td>
<td>0.5454</td>
<td>0.0256</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>55,200</td>
<td>51,000 - 60,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44,900</td>
<td>42,800 - 47,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>58,100</td>
<td>53,700 - 63,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>49,400</td>
<td>46,900 - 52,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>86,800</td>
<td>77,800 - 98,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>30,500</td>
<td>27,100 - 34,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>35,500</td>
<td>31,100 - 41,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>20,800</td>
<td>18,900 - 23,200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

---

Table 91 TNF inhibitors in third place (early RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48489</td>
<td>156</td>
<td>6.4102</td>
<td>0.0247</td>
</tr>
<tr>
<td>Etan</td>
<td>60247</td>
<td>184</td>
<td>6.9485</td>
<td>0.0258</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48739</td>
<td>157</td>
<td>6.5615</td>
<td>0.0246</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60362</td>
<td>185</td>
<td>7.0337</td>
<td>0.0258</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50643</td>
<td>159</td>
<td>6.5449</td>
<td>0.0245</td>
</tr>
<tr>
<td>Base</td>
<td>16479</td>
<td>36</td>
<td>5.5733</td>
<td>0.0240</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>32011</td>
<td>153</td>
<td>0.8369</td>
<td>0.0214</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43768</td>
<td>179</td>
<td>1.3751</td>
<td>0.0231</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32261</td>
<td>154</td>
<td>0.9882</td>
<td>0.0214</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>43883</td>
<td>180</td>
<td>1.4604</td>
<td>0.0231</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34164</td>
<td>156</td>
<td>0.9716</td>
<td>0.0213</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>250</td>
<td>209</td>
<td>0.1513</td>
<td>0.0229</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>115</td>
<td>242</td>
<td>0.0853</td>
<td>0.0256</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11758</td>
<td>226</td>
<td>0.5383</td>
<td>0.0242</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11623</td>
<td>227</td>
<td>0.4722</td>
<td>0.0243</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1903</td>
<td>211</td>
<td>-0.0166</td>
<td>0.0227</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9719</td>
<td>229</td>
<td>0.4888</td>
<td>0.0242</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>38,300</td>
<td>36,400 – 40,400</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>31,800</td>
<td>30,800 – 33,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32,600</td>
<td>31,300 – 34,200</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>11623</td>
<td>227</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1903</td>
<td>211</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9719</td>
<td>229</td>
</tr>
</tbody>
</table>

Adal+MTX more effective than Adal alone; diff cost not significant
Etan+MTX more effective than Etan alone; diff cost not significant
Infl+MTX more costly than Adal+MTX; diff QALY not significant

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 92 TNF inhibitors in third place (late RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47573</td>
<td>154</td>
<td>5.7139</td>
<td>0.0245</td>
</tr>
<tr>
<td>Etan</td>
<td>59532</td>
<td>184</td>
<td>6.4338</td>
<td>0.0254</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47899</td>
<td>154</td>
<td>5.9958</td>
<td>0.0245</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59684</td>
<td>185</td>
<td>6.4139</td>
<td>0.0255</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49792</td>
<td>157</td>
<td>5.7812</td>
<td>0.0246</td>
</tr>
<tr>
<td>Base</td>
<td>16416</td>
<td>37</td>
<td>5.5470</td>
<td>0.0240</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31157</td>
<td>151</td>
<td>0.1669</td>
<td>0.0202</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43116</td>
<td>178</td>
<td>0.8869</td>
<td>0.0220</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31483</td>
<td>151</td>
<td>0.4488</td>
<td>0.0206</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43268</td>
<td>179</td>
<td>0.8669</td>
<td>0.0222</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33376</td>
<td>154</td>
<td>0.2342</td>
<td>0.0202</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>325</td>
<td>205</td>
<td>0.2819</td>
<td>0.0211</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>153</td>
<td>238</td>
<td>-0.0200</td>
<td>0.0240</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11958</td>
<td>222</td>
<td>0.7199</td>
<td>0.0224</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11786</td>
<td>224</td>
<td>0.4181</td>
<td>0.0227</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1894</td>
<td>207</td>
<td>-0.2146</td>
<td>0.0210</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9892</td>
<td>225</td>
<td>0.6327</td>
<td>0.0226</td>
</tr>
</tbody>
</table>
### Comparison ICER (£/QALY) Quasi confidence interval

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adal - Base</strong></td>
<td>187,000</td>
<td>150,000 – 246,000</td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>48,600</td>
<td>46,300 – 51,200</td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td>70,100</td>
<td>64,200 – 77,300</td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>49,900</td>
<td>47,400 – 52,600</td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td>143,000</td>
<td>122,000 – 172,000</td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td>Adal+MTX more effective than Adal; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td>Comparison is inconclusive</td>
<td></td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>16,600</td>
<td>15,500 – 17,900</td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>28,200</td>
<td>25,300 – 31,900</td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>15,600</td>
<td>14,400 – 17,100</td>
</tr>
</tbody>
</table>

**ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error**

### Increased effectiveness of conventional DMARDs

Table 93 TNF inhibitors at the start (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adal</strong></td>
<td>49627</td>
<td>227</td>
<td>11.0243</td>
<td>0.0451</td>
</tr>
<tr>
<td><strong>Etan</strong></td>
<td>62958</td>
<td>270</td>
<td>10.9756</td>
<td>0.0455</td>
</tr>
<tr>
<td><strong>Adal+MTX</strong></td>
<td>49579</td>
<td>229</td>
<td>10.2809</td>
<td>0.0414</td>
</tr>
<tr>
<td><strong>Etan+MTX</strong></td>
<td>63321</td>
<td>274</td>
<td>10.3392</td>
<td>0.0428</td>
</tr>
<tr>
<td><strong>Infl+MTX</strong></td>
<td>51738</td>
<td>234</td>
<td>10.1766</td>
<td>0.0419</td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td>15684</td>
<td>46</td>
<td>11.1251</td>
<td>0.0429</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>33944</td>
<td>223</td>
<td>-0.1008</td>
<td>0.0443</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47273</td>
<td>264</td>
<td>-0.1494</td>
<td>0.0449</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>33895</td>
<td>226</td>
<td>-0.8442</td>
<td>0.0432</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47637</td>
<td>268</td>
<td>-0.7858</td>
<td>0.0439</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36054</td>
<td>230</td>
<td>-0.9485</td>
<td>0.0433</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>50</td>
<td>308</td>
<td>0.7434</td>
<td>0.0435</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>364</td>
<td>358</td>
<td>-0.6364</td>
<td>0.0450</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13329</td>
<td>336</td>
<td>-0.0486</td>
<td>0.0454</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13742</td>
<td>342</td>
<td>0.0584</td>
<td>0.0422</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2159</td>
<td>317</td>
<td>-0.1043</td>
<td>0.0419</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11583</td>
<td>342</td>
<td>0.1626</td>
<td>0.0427</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>Base dominates etanercept</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>Base dominates Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone more effective than adal+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than etan+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>Etan more costly than Adal; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>Etan+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>71,200</td>
<td>46,600</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 94 TNF inhibitors in third place (early RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48455</td>
<td>155</td>
<td>7.8693</td>
<td>0.0272</td>
</tr>
<tr>
<td>Etan</td>
<td>59558</td>
<td>184</td>
<td>8.0946</td>
<td>0.0280</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48472</td>
<td>155</td>
<td>8.0080</td>
<td>0.0270</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60153</td>
<td>186</td>
<td>8.1824</td>
<td>0.0279</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50549</td>
<td>159</td>
<td>8.0049</td>
<td>0.0270</td>
</tr>
<tr>
<td>Base</td>
<td>16730</td>
<td>36</td>
<td>7.5540</td>
<td>0.0260</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31726</td>
<td>152</td>
<td>0.3153</td>
<td>0.0265</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42828</td>
<td>178</td>
<td>0.5405</td>
<td>0.0272</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31742</td>
<td>152</td>
<td>0.4539</td>
<td>0.0266</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43423</td>
<td>180</td>
<td>0.6283</td>
<td>0.0272</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33820</td>
<td>155</td>
<td>0.4509</td>
<td>0.0265</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>16</td>
<td>207</td>
<td>0.1386</td>
<td>0.0270</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>595</td>
<td>238</td>
<td>0.0878</td>
<td>0.0281</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11102</td>
<td>223</td>
<td>0.2253</td>
<td>0.0275</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11681</td>
<td>224</td>
<td>0.1744</td>
<td>0.0275</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2078</td>
<td>210</td>
<td>-0.0031</td>
<td>0.0269</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9604</td>
<td>225</td>
<td>0.1775</td>
<td>0.0274</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>101,000</td>
<td>86,100 121,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>79,200</td>
<td>72,000 88,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>69,900</td>
<td>62,600 79,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>69,100</td>
<td>63,600 75,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>75,000</td>
<td>67,100 85,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>6,780</td>
<td>3,350 Dominated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>49,300</td>
<td>39,500 65,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>67,000</td>
<td>50,800 98,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>54,100</td>
<td>41,200 78,600</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

### Table 95 TNF inhibitors in third place (late RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47597</td>
<td>69</td>
<td>7.2044</td>
<td>0.0121</td>
</tr>
<tr>
<td>Etan</td>
<td>59431</td>
<td>82</td>
<td>7.6188</td>
<td>0.0123</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48022</td>
<td>69</td>
<td>7.4753</td>
<td>0.0120</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59485</td>
<td>82</td>
<td>7.5971</td>
<td>0.0125</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49644</td>
<td>70</td>
<td>7.2394</td>
<td>0.0122</td>
</tr>
<tr>
<td>Base</td>
<td>16729</td>
<td>16</td>
<td>7.5342</td>
<td>0.0116</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>-------</td>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>30868</td>
<td>67</td>
<td>-0.3298</td>
<td>0.0117</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42702</td>
<td>80</td>
<td>0.0846</td>
<td>0.0120</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31292</td>
<td>68</td>
<td>-0.0589</td>
<td>0.0117</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42756</td>
<td>80</td>
<td>0.0629</td>
<td>0.0121</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32915</td>
<td>68</td>
<td>-0.2948</td>
<td>0.0118</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>425</td>
<td>91</td>
<td>0.2709</td>
<td>0.0117</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>54</td>
<td>106</td>
<td>-0.0217</td>
<td>0.0123</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11835</td>
<td>99</td>
<td>0.4144</td>
<td>0.0119</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11464</td>
<td>99</td>
<td>0.1218</td>
<td>0.0121</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1622</td>
<td>92</td>
<td>-0.2359</td>
<td>0.0118</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9841</td>
<td>100</td>
<td>0.3577</td>
<td>0.0121</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td></td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>505,000</td>
<td>394,000</td>
<td>704,000</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td></td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>680,000</td>
<td>491,000</td>
<td>1,100,000</td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1,570</td>
<td>1,090</td>
<td>2,790</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>58,600</td>
<td>26,900</td>
<td>30,400</td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>94,100</td>
<td>78,500</td>
<td>117,000</td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>27,500</td>
<td>25,700</td>
<td>29,600</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

**Survival times on conventional DMARDs**

For the next set of sensitivity analysis, we considered the survival times on conventional DMARDs. We increased and decreased average survival times by 50% compared to base case.
**Decreasing survival times on conventional DMARDs by 50%**

**Table 96 TNF inhibitors at the start (200,000 patients)**

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49941</td>
<td>72</td>
<td>9.2041</td>
<td>0.0126</td>
</tr>
<tr>
<td>Etan</td>
<td>63105</td>
<td>86</td>
<td>9.4889</td>
<td>0.0129</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49885</td>
<td>73</td>
<td>8.7396</td>
<td>0.0120</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63164</td>
<td>86</td>
<td>9.0703</td>
<td>0.0124</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51719</td>
<td>74</td>
<td>8.5969</td>
<td>0.0120</td>
</tr>
<tr>
<td>Base</td>
<td>15728</td>
<td>14</td>
<td>8.7630</td>
<td>0.0122</td>
</tr>
</tbody>
</table>

**Comparison**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34213</td>
<td>71</td>
<td>0.4411</td>
<td>0.0120</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47377</td>
<td>84</td>
<td>0.7259</td>
<td>0.0123</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34157</td>
<td>72</td>
<td>-0.0234</td>
<td>0.0115</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47436</td>
<td>84</td>
<td>0.3073</td>
<td>0.0120</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>35991</td>
<td>73</td>
<td>-0.1661</td>
<td>0.0115</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>56</td>
<td>98</td>
<td>0.4645</td>
<td>0.0118</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>60</td>
<td>114</td>
<td>-0.4186</td>
<td>0.0125</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13163</td>
<td>106</td>
<td>0.2848</td>
<td>0.0125</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13279</td>
<td>107</td>
<td>0.3307</td>
<td>0.0118</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1834</td>
<td>100</td>
<td>-0.1427</td>
<td>0.0113</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11445</td>
<td>108</td>
<td>0.4734</td>
<td>0.0118</td>
</tr>
</tbody>
</table>
### Comparison

<table>
<thead>
<tr>
<th></th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>77,600</td>
<td>73,600 – 82,000</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>65,300</td>
<td>63,100 – 67,600</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td></td>
<td>Base dominates Adal+MTX</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>154,000</td>
<td>143,000 – 167,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>46,200</td>
<td>42,400 – 50,800</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>40,200</td>
<td>37,400 – 43,300</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>24,200</td>
<td>23,000 – 25,500</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

### Table 97 TNF inhibitors in third place (early RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48807</td>
<td>223</td>
<td>6.9374</td>
<td>0.0355</td>
</tr>
<tr>
<td>Etan</td>
<td>60677</td>
<td>263</td>
<td>7.4174</td>
<td>0.0368</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48754</td>
<td>222</td>
<td>7.0436</td>
<td>0.0352</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60888</td>
<td>264</td>
<td>7.5064</td>
<td>0.0368</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50696</td>
<td>229</td>
<td>7.0136</td>
<td>0.0353</td>
</tr>
<tr>
<td>Base</td>
<td>16023</td>
<td>45</td>
<td>6.1308</td>
<td>0.0337</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>32784</td>
<td>220</td>
<td>0.8066</td>
<td>0.0309</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44654</td>
<td>266</td>
<td>1.2866</td>
<td>0.0333</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32731</td>
<td>219</td>
<td>0.9128</td>
<td>0.0311</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44865</td>
<td>258</td>
<td>1.3756</td>
<td>0.0331</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34673</td>
<td>225</td>
<td>0.8828</td>
<td>0.0312</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>53</td>
<td>298</td>
<td>-0.1062</td>
<td>0.0327</td>
</tr>
<tr>
<td>Et+M - Etan</td>
<td>211</td>
<td>346</td>
<td>0.0890</td>
<td>0.0366</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11870</td>
<td>323</td>
<td>0.4799</td>
<td>0.0345</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12134</td>
<td>323</td>
<td>0.4627</td>
<td>0.0346</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1941</td>
<td>301</td>
<td>-0.0300</td>
<td>0.0328</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10193</td>
<td>327</td>
<td>0.4928</td>
<td>0.0348</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>40,600</td>
<td>37,700 44,100</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>34,700</td>
<td>33,000 36,600</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>35,900</td>
<td>33,500 38,500</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>32,600</td>
<td>31,100 34,300</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>39,300</td>
<td>36,600 42,300</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>24,700</td>
<td>21,400 29,200</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>26,200</td>
<td>22,600 31,200</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>20,700</td>
<td>17,900 24,500</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 98 TNF inhibitors in third place (late RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47924</td>
<td>156</td>
<td>6.2769</td>
<td>0.0249</td>
</tr>
<tr>
<td>Etan</td>
<td>60026</td>
<td>185</td>
<td>6.9030</td>
<td>0.0257</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48021</td>
<td>155</td>
<td>6.5259</td>
<td>0.0248</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60179</td>
<td>185</td>
<td>6.9023</td>
<td>0.0259</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49890</td>
<td>159</td>
<td>6.2975</td>
<td>0.0249</td>
</tr>
<tr>
<td>Base</td>
<td>16031</td>
<td>32</td>
<td>6.1492</td>
<td>0.0240</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31893</td>
<td>153</td>
<td>0.1277</td>
<td>0.0211</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43995</td>
<td>181</td>
<td>0.7538</td>
<td>0.0223</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31990</td>
<td>153</td>
<td>0.3767</td>
<td>0.0211</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44148</td>
<td>181</td>
<td>0.7530</td>
<td>0.0226</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33859</td>
<td>156</td>
<td>0.1482</td>
<td>0.0211</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>98</td>
<td>207</td>
<td>0.2490</td>
<td>0.0217</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>153</td>
<td>240</td>
<td>-0.0008</td>
<td>0.0243</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12102</td>
<td>225</td>
<td>0.6261</td>
<td>0.0230</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12158</td>
<td>225</td>
<td>0.3763</td>
<td>0.0232</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1869</td>
<td>209</td>
<td>0.2285</td>
<td>0.0216</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10289</td>
<td>227</td>
<td>0.6048</td>
<td>0.0232</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>250,000</td>
<td>188,000 373,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>58,400</td>
<td>55,100 62,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>84,900</td>
<td>76,300 95,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>58,600</td>
<td>55,300 62,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>228,000</td>
<td>178,000 319,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>19,300</td>
<td>17,900 21,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>32,300</td>
<td>28,600 37,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>17,000</td>
<td>15,600 18,700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

*Increasing survival times on conventional DMARDs by 50%*

**Table 99 TNF inhibitors at the start (40,000 patients)**

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49395</td>
<td>32</td>
<td>9.9653</td>
<td>0.0060</td>
</tr>
<tr>
<td>Etan</td>
<td>62749</td>
<td>38</td>
<td>10.0852</td>
<td>0.0061</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49486</td>
<td>33</td>
<td>9.6172</td>
<td>0.0057</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62868</td>
<td>39</td>
<td>9.7841</td>
<td>0.0059</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51169</td>
<td>33</td>
<td>9.4568</td>
<td>0.0057</td>
</tr>
<tr>
<td>Base</td>
<td>15143</td>
<td>7</td>
<td>9.7590</td>
<td>0.0058</td>
</tr>
</tbody>
</table>

Last amended: 11 October 2005
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34252</td>
<td>32</td>
<td>0.2063</td>
<td>0.0058</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47607</td>
<td>37</td>
<td>0.3262</td>
<td>0.0059</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34344</td>
<td>32</td>
<td>-0.1418</td>
<td>0.0057</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47726</td>
<td>38</td>
<td>0.0251</td>
<td>0.0058</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36027</td>
<td>33</td>
<td>-0.3023</td>
<td>0.0057</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>92</td>
<td>44</td>
<td>-0.3481</td>
<td>0.0057</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>119</td>
<td>51</td>
<td>-0.3010</td>
<td>0.0059</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13355</td>
<td>47</td>
<td>0.1199</td>
<td>0.0059</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13382</td>
<td>48</td>
<td>0.1670</td>
<td>0.0057</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1683</td>
<td>45</td>
<td>-0.1604</td>
<td>0.0056</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11699</td>
<td>49</td>
<td>0.3274</td>
<td>0.0057</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>166,000</td>
<td>157,000 176,000</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>146,000</td>
<td>141,000 151,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>1,900,000</td>
<td>1,300,000 3,530,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone dominates Etan+MTX</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>111,000</td>
<td>101,000 124,000</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>80,200</td>
<td>75,000   86,100</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>35,700</td>
<td>34,500   37,100</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48088</td>
<td>155</td>
<td>7.3082</td>
<td>118</td>
<td>206</td>
<td>0.1719</td>
<td>0.0258</td>
</tr>
<tr>
<td>Etan</td>
<td>59855</td>
<td>184</td>
<td>7.6288</td>
<td>87</td>
<td>238</td>
<td>-0.0986</td>
<td>0.0272</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48206</td>
<td>155</td>
<td>7.4800</td>
<td>11767</td>
<td>223</td>
<td>0.3206</td>
<td>0.0266</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59768</td>
<td>185</td>
<td>7.7273</td>
<td>11562</td>
<td>223</td>
<td>0.2473</td>
<td>0.0265</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50352</td>
<td>159</td>
<td>7.4214</td>
<td>2145</td>
<td>208</td>
<td>0.0586</td>
<td>0.0258</td>
</tr>
<tr>
<td>Base</td>
<td>16584</td>
<td>38</td>
<td>6.8317</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>31505</td>
<td>151</td>
<td>0.4765</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43271</td>
<td>178</td>
<td>0.7971</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31623</td>
<td>151</td>
<td>0.6484</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43184</td>
<td>178</td>
<td>0.8957</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33768</td>
<td>155</td>
<td>0.5897</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>66,100</td>
<td>59,700 - 74,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>54,300</td>
<td>50,900 - 58,100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>48,800</td>
<td>45,200 - 52,900</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>48,200</td>
<td>45,500 - 51,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>57,300</td>
<td>52,700 - 62,700</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>36,700</td>
<td>31,400 - 44,200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>46,700</td>
<td>38,400 - 59,800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>30,800</td>
<td>26,100 - 37,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 101 TNF inhibitors in third place (late RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47696</td>
<td>97</td>
<td>6.6997</td>
<td>0.0167</td>
</tr>
<tr>
<td>Etan</td>
<td>59341</td>
<td>116</td>
<td>7.1776</td>
<td>0.0171</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47947</td>
<td>98</td>
<td>6.9649</td>
<td>0.0167</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59423</td>
<td>116</td>
<td>7.1773</td>
<td>0.0172</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49541</td>
<td>99</td>
<td>6.7117</td>
<td>0.0168</td>
</tr>
<tr>
<td>Base</td>
<td>16589</td>
<td>24</td>
<td>6.8844</td>
<td>0.0163</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31107</td>
<td>95</td>
<td>-0.1847</td>
<td>0.0158</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42752</td>
<td>112</td>
<td>0.2932</td>
<td>0.0162</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31359</td>
<td>95</td>
<td>0.0805</td>
<td>0.0158</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42835</td>
<td>112</td>
<td>0.2929</td>
<td>0.0164</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32952</td>
<td>97</td>
<td>-0.1727</td>
<td>0.0158</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>252</td>
<td>129</td>
<td>0.2652</td>
<td>0.0157</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>83</td>
<td>150</td>
<td>-0.0003</td>
<td>0.0166</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11645</td>
<td>140</td>
<td>0.4779</td>
<td>0.0161</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11476</td>
<td>140</td>
<td>0.2124</td>
<td>0.0163</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1593</td>
<td>130</td>
<td>-0.2532</td>
<td>0.0158</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9883</td>
<td>141</td>
<td>0.4656</td>
<td>0.0163</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>146,000</td>
<td>131,000 - 164,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>390,000</td>
<td>280,000 - 641,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>146,000</td>
<td>132,000 - 165,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>24,400</td>
<td>22,700 - 26,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>54,000</td>
<td>46,800 - 63,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>21,200</td>
<td>19,700 - 23,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

**Survival times on TNF inhibitors**

For the next set of sensitivity analysis, we have considered the survival times on TNF inhibitors. We increased and decreased average survival times by 50% compared to base case.
### Decreasing survival times for TNF inhibitors by 50%

**Table 102 TNF inhibitors at the start (100,000 patients)**

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>39019</td>
<td>76</td>
<td>9.6305</td>
<td>0.0183</td>
</tr>
<tr>
<td>Etan</td>
<td>50542</td>
<td>100</td>
<td>9.8065</td>
<td>0.0186</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>38868</td>
<td>77</td>
<td>9.0372</td>
<td>0.0172</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>50753</td>
<td>102</td>
<td>9.2591</td>
<td>0.0177</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>40577</td>
<td>79</td>
<td>8.9339</td>
<td>0.0174</td>
</tr>
<tr>
<td>Base</td>
<td>15432</td>
<td>21</td>
<td>9.4242</td>
<td>0.0180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>23588</td>
<td>75</td>
<td>0.2063</td>
<td>0.0178</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>35110</td>
<td>99</td>
<td>0.3823</td>
<td>0.0180</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>23436</td>
<td>77</td>
<td>-0.3870</td>
<td>0.0173</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>35321</td>
<td>100</td>
<td>-0.1651</td>
<td>0.0175</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>25145</td>
<td>78</td>
<td>-0.4903</td>
<td>0.0173</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>151</td>
<td>105</td>
<td>0.5933</td>
<td>0.0173</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>211</td>
<td>137</td>
<td>-0.5474</td>
<td>0.0178</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11523</td>
<td>121</td>
<td>0.1760</td>
<td>0.0180</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11885</td>
<td>123</td>
<td>0.2219</td>
<td>0.0170</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1709</td>
<td>106</td>
<td>-0.1033</td>
<td>0.0167</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10176</td>
<td>124</td>
<td>0.3252</td>
<td>0.0169</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>114,000</td>
<td>97,500 - 138,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>91,800</td>
<td>83,900 - 101,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td></td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td></td>
<td>Base dominates Etan+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>65,500</td>
<td>54,300 - 82,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>53,600</td>
<td>46,400 - 63,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>31,300</td>
<td>28,300 - 35,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 103 TNF inhibitors in third place (early RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>39019</td>
<td>76</td>
<td>9.6305</td>
<td>0.0183</td>
</tr>
<tr>
<td>Etan</td>
<td>50542</td>
<td>100</td>
<td>9.8065</td>
<td>0.0186</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>38868</td>
<td>77</td>
<td>9.0372</td>
<td>0.0172</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>50753</td>
<td>102</td>
<td>9.2591</td>
<td>0.0177</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>40577</td>
<td>79</td>
<td>8.9339</td>
<td>0.0174</td>
</tr>
<tr>
<td>Base</td>
<td>15432</td>
<td>21</td>
<td>9.4242</td>
<td>0.0180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>23588</td>
<td>75</td>
<td>0.2063</td>
<td>0.0178</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>35110</td>
<td>99</td>
<td>0.3823</td>
<td>0.0180</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>23436</td>
<td>77</td>
<td>-0.3870</td>
<td>0.0173</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>35321</td>
<td>100</td>
<td>-0.1651</td>
<td>0.0175</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>25145</td>
<td>78</td>
<td>-0.4903</td>
<td>0.0173</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>151</td>
<td>105</td>
<td>0.5933</td>
<td>0.0173</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>211</td>
<td>137</td>
<td>-0.5474</td>
<td>0.0178</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11523</td>
<td>121</td>
<td>0.1760</td>
<td>0.0180</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11885</td>
<td>123</td>
<td>0.2219</td>
<td>0.0170</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1709</td>
<td>106</td>
<td>-0.1033</td>
<td>0.0167</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10176</td>
<td>124</td>
<td>0.3252</td>
<td>0.0169</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>114,000</td>
<td>97,500 - 138,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>91,800</td>
<td>83,900 - 101,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>Base dominates Etan+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>65,500</td>
<td>54,300 - 82,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>53,600</td>
<td>46,400 - 63,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>31,300</td>
<td>28,300 - 35,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 104 TNF inhibitors in third place (late RA values) (1,000,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>38445</td>
<td>52</td>
<td>6.5461</td>
<td>0.0114</td>
</tr>
<tr>
<td>Etan</td>
<td>49046</td>
<td>69</td>
<td>6.9537</td>
<td>0.0115</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>38593</td>
<td>52</td>
<td>6.7096</td>
<td>0.0113</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>48955</td>
<td>69</td>
<td>6.9328</td>
<td>0.0116</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>40184</td>
<td>53</td>
<td>6.5621</td>
<td>0.0114</td>
</tr>
<tr>
<td>Base</td>
<td>16572</td>
<td>16</td>
<td>6.5896</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>21877</td>
<td>51</td>
<td>-0.0435</td>
<td>0.0104</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>32474</td>
<td>67</td>
<td>0.3642</td>
<td>0.0106</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>22021</td>
<td>51</td>
<td>0.1201</td>
<td>0.0104</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>32384</td>
<td>67</td>
<td>0.3432</td>
<td>0.0107</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>23612</td>
<td>52</td>
<td>-0.0275</td>
<td>0.0104</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>144</td>
<td>69</td>
<td>0.1635</td>
<td>0.0104</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>90</td>
<td>91</td>
<td>0.0210</td>
<td>0.0109</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>10597</td>
<td>81</td>
<td>0.4077</td>
<td>0.0106</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>10362</td>
<td>81</td>
<td>0.2231</td>
<td>0.0107</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1591</td>
<td>70</td>
<td>-0.1475</td>
<td>0.0104</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>8772</td>
<td>81</td>
<td>0.3707</td>
<td>0.0107</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>89,200</td>
<td>84,200</td>
<td>94,700</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>183,000</td>
<td>156,000</td>
<td>222,000</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>94,400</td>
<td>88,800</td>
<td>101,000</td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>883</td>
<td>448</td>
<td>29,200</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>26,000</td>
<td>24,700</td>
<td>27,500</td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>46,400</td>
<td>42,300</td>
<td>51,400</td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>23,700</td>
<td>22,300</td>
<td>25,200</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

*Increase survival times for TNF inhibitors by 50%*
### Table 105 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>56623</td>
<td>37</td>
<td>9.7676</td>
<td>0.0059</td>
</tr>
<tr>
<td>Etan</td>
<td>69815</td>
<td>41</td>
<td>9.9351</td>
<td>0.0060</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>56872</td>
<td>37</td>
<td>9.4870</td>
<td>0.0056</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>70138</td>
<td>41</td>
<td>9.6955</td>
<td>0.0058</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>58740</td>
<td>38</td>
<td>9.2840</td>
<td>0.0057</td>
</tr>
<tr>
<td>Base</td>
<td>15439</td>
<td>7</td>
<td>9.4599</td>
<td>0.0057</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>41183</td>
<td>36</td>
<td>0.3077</td>
<td>0.0057</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>54375</td>
<td>40</td>
<td>0.4752</td>
<td>0.0058</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>41433</td>
<td>36</td>
<td>0.0271</td>
<td>0.0056</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>54698</td>
<td>40</td>
<td>0.2356</td>
<td>0.0057</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>43301</td>
<td>37</td>
<td>-0.1759</td>
<td>0.0056</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>249</td>
<td>49</td>
<td>-0.2806</td>
<td>0.0057</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>323</td>
<td>54</td>
<td>-0.2395</td>
<td>0.0059</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13192</td>
<td>51</td>
<td>0.1675</td>
<td>0.0059</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13266</td>
<td>52</td>
<td>0.2086</td>
<td>0.0057</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1868</td>
<td>50</td>
<td>-0.2030</td>
<td>0.0055</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11397</td>
<td>52</td>
<td>0.4116</td>
<td>0.0057</td>
</tr>
</tbody>
</table>
### Comparison of ICER (£/QALY) and Quasi confidence interval

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adal - Base</strong></td>
<td>134,000</td>
<td>129,000 - 139,000</td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>114,000</td>
<td>112,000 - 117,000</td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td>1,530,000</td>
<td>1,080,000 - 2,600,000</td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>232,000</td>
<td>221,000 - 244,000</td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td></td>
<td>Base dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td></td>
<td>Adal alone dominates Adal+MTX</td>
</tr>
<tr>
<td><strong>Et+M – Étan</strong></td>
<td></td>
<td>Étan alone dominates Étan+MTX</td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>78,800</td>
<td>73,600 - 84,800</td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>63,600</td>
<td>60,300 - 67,300</td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>27,700</td>
<td>26,900 - 28,500</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>54434</td>
<td>175</td>
<td>7.3279</td>
<td>0.0264</td>
</tr>
<tr>
<td>Etan</td>
<td>66017</td>
<td>197</td>
<td>7.6925</td>
<td>0.0273</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>54507</td>
<td>176</td>
<td>7.4592</td>
<td>0.0263</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>65659</td>
<td>198</td>
<td>7.7924</td>
<td>0.0275</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>57161</td>
<td>180</td>
<td>7.4456</td>
<td>0.0261</td>
</tr>
<tr>
<td>Base</td>
<td>16552</td>
<td>36</td>
<td>6.5641</td>
<td>0.0251</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>37882</td>
<td>170</td>
<td>0.7637</td>
<td>0.0246</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>49465</td>
<td>191</td>
<td>1.1284</td>
<td>0.0257</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>37955</td>
<td>171</td>
<td>0.8950</td>
<td>0.0247</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>49107</td>
<td>191</td>
<td>1.2282</td>
<td>0.0260</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>40609</td>
<td>176</td>
<td>0.8815</td>
<td>0.0245</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>73</td>
<td>231</td>
<td>0.1313</td>
<td>0.0256</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>358</td>
<td>250</td>
<td>-0.0998</td>
<td>0.0276</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11582</td>
<td>243</td>
<td>0.3646</td>
<td>0.0266</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11152</td>
<td>244</td>
<td>0.3332</td>
<td>0.0268</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2654</td>
<td>235</td>
<td>-0.0135</td>
<td>0.0255</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>8498</td>
<td>246</td>
<td>0.3467</td>
<td>0.0266</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>49,600</td>
<td>46,600 – 53,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43,800</td>
<td>41,900 – 46,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>42,400</td>
<td>40,200 – 44,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>40,000</td>
<td>38,300 – 41,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>46,100</td>
<td>43,600 – 48,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>31,800</td>
<td>27,600 – 37,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>33,500</td>
<td>28,700 – 40,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>24,500</td>
<td>21,100 – 29,300</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 107 TNF inhibitors in third place (late RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>53090</td>
<td>173</td>
<td>6.4433</td>
<td>0.0260</td>
</tr>
<tr>
<td>Etan</td>
<td>65299</td>
<td>197</td>
<td>7.0461</td>
<td>0.0267</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>53729</td>
<td>174</td>
<td>6.7250</td>
<td>0.0258</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>65315</td>
<td>197</td>
<td>7.0410</td>
<td>0.0269</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>55640</td>
<td>178</td>
<td>6.4481</td>
<td>0.0262</td>
</tr>
<tr>
<td>Base</td>
<td>16469</td>
<td>37</td>
<td>6.5205</td>
<td>0.0250</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>36621</td>
<td>168</td>
<td>-0.0772</td>
<td>0.0237</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>48830</td>
<td>189</td>
<td>0.5256</td>
<td>0.0248</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>37260</td>
<td>169</td>
<td>0.2045</td>
<td>0.0239</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>48846</td>
<td>190</td>
<td>0.5205</td>
<td>0.0251</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>39171</td>
<td>173</td>
<td>-0.0724</td>
<td>0.0239</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>639</td>
<td>227</td>
<td>0.2817</td>
<td>0.0239</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>16</td>
<td>248</td>
<td>-0.0051</td>
<td>0.0263</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12209</td>
<td>238</td>
<td>0.6028</td>
<td>0.0252</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11586</td>
<td>241</td>
<td>0.3160</td>
<td>0.0255</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1911</td>
<td>229</td>
<td>-0.2769</td>
<td>0.0242</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9675</td>
<td>243</td>
<td>0.5930</td>
<td>0.0255</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td></td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>92,900</td>
<td>84,900 103,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>182,000</td>
<td>148,000 238,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>93,800</td>
<td>85,600 104,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>2,270</td>
<td>1,310 8,380</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>20,300</td>
<td>18,500 22,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>36,700</td>
<td>31,400 44,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>16,300</td>
<td>14,800 18,100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

For the next set of sensitivity analysis, we considered the possibility of reviewing the effectiveness of TNF inhibitors at 12 weeks instead of 24 weeks. For this analysis, we left the proportions of early dropouts unchanged.
Table 108 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48484</td>
<td>73</td>
<td>9.7319</td>
<td>0.0131</td>
</tr>
<tr>
<td>Etan</td>
<td>62137</td>
<td>87</td>
<td>9.9057</td>
<td>0.0133</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48643</td>
<td>74</td>
<td>9.3104</td>
<td>0.0125</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62125</td>
<td>87</td>
<td>9.5409</td>
<td>0.0129</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50373</td>
<td>75</td>
<td>9.1442</td>
<td>0.0125</td>
</tr>
<tr>
<td>Base</td>
<td>15459</td>
<td>15</td>
<td>9.4681</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>33025</td>
<td>72</td>
<td>0.2638</td>
<td>0.0127</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44679</td>
<td>85</td>
<td>0.4376</td>
<td>0.0129</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>33184</td>
<td>72</td>
<td>-0.1577</td>
<td>0.0124</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>46666</td>
<td>85</td>
<td>0.0728</td>
<td>0.0126</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34914</td>
<td>74</td>
<td>-0.3239</td>
<td>0.0124</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>159</td>
<td>100</td>
<td>-0.4215</td>
<td>0.0126</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>13</td>
<td>115</td>
<td>0.3648</td>
<td>0.0129</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13654</td>
<td>108</td>
<td>0.1738</td>
<td>0.0130</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13482</td>
<td>109</td>
<td>0.2305</td>
<td>0.0125</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1730</td>
<td>101</td>
<td>-0.1662</td>
<td>0.0121</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11752</td>
<td>109</td>
<td>0.3967</td>
<td>0.0125</td>
</tr>
</tbody>
</table>
### Comparison ICER (£/QALY) Quasi confidence interval

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adal - Base</strong></td>
<td>125,000</td>
<td>114,000 139,000</td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>107,000</td>
<td>101,000 113,000</td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td></td>
<td>Base dominates Adal+MTX</td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>641,000</td>
<td>476,000 983,000</td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td></td>
<td>Base dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>78,600</td>
<td>68,300 92,500</td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>58,500</td>
<td>52,700 65,700</td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>29,600</td>
<td>27,800 31,700</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 109 TNF inhibitors in third place (early RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48484</td>
<td>73</td>
<td>9.7319</td>
<td>0.0131</td>
</tr>
<tr>
<td>Etan</td>
<td>62137</td>
<td>87</td>
<td>9.9057</td>
<td>0.0133</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48643</td>
<td>74</td>
<td>9.3104</td>
<td>0.0125</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62125</td>
<td>87</td>
<td>9.5409</td>
<td>0.0129</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50373</td>
<td>75</td>
<td>9.1442</td>
<td>0.0125</td>
</tr>
<tr>
<td>Base</td>
<td>15459</td>
<td>15</td>
<td>9.4681</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>33025</td>
<td>72</td>
<td>0.2638</td>
<td>0.0127</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44679</td>
<td>85</td>
<td>0.4376</td>
<td>0.0129</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>33184</td>
<td>72</td>
<td>-0.1577</td>
<td>0.0124</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>46666</td>
<td>85</td>
<td>0.0728</td>
<td>0.0126</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34914</td>
<td>74</td>
<td>-0.3239</td>
<td>0.0124</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>159</td>
<td>100</td>
<td>-0.4215</td>
<td>0.0126</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>13</td>
<td>115</td>
<td>0.3648</td>
<td>0.0129</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13654</td>
<td>108</td>
<td>0.1738</td>
<td>0.0130</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13482</td>
<td>109</td>
<td>0.2305</td>
<td>0.0125</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1730</td>
<td>101</td>
<td>-0.1662</td>
<td>0.0121</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11752</td>
<td>109</td>
<td>0.3967</td>
<td>0.0125</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adal - Base</strong></td>
<td>125,000</td>
<td>114,000 – 139,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>107,000</td>
<td>101,000 – 113,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>641,000</td>
<td>476,000 – 983,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td></td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Adal</strong></td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>29,600</td>
<td>27,800 – 31,700</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47290</td>
<td>156</td>
<td>7.0977</td>
<td>0.0258</td>
</tr>
<tr>
<td>Etan</td>
<td>59222</td>
<td>186</td>
<td>7.5276</td>
<td>0.0267</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47235</td>
<td>157</td>
<td>7.2221</td>
<td>0.0257</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59279</td>
<td>187</td>
<td>7.6075</td>
<td>0.0269</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49380</td>
<td>161</td>
<td>7.2645</td>
<td>0.0258</td>
</tr>
<tr>
<td>Base</td>
<td>16573</td>
<td>36</td>
<td>6.5886</td>
<td>0.0249</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>30717</td>
<td>153</td>
<td>0.5091</td>
<td>0.0240</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42649</td>
<td>181</td>
<td>0.9389</td>
<td>0.0253</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>30662</td>
<td>154</td>
<td>0.6335</td>
<td>0.0241</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42706</td>
<td>181</td>
<td>1.0188</td>
<td>0.0253</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32807</td>
<td>157</td>
<td>0.6579</td>
<td>0.0240</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>55</td>
<td>210</td>
<td>-0.1244</td>
<td>0.0249</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>56</td>
<td>242</td>
<td>-0.0799</td>
<td>0.0268</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11932</td>
<td>227</td>
<td>0.4299</td>
<td>0.0259</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12044</td>
<td>228</td>
<td>0.3854</td>
<td>0.0259</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2146</td>
<td>212</td>
<td>0.0244</td>
<td>0.0250</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9898</td>
<td>229</td>
<td>0.3609</td>
<td>0.0259</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>60,300</td>
<td>55,100 66,700</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>45,400</td>
<td>43,100 48,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>48,400</td>
<td>45,000 52,400</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>41,900</td>
<td>39,900 44,100</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>49,900</td>
<td>46,500 53,800</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>27,800</td>
<td>24,600 31,800</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>31,300</td>
<td>27,400 36,300</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>27,400</td>
<td>23,800 32,300</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 110 TNF inhibitors in third place (late RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>46766</td>
<td>98</td>
<td>6.4925</td>
<td>0.0162</td>
</tr>
<tr>
<td>Etan</td>
<td>58794</td>
<td>117</td>
<td>7.0370</td>
<td>0.0167</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>46767</td>
<td>98</td>
<td>6.7394</td>
<td>0.0162</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>58839</td>
<td>117</td>
<td>7.0174</td>
<td>0.0168</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>48613</td>
<td>100</td>
<td>6.5214</td>
<td>0.0163</td>
</tr>
<tr>
<td>Base</td>
<td>16566</td>
<td>23</td>
<td>6.5725</td>
<td>0.0158</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>30201</td>
<td>96</td>
<td>-0.0799</td>
<td>0.0148</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42229</td>
<td>113</td>
<td>0.4646</td>
<td>0.0155</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>30201</td>
<td>96</td>
<td>0.1669</td>
<td>0.0149</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42273</td>
<td>114</td>
<td>0.4449</td>
<td>0.0156</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32047</td>
<td>98</td>
<td>-0.0510</td>
<td>0.0149</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1</td>
<td>131</td>
<td>0.2469</td>
<td>0.0149</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>44</td>
<td>152</td>
<td>-0.0197</td>
<td>0.0162</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12028</td>
<td>142</td>
<td>0.5445</td>
<td>0.0155</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12072</td>
<td>142</td>
<td>0.2780</td>
<td>0.0157</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1846</td>
<td>132</td>
<td>-0.2180</td>
<td>0.0151</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10226</td>
<td>144</td>
<td>0.4960</td>
<td>0.0157</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>90,900</td>
<td>85,200 97,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>181,000</td>
<td>153,000 220,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>95,000</td>
<td>88,800 102,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>22,100</td>
<td>20,800 23,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>43,400</td>
<td>38,900 49,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>20,600</td>
<td>19,300 22,200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

For the next sensitivity analysis, we considered the rate of short-term quitters on TNF inhibitors. Again we considered a 50% decrease and 50% increase on base case.

*Decreasing short-term quitters on TNF inhibitors by 50%*

Table 111 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>50452</td>
<td>72</td>
<td>9.6942</td>
<td>0.0132</td>
</tr>
<tr>
<td>Etan</td>
<td>63383</td>
<td>85</td>
<td>9.8883</td>
<td>0.0134</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>50622</td>
<td>72</td>
<td>9.2897</td>
<td>0.0125</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63473</td>
<td>86</td>
<td>9.5124</td>
<td>0.0128</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>52466</td>
<td>74</td>
<td>9.1332</td>
<td>0.0125</td>
</tr>
<tr>
<td>Base</td>
<td>15414</td>
<td>15</td>
<td>9.4410</td>
<td>0.0128</td>
</tr>
<tr>
<td>Comparison</td>
<td>Diff. Cost (£)</td>
<td>Q.S.E.</td>
<td>Diff. QALY</td>
<td>Q.S.E.</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Adal - Base</td>
<td>35038</td>
<td>70</td>
<td>0.2532</td>
<td>0.0127</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47969</td>
<td>83</td>
<td>0.4473</td>
<td>0.0129</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>35208</td>
<td>71</td>
<td>-0.1513</td>
<td>0.0123</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>48059</td>
<td>84</td>
<td>0.0714</td>
<td>0.0126</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>37052</td>
<td>73</td>
<td>-0.3078</td>
<td>0.0123</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>170</td>
<td>98</td>
<td>-0.4045</td>
<td>0.0125</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>90</td>
<td>113</td>
<td>-0.3759</td>
<td>0.0129</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12931</td>
<td>106</td>
<td>0.1941</td>
<td>0.0130</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12851</td>
<td>107</td>
<td>0.2226</td>
<td>0.0124</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1844</td>
<td>99</td>
<td>-0.1565</td>
<td>0.0121</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11007</td>
<td>108</td>
<td>0.3792</td>
<td>0.0124</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>138,000</td>
<td>126,000-154,000</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>107,000</td>
<td>101,000-114,000</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>673,000</td>
<td>497,000-1,040,000</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>66,600</td>
<td>58,700-77,000</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>57,700</td>
<td>51,900-65,000</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>29,000</td>
<td>27,200-31,200</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 112 TNF inhibitors in third place (early RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49106</td>
<td>155</td>
<td>7.1188</td>
<td>0.0257</td>
</tr>
<tr>
<td>Etan</td>
<td>60523</td>
<td>184</td>
<td>7.5219</td>
<td>0.0269</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49417</td>
<td>155</td>
<td>7.2940</td>
<td>0.0258</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60786</td>
<td>185</td>
<td>7.6250</td>
<td>0.0268</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51626</td>
<td>159</td>
<td>7.2479</td>
<td>0.0257</td>
</tr>
<tr>
<td>Base</td>
<td>16581</td>
<td>36</td>
<td>6.5877</td>
<td>0.0250</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>32525</td>
<td>151</td>
<td>0.5311</td>
<td>0.0241</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43943</td>
<td>179</td>
<td>0.9342</td>
<td>0.0250</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32836</td>
<td>151</td>
<td>0.7062</td>
<td>0.0243</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>44205</td>
<td>179</td>
<td>1.0373</td>
<td>0.0252</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>35045</td>
<td>155</td>
<td>0.6602</td>
<td>0.0239</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>311</td>
<td>206</td>
<td>0.1752</td>
<td>0.0249</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>263</td>
<td>239</td>
<td>0.1031</td>
<td>0.0267</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11417</td>
<td>223</td>
<td>0.4031</td>
<td>0.0256</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11369</td>
<td>224</td>
<td>0.3311</td>
<td>0.0259</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2209</td>
<td>209</td>
<td>-0.0461</td>
<td>0.0249</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9160</td>
<td>225</td>
<td>0.3771</td>
<td>0.0256</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>61,200</td>
<td>56,100 67,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47,000</td>
<td>44,600 49,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>46,500</td>
<td>43,500 50,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42,600</td>
<td>40,600 44,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>53,100</td>
<td>49,500 57,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td></td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>28,300</td>
<td>25,000 32,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>34,300</td>
<td>29,600 40,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td></td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>24,300</td>
<td>21,200 28,400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 113 TNF inhibitors in third place (late RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48575</td>
<td>153</td>
<td>6.4850</td>
<td>0.0257</td>
</tr>
<tr>
<td>Etan</td>
<td>59988</td>
<td>183</td>
<td>7.0166</td>
<td>0.0264</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48792</td>
<td>154</td>
<td>6.7282</td>
<td>0.0256</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60202</td>
<td>185</td>
<td>6.9915</td>
<td>0.0266</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50721</td>
<td>157</td>
<td>6.4898</td>
<td>0.0257</td>
</tr>
<tr>
<td>Base</td>
<td>16582</td>
<td>36</td>
<td>6.5527</td>
<td>0.0248</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31993</td>
<td>150</td>
<td>-0.0676</td>
<td>0.0236</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43405</td>
<td>177</td>
<td>0.4640</td>
<td>0.0244</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32210</td>
<td>150</td>
<td>0.1755</td>
<td>0.0236</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43619</td>
<td>179</td>
<td>0.4388</td>
<td>0.0248</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34138</td>
<td>154</td>
<td>-0.0628</td>
<td>0.0234</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>217</td>
<td>203</td>
<td>0.2431</td>
<td>0.0237</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>214</td>
<td>237</td>
<td>-0.0252</td>
<td>0.0256</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11412</td>
<td>221</td>
<td>0.5316</td>
<td>0.0246</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11410</td>
<td>222</td>
<td>0.2633</td>
<td>0.0248</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1929</td>
<td>206</td>
<td>-0.2383</td>
<td>0.0237</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9481</td>
<td>224</td>
<td>0.5016</td>
<td>0.0248</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>93,500</td>
<td>84,600 105,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>184,000</td>
<td>145,000 251,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>99,400</td>
<td>89,300 112,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>21,500</td>
<td>19,500 23,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>43,300</td>
<td>36,300 53,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>18,900</td>
<td>17,000 21,200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Increasing short-term quitters on TNF inhibitors by 50%

Table 114 TNF inhibitors at the start (20,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48437</td>
<td>73</td>
<td>9.7377</td>
<td>0.0131</td>
</tr>
<tr>
<td>Etan</td>
<td>62259</td>
<td>86</td>
<td>9.8989</td>
<td>0.0133</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48694</td>
<td>73</td>
<td>9.3090</td>
<td>0.0125</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62435</td>
<td>87</td>
<td>9.5416</td>
<td>0.0128</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50400</td>
<td>74</td>
<td>9.1485</td>
<td>0.0125</td>
</tr>
<tr>
<td>Base</td>
<td>15416</td>
<td>15</td>
<td>9.4544</td>
<td>0.0128</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>33021</td>
<td>71</td>
<td>0.2834</td>
<td>0.0127</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>46843</td>
<td>84</td>
<td>0.4445</td>
<td>0.0129</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>33278</td>
<td>72</td>
<td>-0.1453</td>
<td>0.0124</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47019</td>
<td>85</td>
<td>0.0873</td>
<td>0.0127</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34984</td>
<td>73</td>
<td>-0.3058</td>
<td>0.0123</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>257</td>
<td>99</td>
<td>-0.4287</td>
<td>0.0125</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>176</td>
<td>115</td>
<td>-0.3573</td>
<td>0.0130</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13822</td>
<td>107</td>
<td>0.1611</td>
<td>0.0130</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13741</td>
<td>108</td>
<td>0.2326</td>
<td>0.0125</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1705</td>
<td>101</td>
<td>-0.1605</td>
<td>0.0121</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>12036</td>
<td>109</td>
<td>0.3931</td>
<td>0.0125</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>117,000</td>
<td>107,000 - 128,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>105,000</td>
<td>99,600 - 112,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>539,000</td>
<td>417,000 - 760,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal alone dominates Adal+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>85,800</td>
<td>73,900 - 102,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>59,100</td>
<td>53,300 - 66,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>30,600</td>
<td>28,700 - 32,800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 115 TNF inhibitors in third place (early RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47180</td>
<td>156</td>
<td>7.1552</td>
<td>0.0257</td>
</tr>
<tr>
<td>Etan</td>
<td>59491</td>
<td>185</td>
<td>7.5395</td>
<td>0.0268</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47416</td>
<td>156</td>
<td>7.2911</td>
<td>0.0257</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59836</td>
<td>185</td>
<td>7.6482</td>
<td>0.0268</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49356</td>
<td>159</td>
<td>7.2704</td>
<td>0.0256</td>
</tr>
<tr>
<td>Base</td>
<td>16599</td>
<td>36</td>
<td>6.5821</td>
<td>0.0249</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>30581</td>
<td>153</td>
<td>0.5727</td>
<td>0.0241</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42892</td>
<td>180</td>
<td>0.9571</td>
<td>0.0250</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>30817</td>
<td>153</td>
<td>0.7086</td>
<td>0.0241</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43238</td>
<td>180</td>
<td>1.0658</td>
<td>0.0250</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32757</td>
<td>156</td>
<td>0.6879</td>
<td>0.0238</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>236</td>
<td>209</td>
<td>0.1359</td>
<td>0.0249</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>346</td>
<td>240</td>
<td>0.1087</td>
<td>0.0265</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12311</td>
<td>227</td>
<td>0.3844</td>
<td>0.0257</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12420</td>
<td>226</td>
<td>0.3571</td>
<td>0.0258</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1939</td>
<td>211</td>
<td>-0.0207</td>
<td>0.0248</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10481</td>
<td>228</td>
<td>0.3778</td>
<td>0.0256</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>53,400</td>
<td>49,200</td>
<td>58,300</td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44,800</td>
<td>42,600</td>
<td>47,300</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>43,500</td>
<td>40,700</td>
<td>46,700</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>40,600</td>
<td>38,700</td>
<td>42,600</td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>47,600</td>
<td>44,500</td>
<td>51,200</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>32,000</td>
<td>28,100</td>
<td>37,200</td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>34,800</td>
<td>30,300</td>
<td>40,900</td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>27,700</td>
<td>24,300</td>
<td>32,400</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 116 TNF inhibitors in third place (late RA values) (200,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>46741</td>
<td>98</td>
<td>6.5378</td>
<td>0.0163</td>
</tr>
<tr>
<td>Etan</td>
<td>58960</td>
<td>117</td>
<td>7.0687</td>
<td>0.0167</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47004</td>
<td>98</td>
<td>6.7784</td>
<td>0.0162</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59140</td>
<td>117</td>
<td>7.0570</td>
<td>0.0169</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>48846</td>
<td>100</td>
<td>6.5518</td>
<td>0.0163</td>
</tr>
<tr>
<td>Base</td>
<td>16591</td>
<td>23</td>
<td>6.5936</td>
<td>0.0158</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>30150</td>
<td>96</td>
<td>-0.0559</td>
<td>0.0148</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42369</td>
<td>113</td>
<td>0.4750</td>
<td>0.0155</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>30413</td>
<td>96</td>
<td>0.1848</td>
<td>0.0149</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42549</td>
<td>114</td>
<td>0.4634</td>
<td>0.0157</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>32255</td>
<td>98</td>
<td>-0.0418</td>
<td>0.0149</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>263</td>
<td>130</td>
<td>0.2407</td>
<td>0.0150</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>180</td>
<td>151</td>
<td>-0.0117</td>
<td>0.0163</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>12219</td>
<td>141</td>
<td>0.5309</td>
<td>0.0154</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>12136</td>
<td>142</td>
<td>0.2786</td>
<td>0.0158</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1842</td>
<td>131</td>
<td>-0.2266</td>
<td>0.0150</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10294</td>
<td>143</td>
<td>0.5052</td>
<td>0.0158</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>89,200</td>
<td>83,700</td>
<td>95,400</td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>165,000</td>
<td>142,000</td>
<td>196,000</td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>91,800</td>
<td>86,000</td>
<td>98,500</td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1,090</td>
<td>547</td>
<td>199,000</td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>23,000</td>
<td>21,700</td>
<td>24,600</td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>43,600</td>
<td>39,000</td>
<td>49,300</td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>20,400</td>
<td>19,100</td>
<td>21,900</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

For the next sensitivity analysis, we considered the rate of short-term quitters on conventional DMARDs. Again we considered a 50% decrease and 50% increase on base case.
Decrease short-term quitters on conventional DMARDs by 50%

Table 117 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>46453</td>
<td>102</td>
<td>9.6941</td>
<td>0.0186</td>
</tr>
<tr>
<td>Etan</td>
<td>62850</td>
<td>122</td>
<td>9.8579</td>
<td>0.0188</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49324</td>
<td>103</td>
<td>9.2843</td>
<td>0.0176</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>62699</td>
<td>123</td>
<td>9.5093</td>
<td>0.0181</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51071</td>
<td>105</td>
<td>9.1314</td>
<td>0.0177</td>
</tr>
<tr>
<td>Base</td>
<td>15151</td>
<td>21</td>
<td>9.3912</td>
<td>0.0181</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34302</td>
<td>100</td>
<td>0.3029</td>
<td>0.0179</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47700</td>
<td>119</td>
<td>0.4667</td>
<td>0.0182</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34174</td>
<td>102</td>
<td>-0.1069</td>
<td>0.0174</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47548</td>
<td>120</td>
<td>0.1181</td>
<td>0.0178</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>35921</td>
<td>103</td>
<td>-0.2598</td>
<td>0.0173</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>128</td>
<td>139</td>
<td>0.4098</td>
<td>0.0176</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>151</td>
<td>162</td>
<td>0.3486</td>
<td>0.0182</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13397</td>
<td>151</td>
<td>0.1638</td>
<td>0.0183</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13375</td>
<td>152</td>
<td>0.2250</td>
<td>0.0175</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1747</td>
<td>142</td>
<td>-0.1529</td>
<td>0.0170</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11628</td>
<td>153</td>
<td>0.3779</td>
<td>0.0174</td>
</tr>
</tbody>
</table>
### Comparison ICER (£/QALY) Quasi confidence interval

<table>
<thead>
<tr>
<th>Comparison</th>
<th>ICER (£/QALY)</th>
<th>Quasi confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adal - Base</strong></td>
<td>113,000</td>
<td>101,000 128,000</td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>102,000</td>
<td>94,800 111,000</td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td></td>
<td>Base dominates Adal+MTX</td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>403,000</td>
<td>309,000 576,000</td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td></td>
<td>Base dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>81,800</td>
<td>66,800 105,000</td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>59,400</td>
<td>51,400 70,500</td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td></td>
<td>Adal+MTX dominates Infl+MTX</td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>30,800</td>
<td>28,100 34,000</td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
### Table 118 TNF inhibitors in third place (early RA values) (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48006</td>
<td>154</td>
<td>7.0303</td>
<td>0.0255</td>
</tr>
<tr>
<td>Etan</td>
<td>59470</td>
<td>183</td>
<td>7.4048</td>
<td>0.0265</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47967</td>
<td>155</td>
<td>7.1547</td>
<td>0.0255</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59784</td>
<td>184</td>
<td>7.5185</td>
<td>0.0265</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50178</td>
<td>159</td>
<td>7.1075</td>
<td>0.0252</td>
</tr>
<tr>
<td>Base</td>
<td>16354</td>
<td>37</td>
<td>6.4294</td>
<td>0.0247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31652</td>
<td>150</td>
<td>0.6009</td>
<td>0.0238</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43116</td>
<td>177</td>
<td>0.9754</td>
<td>0.0249</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31614</td>
<td>151</td>
<td>0.7254</td>
<td>0.0240</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43431</td>
<td>178</td>
<td>1.0892</td>
<td>0.0249</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33824</td>
<td>155</td>
<td>0.6781</td>
<td>0.0237</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>39</td>
<td>205</td>
<td>-0.1245</td>
<td>0.0245</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>314</td>
<td>238</td>
<td>0.1137</td>
<td>0.0265</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11464</td>
<td>223</td>
<td>0.3745</td>
<td>0.0253</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11817</td>
<td>224</td>
<td>0.3638</td>
<td>0.0256</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2210</td>
<td>208</td>
<td>-0.0473</td>
<td>0.0244</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9606</td>
<td>226</td>
<td>0.4111</td>
<td>0.0253</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>52,700</td>
<td>48,800 - 57,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>44,200</td>
<td>42,000 - 46,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>43,600</td>
<td>40,900 - 46,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>39,900</td>
<td>38,100 - 41,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>49,900</td>
<td>46,600 - 53,700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>30,600</td>
<td>26,800 - 35,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>32,500</td>
<td>28,300 - 38,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Infl+MTX more costly than Adal+MTX; diff QALY not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>23,400</td>
<td>20,700 - 26,900</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 119 TNF inhibitors in third place (late RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>47634</td>
<td>154</td>
<td>6.3665</td>
<td>0.0254</td>
</tr>
<tr>
<td>Etan</td>
<td>59039</td>
<td>183</td>
<td>6.9434</td>
<td>0.0262</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>47371</td>
<td>153</td>
<td>6.6312</td>
<td>0.0253</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>59186</td>
<td>183</td>
<td>6.9076</td>
<td>0.0264</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>49605</td>
<td>158</td>
<td>6.3925</td>
<td>0.0255</td>
</tr>
<tr>
<td>Base</td>
<td>16342</td>
<td>37</td>
<td>6.4674</td>
<td>0.0247</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31291</td>
<td>150</td>
<td>-0.1009</td>
<td>0.0232</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42697</td>
<td>177</td>
<td>0.4760</td>
<td>0.0241</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31029</td>
<td>149</td>
<td>0.1638</td>
<td>0.0233</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>42843</td>
<td>177</td>
<td>0.4402</td>
<td>0.0245</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33263</td>
<td>154</td>
<td>-0.0749</td>
<td>0.0233</td>
</tr>
<tr>
<td>Adal – Ad+M</td>
<td>263</td>
<td>203</td>
<td>-0.2647</td>
<td>0.0232</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>146</td>
<td>236</td>
<td>-0.0358</td>
<td>0.0254</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11405</td>
<td>221</td>
<td>0.5769</td>
<td>0.0242</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11815</td>
<td>221</td>
<td>0.2764</td>
<td>0.0247</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>2234</td>
<td>206</td>
<td>-0.2387</td>
<td>0.0234</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9580</td>
<td>224</td>
<td>0.5151</td>
<td>0.0245</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adal - Base</strong></td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>89,700</td>
<td>81,400</td>
<td>99,800</td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td>189,000</td>
<td>147,000</td>
<td>265,000</td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>97,300</td>
<td>87,600</td>
<td>110,000</td>
<td></td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>19,800</td>
<td>18,100</td>
<td>21,800</td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>42,700</td>
<td>36,100</td>
<td>52,300</td>
<td></td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>18,600</td>
<td>16,800</td>
<td>20,800</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Increase short-term quitters on conventional DMARDs by 50%

Table 120 TNF inhibitors at the start (40,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>49880</td>
<td>102</td>
<td>9.6920</td>
<td>0.0186</td>
</tr>
<tr>
<td>Etan</td>
<td>62904</td>
<td>121</td>
<td>9.8858</td>
<td>0.0189</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>49987</td>
<td>103</td>
<td>9.2324</td>
<td>0.0177</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>63218</td>
<td>122</td>
<td>9.4851</td>
<td>0.0182</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>51853</td>
<td>104</td>
<td>9.0711</td>
<td>0.0178</td>
</tr>
<tr>
<td>Base</td>
<td>15674</td>
<td>21</td>
<td>9.3971</td>
<td>0.0181</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>34206</td>
<td>101</td>
<td>0.2949</td>
<td>0.0182</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>47230</td>
<td>118</td>
<td>0.4886</td>
<td>0.0184</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>34313</td>
<td>102</td>
<td>-0.1647</td>
<td>0.0177</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>47544</td>
<td>119</td>
<td>0.0880</td>
<td>0.0181</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>36180</td>
<td>103</td>
<td>-0.3261</td>
<td>0.0176</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>107</td>
<td>139</td>
<td>-0.4596</td>
<td>0.0179</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>314</td>
<td>161</td>
<td>-0.4007</td>
<td>0.0185</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>13024</td>
<td>150</td>
<td>0.1938</td>
<td>0.0185</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>13231</td>
<td>152</td>
<td>0.2527</td>
<td>0.0178</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1866</td>
<td>141</td>
<td>-0.1613</td>
<td>0.0173</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>11365</td>
<td>153</td>
<td>0.4141</td>
<td>0.0178</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adal - Base</strong></td>
<td>116,000</td>
<td>103,000</td>
<td>132,000</td>
<td></td>
</tr>
<tr>
<td><strong>Etan - Base</strong></td>
<td>96,700</td>
<td>89,900</td>
<td>105,000</td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Base</strong></td>
<td>Base dominates Adal+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Base</strong></td>
<td>540,000</td>
<td>383,000</td>
<td>918,000</td>
<td></td>
</tr>
<tr>
<td><strong>In+M - Base</strong></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ad+M – Adal</strong></td>
<td>Adal alone more effective than Adal+MTX; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Etan</strong></td>
<td>Etan alone more effective than Etan+MTX; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Etan – Adal</strong></td>
<td>67,200</td>
<td>56,400</td>
<td>83,200</td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – Ad+M</strong></td>
<td>52,400</td>
<td>45,800</td>
<td>61,100</td>
<td></td>
</tr>
<tr>
<td><strong>In+M – Ad+M</strong></td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Et+M – In+M</strong></td>
<td>27,400</td>
<td>25,200</td>
<td>30,200</td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 121 TNF inhibitors in third place (early RA values) (100,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48625</td>
<td>155</td>
<td>7.2782</td>
<td>0.0263</td>
</tr>
<tr>
<td>Etan</td>
<td>60515</td>
<td>186</td>
<td>7.6775</td>
<td>0.0271</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48899</td>
<td>156</td>
<td>7.4142</td>
<td>0.0261</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60471</td>
<td>186</td>
<td>7.7548</td>
<td>0.0271</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50834</td>
<td>160</td>
<td>7.3535</td>
<td>0.0262</td>
</tr>
<tr>
<td>Base</td>
<td>16612</td>
<td>36</td>
<td>6.6526</td>
<td>0.0256</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>32013</td>
<td>153</td>
<td>0.6256</td>
<td>0.0246</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43903</td>
<td>181</td>
<td>1.0249</td>
<td>0.0257</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>32286</td>
<td>154</td>
<td>0.7616</td>
<td>0.0247</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43859</td>
<td>182</td>
<td>1.1022</td>
<td>0.0258</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>34221</td>
<td>157</td>
<td>0.7009</td>
<td>0.0246</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>273</td>
<td>208</td>
<td>0.1360</td>
<td>0.0252</td>
</tr>
<tr>
<td>Etan – Et+M</td>
<td>44</td>
<td>240</td>
<td>-0.0773</td>
<td>0.0269</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11890</td>
<td>226</td>
<td>0.3993</td>
<td>0.0262</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11573</td>
<td>227</td>
<td>0.3406</td>
<td>0.0262</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1935</td>
<td>211</td>
<td>-0.0607</td>
<td>0.0253</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>9637</td>
<td>230</td>
<td>0.4012</td>
<td>0.0260</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td>51,200</td>
<td>47,400 55,600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>42,800</td>
<td>40,800 45,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>42,400</td>
<td>39,800 45,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>39,800</td>
<td>38,000 41,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td>48,800</td>
<td>45,600 52,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>Adal+MTX more effective than Adal alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>Etan+MTX more effective than Etan alone; diff cost not significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>29,800</td>
<td>26,200 34,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>34,000</td>
<td>29,300 40,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>24,000</td>
<td>21,100 27,900</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error
Table 122 TNF inhibitors in third place (late RA values) (1,000,000 patients)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost (£)</th>
<th>Q.S.E.</th>
<th>QALYs</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal</td>
<td>48141</td>
<td>31</td>
<td>6.6360</td>
<td>0.0052</td>
</tr>
<tr>
<td>Etan</td>
<td>60046</td>
<td>37</td>
<td>7.1904</td>
<td>0.0054</td>
</tr>
<tr>
<td>Adal+MTX</td>
<td>48342</td>
<td>31</td>
<td>6.8772</td>
<td>0.0052</td>
</tr>
<tr>
<td>Etan+MTX</td>
<td>60132</td>
<td>37</td>
<td>7.1840</td>
<td>0.0054</td>
</tr>
<tr>
<td>Infl+MTX</td>
<td>50084</td>
<td>32</td>
<td>6.6542</td>
<td>0.0053</td>
</tr>
<tr>
<td>Base</td>
<td>16645</td>
<td>7</td>
<td>6.6639</td>
<td>0.0051</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Diff. Cost (£)</th>
<th>Q.S.E.</th>
<th>Diff. QALY</th>
<th>Q.S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adal - Base</td>
<td>31497</td>
<td>30</td>
<td>-0.0278</td>
<td>0.0048</td>
</tr>
<tr>
<td>Etan - Base</td>
<td>43401</td>
<td>36</td>
<td>0.5266</td>
<td>0.0050</td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>31787</td>
<td>31</td>
<td>0.2133</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>43488</td>
<td>36</td>
<td>0.5202</td>
<td>0.0050</td>
</tr>
<tr>
<td>In+M - Base</td>
<td>33439</td>
<td>31</td>
<td>-0.0097</td>
<td>0.0048</td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>290</td>
<td>41</td>
<td>0.2412</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td>86</td>
<td>48</td>
<td>-0.0064</td>
<td>0.0052</td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>11904</td>
<td>45</td>
<td>0.5544</td>
<td>0.0050</td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>11701</td>
<td>45</td>
<td>0.3068</td>
<td>0.0050</td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>1652</td>
<td>42</td>
<td>-0.2230</td>
<td>0.0048</td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>10049</td>
<td>45</td>
<td>0.5298</td>
<td>0.0051</td>
</tr>
<tr>
<td>Comparison</td>
<td>ICER (£/QALY)</td>
<td>Quasi confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adal - Base</td>
<td></td>
<td>Base dominates adalimumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan - Base</td>
<td>82,400</td>
<td>80,900 84,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Base</td>
<td>149,000</td>
<td>143,000 156,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Base</td>
<td>83,600</td>
<td>82,000 85,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M - Base</td>
<td></td>
<td>Base dominates Infl+MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad+M – Adal</td>
<td>1,200</td>
<td>934 1,690</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Etan</td>
<td></td>
<td>Comparison is inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etan – Adal</td>
<td>21,500</td>
<td>21,100 21,900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – Ad+M</td>
<td>38,100</td>
<td>36,900 39,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In+M – Ad+M</td>
<td>Adal+MTX dominates Infl+MTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et+M – In+M</td>
<td>19,000</td>
<td>18,600 19,400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICER = Incremental Cost-Effectiveness Ratio, QSE = Quasi Standard Error

* This simulation run was extended to 1,000,000 patients in the hope of obtaining a significant difference in QALY outcomes between the Infliximab option and the baseline option.

Satisfactory precision in other major comparisons was obtained with much smaller numbers.
Appendix 11 Ongoing research

Additional ongoing/unpublished trials

Source – ClinicalTrials.gov http://www.clinicaltrials.gov/ct

http://www.clinicaltrials.gov/ct/show/NCT00034060?order=1
The Role of Cytokines on Growth Hormone Suppression in Premenopausal Women with Rheumatoid Arthritis and the Effect of Treatment with Etanercept. Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Effectiveness and Safety of Enbrel® (etanercept) in Rheumatoid Arthritis Subjects who have Failed Remicade® (infliximab). Sponsored by Abbott Laboratories.

http://www.clinicaltrials.gov/ct/show/NCT00095147?order=4
Abatacept and Infliximab in Combination with Methotrexate in Subjects with Rheumatoid Arthritis. Sponsored by Bristol-Myers Squibb

Clinically Important Changes in Rheumatoid Arthritis. Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Source – Controlled-Trials.com http://www.controlled-trials.com/

http://www.controlled-trials.com/mrct/trial/INFLIXIMAB%7CADALIMUMAB%7CETANERCEPT%7CRHEUMATOID%20ARTHRITIS/1059/67577.html
Preference of Rheumatoid Arthritis (RA) Patients of Enbrel® (etanercept) Auto-Injector versus Enbrel® Pre-Filled Syringes. Sponsored by Amgen

http://www.controlled-trials.com/mrct/trial/INFLIXIMAB%7CADALIMUMAB%7CETANERCEPT%7CRHEUMATOID%20ARTHRITIS/1059/67629.html
OPPOSITE: Open-label, Pilot Protocol of Patients with Rheumatoid Arthritis who Switch to Infliximab after an Incomplete Response To Etanercept. Sponsored by Centocor
10 REFERENCES


4 Wiles NJ, Scott DGI, Barrett EM, Merry P, Arie E, Gaffney K, et al. Benchmarking: the five year outcome of rheumatoid arthritis assessed using a pain score, the Health Assessment Questionnaire and the Short Form-36 in a community and a clinic based sample. ARD 2001; 60:956-961.


41 van Gestel AM, Haagsma CJ, Van Riel PLCM. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis & Rheumatism* 1998; 41:1845-1850.
53 Ward MM. Recent improvements in survival in patients with rheumatoid arthritis: better outcomes or different study designs? *Arthritis & Rheumatism* 2001; 44:1467-1469.


74 Ormerod LP. Tuberculosis and anti-TNF-α treatment. Thorax 2004; 59(921).


84 British Society for Rheumatology. Guidelines for prescribing TNF blockers in adults with rheumatoid arthritis. URL: www.rheumatology.org.uk


91 Cohen M. Accentuate the positive: we are better than guidelines. *Arthritis & Rheumatism* 1997; 40:2-4.
109 Yocum D, Rahman MU, Han C, Bala M, Han J, Westhovens R. Infliximab rapidly improves all components of physical function assessed by the HAQ in patients with rheumatoid arthritis: results from the START trial [abstract]. *ACR Annual Scientific Meeting* 2004.


141 De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, Breedveld FC, Han KH, Kerstens PJS, Ronday HK, et al. Clinical and radiological outcomes after one-year follow-up of the BeSt study, a randomized trial comparing four different treatment strategies in early rheumatoid arthritis (RA) [abstract]. *Arthritis & Rheumatism* 2003; 48(Suppl):3649.

379


195 Jobanputra, P., Hunter, M., Clark, D., Lambert, C., Hurst, N. An audit of methotrexate and folic acid for 
193 Sokka, T., Hakkinen, A., Krishnan, E., Hannonen, P. Similar prediction of mortality by the health assessment 
194 Hurst, N., Kind, P., Ruta, D., Hunter, M., Stubbings, A. Measuring health-related quality of life in rheumatoid arthritis: 
190 Maetzel, A., Wong, W., Strand, V., Tugwell, P., Bombardier, C. Meta-analysis of treatment 
188 Scott, D. L., Strand, V. The effects of disease-modifying anti-rheumatic drugs on the Health Assessment 
188 Scott, D. L., Strand, V. The effects of disease-modifying anti-rheumatic drugs on the Health Assessment 
197 Wolfe, F. Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ 
195 Jobanputra, P., Hunter, M., Clark, D., Lambert, C., Hurst, N. An audit of methotrexate and folic acid for 
193 Sokka, T., Hakkinen, A., Krishnan, E., Hannonen, P. Similar prediction of mortality by the health assessment 
190 Maetzel, A., Wong, W., Strand, V., Tugwell, P., Wells, G., Bombardier, C. Meta-analysis of treatment 


223 Saadeh CK, Brown DM, Chumney-Malacara JM, Crow J. Infliximab therapy for rheumatoid arthritis (RA) induced significant control of asthma in patients with both RA and asthma or asthma/COPD in addition to improving RA status. *Journal of Allergy and Clinical Immunology* 2002; 109(1):741.


234 Etanercept/anakinra RA combination therapy has increased risk compared to etanercept monotherapy. *Formulary* 2004; 39(8):394+397.


Last amended: 11 October 2005

