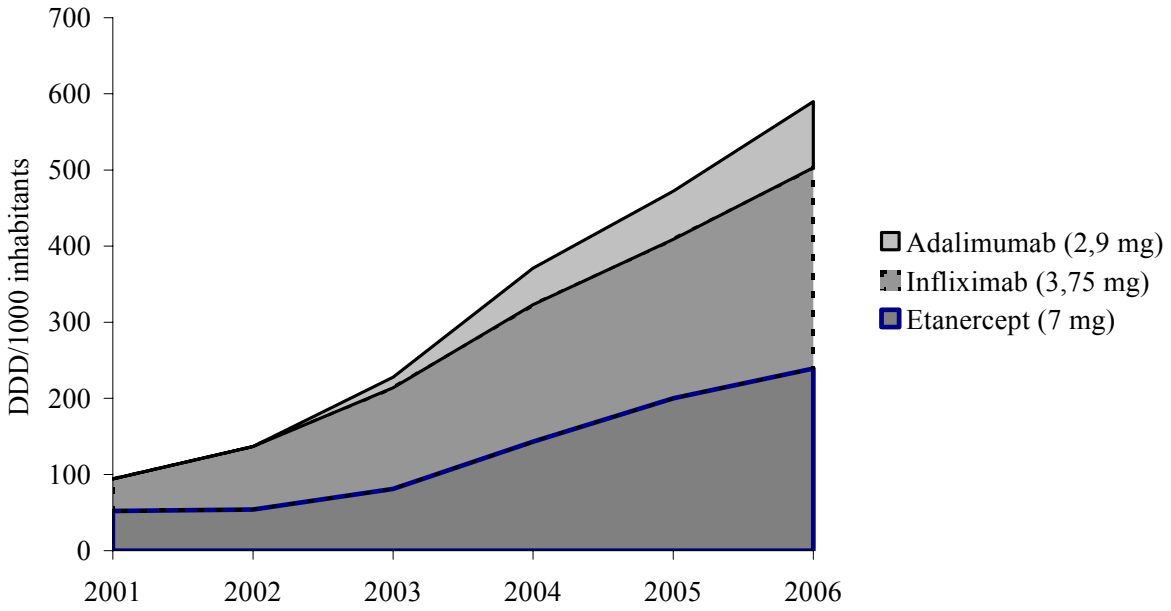
Appendices

Appendices

A Consumption of TNF-a inhibitors in Norway

Consumption of TNF-a inhibitors in terms of defined daily dose (DDD) per 1000 inhabitants per year



Estimated number of patients per year based on sales of TNF-α inhibitors
In terms of defined daily doses (DDD)

	2001	2002	2003	2004	2005	2006
DDD per year per 1000 inhabitants	94	137	228	371	472	590
DDD per day per 1000 inhabitants	0.26	0.38	0.62	1.02	1.29	1.62
DDD per day per 4,5 million inhabitants	1 159	1 689	2 811	4 574	5 819	7 274

Source: Drug Consumption in Norway 2005/2006 volumes, Norwegian Institute of Public Health
http://www.legemiddelforbruk.no

B OMERACT reference case recommendations

	Topic	Recommendation
1.	Model horizon	Trial based analysis, minimum 1 year; Model based analyses, minimum 5–10 yrs.
2.	Duration of treatment	Continuous
3.	Extrapolation beyond trial duration	Report clinical trial data alone and extrapolate (model) using a synthesis of evidence from observational studies, trials, and other sources with sensitivity analysis (minimize use of expert opinion).
4.	Modelling beyond trial duration	No additional benefit or harm after therapy is stopped.
5.	Synthesis of comparisons where clinical trials do not exist	Synthetic comparisons by using relative effects from controlled trials.
6.	Outcome measures	Joint count, Pain by VAS, Physical measure of function (e.g., HAQ), Measure of inflammation (CRP/ESR), HRQoL, Toxicity (report adverse events with patients as the unit of analysis)
7.	Mortality	Hazard rates for mortality from observational studies
8.	Valuation of health (e.g. QALYs)	Patients' values for clinical choices, general population's values for health policy decisions
9.	Resource use	Include all associated direct medical and nonmedical costs in the analysis, but report indirect costs (productivity losses) separately When estimating mean costs in the presence of censoring due to discontinuation of therapy, adjust using appropriate statistical methods to allow for unequal exposure to risk of resource use.
10.	Discontinuation of treatment	Use discontinuation rates from trials, adjusted using observational data.
11.	Therapeutic sequence	Include modelling of most commonly used therapeutic sequence with sensitivity analysis to consider other strategies
12.	Population risk stratification	Include clear definition of underlying population including low and high risk groups.

VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; HRQoL: health related quality of life; CRP: C-reactive protein; ESR: erythrocyte sedimentation
rate; QALY: quality-adjusted life-years.
Source: Gabriel et al. (2003)

C Search strategies

PubMed:

1 rheumatoid arthritis.mp.
2 juvenile or Bechterew$ or psoria$ or polyarth$ or ankylosing spondylitis.
3 etanercept or infliximab or adalimumab
4 Enbrel or Remicade or Humira.
5 tumour necrosis factor or tumor necrosis factor or TNF$ or biologic$
6 1 not 2
7 3 or 4 or 5
8 6 and 7
9 cost effectiveness or cost utility or cost benefit or health eeconomic$ or ecpnomic evaluation or pharmacoeconomic$ or pharmaco-economic$.
10 8 and 9

NHS Economic Evaluatios Database:

TNF OR tumor necorsis factor OR biologic OR adalimumab OR etanercept OR infliximab AND rheumatoid arthritis

D Study summaries

D.1 Chen 2006

Study background

Chen 2006 (1) was a cost-utility study conducted by the West Midlands Health Technology Assessment Collaboration (WMHTAC) for the UK National Institute for Health and Clinical Excellence (NICE) as part of the institute's current reappraisal of the use of TNF-inhibitors for RA patients in England and Wales.

Patients

Two patient populations were modelled:
i) Patients with early RA, which was defined as a disease duration of 3 years or less, who were either MTX-naïve or who had not failed MTX.
ii) Patients with late RA, i.e. disease duration of longer than 3 years, who had failed MTX.

Intervention and comparison

The effects of placing TNF-inhibitors at different positions; first, third and last, in a standard UK DMARD sequence were investigated and compared to a sequence without TNF-inhibitors. The use of several TNF-inhibitors in the same sequence was also modelled, but shall not be commented on here as no comparisons can be made to other studies. The standard sequence was derived from a survey of British rheumatologists.

Intervention: TNF-inhibitor, with or without MTX in the 1st, 3rd or final position in a standard UK DMARD sequence (see below).

Comparison: Standard UK DMARD sequence based on a survey of rheumatologists

1. MTX
2. SSZ / MTX + SSZ / MTX +SSZ + hydrochloroquine, (HCQ)
3. leflunomide
4. intramuscular gold
5. azatiopine
6. cyclosporine

(the order and combination of drugs may vary depending on response and toxicity)

Study perspective, time horizon and model type

The study perspective was that of the health services in England and Wales, the modelling time horizon was the patients' expected remaining lifetime and the model, known as the Birmingham Rheumatoid Arthritis Model (BRAM), was a discrete event simulation. The model assessed the costs and benefits of the different strategies from the point at which they separate. This means that both strategies might involve the same choice of drugs in the initial stages, but that the associated costs and benefits were not calculated. Therefore – other things being equal – the discounted ICER will be higher compared to studies in which discounting takes place to the point at which treatment starts. Comparison strategy values will also vary depending on the position of the divergence in the sequence.

Efficacy data and modelled outcomes

The trials that were used in the BRAM are shown below. Some of them have been evaluated in the NOKC report on TNF trials (2), and their corresponding quality assessment result drawn from that report is provided in the rightmost column.

Table A.1 Efficacy data: Chen 2006

Study	Therapy	Study type	Duration	Quality*
Breedveld 2006 (3)	adalimumab + MTX	RCT	2 years	Medium
van de Putte 2004 (4)	adalimumab	RCT	26 weeks	High
Rau 2004 (5)	adalimumab	RCT	12 weeks	High
Keystone 2004 (6)	adalimumab + MTX	RCT	1 year	High
Weisman 2003 (7)	adalimumab	RCT	27 months	Medium
Weinblatt 2003 (8)	adalimumab + MTX	RCT	24 weeks	High
van de Putte 2003 (9)	adalimumab	RCT	12 weeks	High
Furst 2003 (10)	adalimumab	RCT	24 weeks	High
den Broeder 2002 (11)	adalimumab	RCT	3 months	Medium
Moreland 1996 (12)	etanercept	RCT	3 months	Medium
Moreland 1997 (13)	etanercept	RCT	3 months	Medium
Moreland 1999 (14)	etanercept	RCT	6 months	High
Weinblatt 1999 (15)	etanercept + MTX	RCT	24 weeks	Medium
Bathon 2000 (16)	etanercept	RCT	1 year	High
Genovese 2002 (17)	etanercept	RCT	2 years	na
Codreanu 2003 (abstract)	etanercept (+ SSZ)	RCT	na	na
Klareskog 2004 (TEMPO) (18)	etanercept + MTX	RCT	24 weeks	High
Keystone 2004 (19)	etanercept + MTX	RCT	16 weeks	High
Lan 2004 (20)	etanercept + MTX	RCT	12 weeks	Medium
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
Lipsky 2000 (ATTRACT) (22)	infliximab + MTX	RCT	54 weeks	High
Elliott 1994 ((23))	infliximab	RCT	4 weeks	Medium
Kavanaugh 2000 ((24))	infliximab + MTX	RCT	24 weeks	Medium
Maini 1998 (25)	infliximab	RCT	26 weeks	High
St Clair 2004 (26)	infliximab + MTX	RCT	54 weeks	Medium
Durez 2004 (26;27)	infliximab + MTX	RCT	6 weeks	High
Taylor 2004 (28)	infliximab + MTX	RCT	54 weeks	High
Quinn 2005 (29)	infliximab + MTX	RCT	12 months	High
Yocum 2004 (abstract)	infliximab + MTX	RCT	na	na
Geborek 2002 (30)	etanercept/infliximab	OBS	2 years	na

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), . na=not applicable.
Sources: Chen 2006 (1), table 1 and Arentz-Hansen 2006 (2), tables 5, 7 and 9.

Data from the observational study Geborek 2002 (30) on patients in Southern Sweden were used to calculate early cessation. However, this study did not include adalimumab, and so it was assumed that adalimumab withdrawal was identical to infliximab withdrawal data.

HAQ change was modelled based on an initial distribution of UK RA patients provided in Wales 2001 (31) and beta distributions based on trial results. Upon quitting treatment, HAQ is assumed to increase by the same figure as the decrease following initial response. An underlying positive change in HAQ of 0.06 a year was assumed for palliative treatment, which implies 2 years between the smallest meaningful change of 0.125 units. TNF inhibitors

were assumed to halve this progression to 0.03 units per year, (4 years between each 0.125 change) while conventional DMARDs involved a progression of 0.045 (2.7 years between each 0.125 change). The patient's HAQ status upon treatment cessation relative to comparison strategy would thus depend on the net HAQ change. The transition from HAQ to QALYs was performed using a dataset from a UK observational study, Hurst 1997 (32), who elicited quality of life of RA patients through the EQ-5D method. The HAQ-HRQoL relationship was represented by the formula:

HRQoL=0.862-0.327 x HAQ

Mortality: Relative mortality risk was in addition to age and gender also linked to HAQ through the equation:

Relative mortality risk=1.33 x HAQ

The number of QALYs gained on average per patient for each strategy was calculated by weighting expected survival by HRQoL.

Costs

Direct costs: Costs of drugs and monitoring were incorporated, but not costs associated with hospitalisation (including costs of joint replacement surgery), not even in the otherwise extensive sensitivity analysis.

Indirect costs: Not included

Results

Discounting: In line with NICE requirements, costs were discounted at 6 % and outcomes at 1.5 %. Since costs were discounted at a higher rate than benefits, the ICERs would be slightly lower than in a model in which the rates were identical, other things being equal.

Comparison strategy: Since the costs and outcomes related to the various strategies were calculated from the point of strategy divergence, the comparison strategy values differed according to the position of the TNF-inhibitor in the sequence. For example, third line treatment interventions were only compared to comparison strategy costs and outcomes accruing from the time at which the patient had reached third line and onwards. First line treatment interventions, on the other hand, were compared to comparison strategy values incorporating the entire sequence. In addition, comparison strategy costs and outcomes varied depending on whether the underlying efficacy data was of the "early" or "late" kind.

The costs of the comparison strategies shown in table A2 were fairly similar since traditional DMARDs do not vary much in terms of price. The relatively higher number of QALYs gained in first line therapy is due to the effect of initial treatment (with MTX, SSZ and HCQ) being excluded in the third line strategy figures (as noted, costs and benefits were only calculated from the point at which the strategies separate).

Table A.2 Comparison strategy strategies: Costs and outcomes, various strategies involving a standard DMARD sequence in the UK, Chen 2006

Comparison strategy	Cost GBP 2004	Cost NOK 2005	QALYs Gained
3rd line, late RA	16 509	207 000	5.4 SHOULD BE 5.4 and not 54?
3rd line, early RA	16 494	207 000	5.4
1st line, early RA	15 331	192 000	8.3

Source: Chen 2006 (1), tables 51-53

Table A.3 ICERs: Adalimumab (+MTX) compared to a standard DMARD sequence in the UK. Base-case results from the BRAM model, Chen 2006

Strategy	Incremental		ICER	
	Cost	QALYs	GBP 2004	NOK 2005
adalimumab mono 3rd line early RA	31 770	0.92	35 000	441 000
adalimumab + MTX 3rd line early RA	32 042	1.06	30 000	378 000
adalimumab mono 1st line early RA	34 207	0.65	53 000	667 000
adalimumab + MTX 1st line early RA	34 319	0.20	170 000	2 141 000
adalimumab mono 3rd line late RA	30 934	0.22	140 000	1 763 000
adalimumab + MTX 3rd line late RA	31 454	0.49	64 000	806 000
etanercept mono3rd line early RA	44 454	1.46	30 000	378 000
etanercept + MTX 3rd line early RA	44 761	1.57	28 000	353 000
etanercept mono 1st line early RA	48 561	0.98	49 000	617 000
etanercept + MTX 1st line early RA	48 748	0.62	78 000	982 000
etanercept mono 3r d line late RA	43 832	0.92	47 000	592 000
etanercept + MTX 3rd line late RA	43 821	0.88	50 000	630 000
infliximab + MTX 3rd line early RA	31 679	1.04	30 000	378 000
infliximab + MTX 1st line early RA	33 748	0.05	650 000	8 185 000
infliximab + MTX 3rd line late RA	30 770	0.22	140 000	1 763 000

Source: Chen 2006 (1), table 50

Sensitivity analysis

The results were sensitive to the assumptions regarding HAQ progression while on TNF-therapy. No sensitivity analysis on costs was performed.

D.2 Bansback 2005

Study background

Bansback 2005 (33) was a cost-utility study of adalimumab (+MTX) in Sweden, but the other two TNF-inhibitors were included in comparison strategies. The study was carried out by a group associated with the University of Sheffield's School of Health and Related Research (ScHARR), who have been involved in economic evaluations of TNF-inhibitors in several countries, particularly in the UK.

Patients

Moderate to severe RA patients failing 2 DMARD treatments were included in the study.

Intervention and comparison

Intervention: adalimumab mono or with MTX as 3rd line treatment in a Swedish DMARD sequence. The position of individual DMARDs in the sequence was not described in the study, except for the beginning which is given as MTX, SSZ or HCQ or combinations of these drugs, which were followed by three unidentified DMARDs and palliative treatment. However, it was claimed that the model's patient pathway followed Swedish clinical practice.

Comparisons: DMARD sequence without TNF-inhibitors, DMARD sequence with etanercept (mono or with MTX) as third line therapy, and DMARD sequence with infliximab + MTX as third line therapy.

Study perspective, time horizon and model type

The study perspective was that of the Swedish health services, the time horizon lifetime and the model type a patient based transition state based on work by Jobanputra 2002 (34) and Brennan 2004 (35).

Efficacy data and modelled outcomes

Two trials (6;8) formed the basis for response data for adalimumab + MTX, one being a longer follow-up study which enabled the authors to conduct separate analyses, one based on a single trial and the other on pooled data. DAS28, used to determine treatment continuation in clinical practice in Sweden was not found in all trials, so the authors therefore used ACR20 and ACR50 response rates as proxies to model two different response thresholds: The former was assumed to approximate a moderate DAS28 response, whilst the latter entailed a good response on the parameter. The adalimumab monotherapy results were based on a single trial (9). A Swedish observational study was used to calculate rates of withdrawal and adverse events (30).

Table A.4 Efficacy data: Adalimumab (+MTX), Bansback 2005

Study	Therapy	Study type	Duration	Quality*
DF009, Weinblatt 2003 (8)	adalimumab + MTX	RCT	24 weeks	High
DF019, Keystone 2004 (6)	adalimumab + MTX	RCT	1 year	High
DF011, van de Putte 2003 (9)	adalimumab	RCT	12 weeks	High
Moreland 1999 (14)	etanercept	RCT	6 months	High
Weinblatt 1999 (15)	etanercept + MTX	RCT	24 weeks	Medium
Geborek 2002 (30)	etanercept	OBS	2 years	na
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
Geborek 2002 (30)	infliximab†/etanercept	OBS	2 years	na

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), na=not applicable
†early cessation data lacking for adalimumab, was therefore assumed identical to infliximab in Geborek study
Sources: Bansback 2005 (36) and Arentz-Hansen 2006 (2), tables 5, 7 and 9

Being an ACR20, but not an ACR50 responder, was associated with a HAQ improvement of 30 %, whilst ACR50 responders experienced an average HAQ improvement of 60 %. When a patient ceased using a particular drug, HAQ-DI was assumed to revert by the same magnitude as the initial response associated with the drug. HRQoL was calculated using the Health Utilities Index (HUI-3) method to value health states. The link to HAQ-DI was described as:

HRQoL=0,76-0,28 x HAQ

Mortality: No treatment benefit with respect to reduced mortality risk was modelled, thus mortality was not linked to HAQ as it was in the Chen 2006 study.

Costs

Direct costs: drugs, monitoring, administration (based on expert opinion) hospital services including joint replacement surgery (based on an estimated linear relationship between hospital costs and HAQ-DI.

Indirect costs: none calculated

Results

Discounting: Costs and benefits were discounted at 3 %.

Comparison strategy: The costs and outcomes of the comparison strategy (traditional DMARD sequence) are shown below. The modelled QALYs gained in both scenarios with a traditional sequence in Bansback were significantly lower than those in the Chen 2006 UK comparison strategy. The differences in discount rate would only in part contribute to this variation.

Table A.5 Comparison strategy: Total costs and outcomes of a standard DMARD sequence) in "ACR50/DAS28 Good" and "ACR20/DAS28 Moderate" modelling scenarios in Sweden, Bansback 2005

Comparison strategies	Cost euro 2001	Cost NOK 2005	QALYs gained
ACR50/DAS28 Good	70 387	600 000	1.2
ACR20/DAS28 Moderate	68 757	585 000	1.7

Source: Bansback 2005 (33), table 4

Table A.6 ICERs: Adalimumab (+MTX) compared to a standard DMARD sequence in Sweden. Base-case results, Bansback 2005

Strategy	Incremental		ICER	
	Costs, euro	QALYs	euro 2001	NOK 2005
ACR50/DAS28 Good response				
adalimumab + MTX	38 595	1.3	34 167	291 000
adalimumab + MTX pooled	32 222	0.9	34 922	298 000
adalimumab mono	19 671	0.5	41 561	354 000
etanercept + MTX	32 742	0.9	35 760	305 000
etanercept mono	32 034	0.9	36 927	315 000
infliximab + MTX	31 711	0,7	48 333	412 000
ACR20/DAS28 Moderate response %				
adalimumab + MTX	49 221	1.2	40 875	348 000
adalimumab + MTX pooled	45 705	1.0	44 018	375 000
adalimumab mono	47 684	0.7	65 499	558 000
etanercept + MTX	64 832	1.2	51 976	443 000
etanercept mono	43 593	1.0	42 480	362 000
infliximab + MTX	45 974	0,7	64 935	553 000

Source: Bansback 2005 (33), table 4

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Sensitivity analysis

The results were sensitive to, baseline age, the standardised mortality ratio, and HAQ-DI/utility, but not to changes in direct costs.

D.3 Coyle 2006

Study background

Coyle 2006 (37) was a systematic review and economic evaluation (cost-utility and cost-effectiveness analyses) of etanercept and infliximab published by the Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA).

Patients

Patients with long-standing RA

Intervention and comparison

Intervention TNF-inhibitor (etanercept or infliximab) before or after intramuscular gold in a typical Canadian DMARD sequence (see below)

Comparison: intramuscular gold as fourth line therapy following MTX /(MTX + SSZ)/(MTX + SSZ + hydrochloroquine (HCQ))

Altogether five DMARD strategies were compared with respect to treatment of patients with long-standing RA. The sequences were based on a survey amongst Canadian rheumatologists. The comparison strategy involved intramuscular gold as fourth line therapy following MTX alone or in combination with sulphasalazine (SSZ) and hydrochloroquine (HCQ). A strategy involving etanercept before and after gold in the sequence was compared.

Study perspective, time horizon and model type

The study was carried out from the health services' point of view and had a five year time-horizon. The model, of the Markov type, involved cycle lengths of six months.

Efficacy data and modelled outcomes

The efficacy data were drawn from the Moreland 1999 etanercept monotherapy trial (14), Long term data were not available, according to the authors.

Table A.7 Efficacy data: Etanercept, Coyle 2006

Study	Therapy	Study Type	Duration	Quality*
Moreland 1999 (14)	etanercept	RCT	6 months	High
Maini 1999 (21)	infliximab + MTX	RCT	30 weeks	High
Lipsky 2000 (22)	infliximab + MTX	RCT	54 weeks	High

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2),
na=not applicable
Sources: Coyle 2006 (37) and Arentz-Hansen 2006 (2), tables 5, 7 and 9

Response was measured on the ACR20, 50 and 70 parameters, though the model allowed for some patients to continue on the same therapy despite not responding on ACR20, as might happen in clinical practice. Moreland's 6-month response data were extrapolated for the entire 5-year period. HAQ progression was not emphasised in the economic analysis, and the gains in HRQoL associated with the various health states were identical with he ones employed by Jobanputra et al. in the so called Birmingham Preliminary Model, based on EQ-5D and HAQ. Overall, the link between response and HRQoL gain over 5 years was not clearly described in Coyle 2006.

Mortality: No effects on mortality were modelled.

Costs

Direct costs: Costs of drugs, monitoring and adverse events were included, but not those associated with hospitalisation. The costs of managing adverse events were set similar for etanercept, infliximab and gold. The monitoring costs associated with the TNF inhibitors were significantly less than those for gold, but the former drugs were far more expensive.

Indirect costs: Not included

Results

Discounting: All costs and outcomes were discounted at the 5 % level

Comparison strategy:: The cost and outcome values of the standard DMARD strategy are shown below. Both the costs and outcomes may seem small compared those of other studies, but one should bear in mind that Coyle 2006 had a time horizon of only 5 years.

Table A.8 Comparison strategy: Total costs and outcomes, Canadian traditional DMARD sequence, Coyle 2006

Comparison strategy	Cost CAD 2005	Cost NOK 2005	QALYs gained
Standard DMARD sequence	9 200	49 000	0.09

Source: Coyle 2006 (37), table 8

Placing etanercept before and after gold in the sequence produced ICERs of CAD 144 700 (NOK 770 000) and CAD 125 700 (NOK 670 000) respectively. It turned out that placing etanercept after rather than before gold in the sequence, was less costly as well as less effective (0.36 vs. 0.34 QALYs gained). However, both strategies cost more than CAD 120 000 per QALY which is more than double the Canadian threshold value of CAD 50 000 per QALY gained (NOK 266 000, 2005), and they were therefore not considered cost-effective when only direct costs were taken into account.

Table A.9 ICERs: Etanercept before and after gold in a Canadian DMARD sequence, compared to a similar sequence without TNF-inhibitors. Base-case results, Coyle 2006

Strategy	Incremental		ICER	
	Costs, CAD	QALYs	CAD 2005	NOK 2005
etanercept before gold	39 200	0.27	144 700	770 000
etanercept after gold	32 000	0.22	125 700	670 000
Infliximab + MTX before gold	28 700	0.25	113 000	600 000
Infliximab + MTX after gold	21 700	0.22	97 800	522 000

Source: Coyle 2006 (37), table 8

Sensitivity analysis

The results were moderately sensitive to utility gains from therapy.

D.4 Kobelt 2005

Study background

Kobelt 2005 (38) was a cost-utility study from Sweden sponsored by Wyeth.

Patients

The modelled patients had active RA and had failed DMARDs other than MTX

Intervention and comparison

Intervention: etanercept + MTX

Comparison: MTX monotherapy.

No treatment sequences were described

Study perspective, time horizon and model type

The study had a societal study perspective, which means that indirect costs were included. The Markov model had a 10-year time horizon. The model was developed with five states determined by functional status as measured by the HAQ[1]. These were in turn separated into high and low disease activity (determined by the DAS28 score). The cycle length was one year, which may seem somewhat long compared to other models where response is usually measured over 6 months.

Efficacy data and modelled outcomes

Etanercept + MTX efficacy data were drawn from a 2-year trial (TEMPO) of patients with active RA who had failed DMARDs other than MTX.

Table A.10 Efficacy data: Etanercept (+MTX), Kobelt 2005

Study	Therapy	Study type	Duration	Quality*
Klareskog 2004 (TEMPO) (18)	etanercept + MTX	RCT	2 years	High

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2)
Sources: Kobelt 2005 (38) and Arentz-Hansen 2006 (2), table 7

Cost and utility data were elicited from a follow-up survey of 616 patients in Malmö from 2002 (39) . Given that disease activity was measured on DAS28 in the trial and on global VAS in the survey, Kobelt et al. calculated that the cut-off point between high and low disease activity on the former; 3.2, corresponded to a score of 41 on the latter.

Data from the TEMPO trial's second year were extrapolated to a 10-yaer time horizon. The 2nd year withdrawal rates were respectively 22 %, 16 %, and 13 % in the methotrexate, etanercept, and etanercept plus methotrexate groups. No treatment effect was assumed after discontinuation of treatment as HAQ values reverted to comparison strategy in the model (or higher if deteriorated during the trial) if this occurred. Annual HAQ increase following treatment termination was 0.03, based on findings by Scott et al (40).

[1] Cur-off points HAQ 0.6, 1.1, 1.6, 2.1

HROoL: QALYs were based on EQ-5D and correlated with both HAQ and disease activity through regression. The exact formula was not supplied, but a table with HRQoL values grouped by HAQ level was provided. Disease activity was found to have a significant effect on HRQoL, regardless of HAQ score.

Mortality: Mortality was linked to HAQ and disease activity. In the health states with a HAQ lower than 1.1, mortality risk was normal. In the remaining two the risk was adjusted by 1.3 and 2.0 depending on whether disease activity was low or high.

Costs

Direct costs: With regard to resource consumption, Kobelt et al. sought to include all direct and indirect costs. The definition of direct costs was somewhat broader than that used in other studies, and included investments, devices, informal care and transportation

Indirect costs: Indirect costs included early retirement and costs linked to productivity loss.

Results

Discounting: Costs and benefits were discounted at 3 %.

Comparison strategy: Comparison strategy costs, shown below, were relatively high compared to other studies which often even had a longer time perspective, which might be due to the extensive inclusion of cost data. .

Table A.11 Comparison strategy: Total costs and outcomes for MTX in Sweden (10 year model), Kobelt 2005

Comparison strategy	Cost euro 2004	Cost NOK 2005	QALYs gained
MTX	149 942	1 273 000	3.43

Source: Kobelt 2005 (38), table 6

The 10-year extrapolation, shown in the table below, produced an ICER of euro 46 494 (NOK 396000, 2005) per QALY gained. The probability of the ICERs being below a threshold of euro 50 000 (NOK 427 000, 2005) was reported as being 88 %. Sensitivity analysis showed that the results were sensitive both to utility/effectiveness changes and costs. The 10-year extrapolation results should thus be considered with a great degree of caution.

Table A.12 ICER: Etanercept + MTX compared to MTX in Sweden. Base-case results (10 year model), Kobelt 2005

Strategy	Incremental		ICER	
	Costs, euro	QALYs	euro 2004	NOK 2005
etanercept + MTX	42 148	0.91	46 494	395 000

Source: Kobelt 2005 (38), table 6

The patients modelled had not failed MTX, so it is likely that it the intervention was intended at an early stage. A notable drawback with regard to the description of costs, both direct and indirect, was that the composition was not comprehensively accounted for or discussed. How, for example, have resources spent on “investments and medical devices” been allocated to RA patients?

Sensitivity analysis

The results were most sensitive to assumptions about costs and utility and HAQ (treatment effectiveness. Cost-effectiveness ratios were relatively lower for people of working age. A probabilistic sensitivity analysis was carried out, which found that etanercept + MTX was cost-effective with a threshold of euro 50 000 (NOK 425 000, 2005) over 10 years.

D.5 Brennan 2004

Study background

Brennan 2004 (35) was a cost-utility study from the UK. The model described in the study was submitted by Wyeth to NICE as part of the institute's 2002 assessment of the use of TNF inhibitors for RA in England and Wales, and the subsequent development of guidelines.

Patients

The population modelled comprised adult RA patients who had failed 2 six-month treatments with DMARDs, one of which had to be MTX, in line with contemporary British Society for Rheumatology (BSR) guidelines. Other comparison strategy characteristics were consistent with the Moreland 1999 clinical trial (14).

Intervention and comparison

Intervention: A DMARD sequence which included etanercept as third line treatment after MTX and SSZ and before intramuscular gold,

1. MTX
2. SSZ
3. etanercept
4. intramuscular gold
5. leflunomide
6. cyclosporine + MTX

Comparison: A similar sequence without the biologic

The choice of sequences compared was intended to reflect the most popular DMARDs in the UK.

Study perspective, time horizon and model type

In accordance with NICE recommendations, the study perspective was that of the health services. The discrete event simulation model had a lifetime perspective.

Efficacy data and modelled outcomes

The results from the Moreland 1999 (41) etanercept monotherapy trial formed the efficacy input in the model:

Table A.13 Efficacy data: Etanercept, Brennan 2004

Study	Therapy	Study Type	Duration	Quality*
Moreland 1999 (14)	etanercept	RCT	6 months	High

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2)
Sources: Brennan 2004 (35) and Arentz-Hansen 2006 (2), table 5

In the model, an ACR20 response determined whether a patient continued on the same drug or switched to another, and also assigned the patient to different HAQ development paths. As opposed to DAS28, ACR20 is a relative variable and – although prevalent in clinical trials - in little use in clinical practice, as the authors acknowledged themselves. The model assumed that HAQ score after withdrawal was marginally higher than at comparison strategy since

patients were likely to experience a gradual underlying deterioration in HAQ even with treatment.

HRQoL: Brennan 2004 based their HRQoL assumptions on a number of studies, including Hurst 1997 (32) and Kobelt 1999, which used EQ-5D to estimate utility in rheumatoid arthritis patients. The resulting relationship between HAQ and HRQoL is denoted by:

HRQoL=0.86 - 0.20 x HAQ.

The slope of the curve was less steep than in other studies (Bansback 2005: 0.28; Chen 2006: 0.33) which implied a relatively lower QALY improvement for a given positive change in HAQ.

Mortality: Mortality risk was assumed to decrease with HAQ improvement, but the exact relationship was not provided. However, the sensitivity analysis showed that it bore little influence on the result (42).

Costs

Direct costs, apart from those of drugs/monitoring, are drawn from estimates based on HAQ regression carried out by Yelin and Wanke 1999 (43) and Kobelt's study from the same year (44). When converted to British pounds (2000 values), this meant that a one point reduction in HAQ produced a GBP 860 increase in direct healthcare costs. However, the population in the underlying studies was limited, and unit costs may not necessarily be transplanted from one context to another without problems.
Indirect costs:

Indirect costs: Indirect costs were only included in the sensitivity analysis.

Results

Discounting: Costs were discounted by 6 % and benefits (outcomes(by 1.5 %, following NICE recommendations.

Comparison strategy: The lifetime cost and outcomes of the traditional DMARD sequence is shown below:

Table A.14 Comparison strategy: Total costs and outcomes for a standard DMARD sequence in the UK, Brennan 2004

Comparison strategy	Cost GBP 2001	Cost NOK 2005	QALYs gained
MTX	9 199	126 000	5.87

Source: Brennan 2004 (35), table 3

The strategy including etanercept was estimated to cost GBP 27 014 more than the one without, whilst producing 1.6 QALYs (all figures per patient). This rendered an incremental cost per QALY gained of GBP 16 330 (NOK 224 000, 2005). Productivity costs were included in the sensitivity analysis by combining UK wage rates with Swedish HAQ-related employment data. This reduced the incremental cost per QALY to under GBP 10 000 (NOK 137 000, 2005).

Table A.15 ICERs: Etanercept compared to MTX in the UK. Base-case results, Brennan 2004

Strategy	Incremental		ICER	
	Costs, GBP	QALYs	GBP 2001	NOK 2005
etanercept monotherapy	27 014	1.6	16 330	224 000

Source: Brennan 2004 (35), table 3

The only other variable seen to have any major effect on the result in the sensitivity analysis is the long term underlying HAQ progression. If this was set equal for etanercept and other DMARDS, then costs per QALY would rise to above GBP 42 000 (NOK 575 000, 2005) Changing other variables such as mortality risk and even the sequence of DMARDs, only brought about marginal changes.

Sensitivity analysis

The results were sensitive to assumptions about HAQ progression while on active treatment, and especially inclusion of indirect costs.

D.6 Tanno 2006

Study background

Tanno 2006 (45) was a cost-utility study from Japan sponsored by the Japanese government.

Patients

The study focused on Japanese adult RA patients who had failed first line treatment with bucillamine.

Intervention and comparison

Intervention: Bucillamine → etanercept mono → MTX → SSZ → MTX + SSZ → no DMARD

Comparison: As above but without etanercept monotherapy

Study perspective, time horizon and model type

The study had a societal perspective, a lifetime time horizon and utilised a Markov model with 6 month cycles.

Efficacy data and modelled outcomes

The underlying trial data comprised Moreland 1999 (14).

Table A.16 Efficacy data: Etanercept, Tanno 2006

Study	Therapy	Study Type	Duration	Quality*
Moreland 1999 (14)	etanercept	RCT	6 months	High

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2)
Sources: Tanno 2006 (45) and Arentz-Hansen 2006 (2), table 5

The ACR20 responders on etanercept were assumed to have their HAQ improve by a factor of 0.53 every six months. No improvement on HAQ was assumed if the patient did not respond or had to withdraw due to adverse events

HRQoL: HRQoL was linked to HAQ based on a survey of Japanese RA patients (EQ-5D) and described by the equation:

$$HRQoL=0.74-0.17 \times HAQ$$

The gradient was low compared to other studies, which probably reflects the higher resilience of Japanese versus Western patients.

Mortality: Mortality risk was assumed to decrease following improvements in HAQ.

Costs

Direct costs: Direct costs included costs of drugs, monitoring and hospitalisation. Hospitalisation costs were linked to HAQ development based on a Japanese survey.

Indirect costs: Inability to work was calculated and linked to HAQ based on a Japanese survey of RA patients. The average wage over six months was used as to estimate the loss. Costs of early mortality were also estimated in the same manner (lost work capacity up to age of 60).

Results

Discounting Costs were discounted at 6 % and outcomes at 1.5 %, which means that NICE recommendations were followed in this respect.

Comparison strategy: The lifetime costs and outcomes associated with a traditional DMARD sequence in Japan are shown below:

Table A.17 Comparison strategy: Total costs and outcomes for a standard DMARD sequence in Japan, Tanno 2006

Comparison strategy	Cost JPY million 2005	Cost NOK million 2005	QALYs gained
Standard DMARD sequence	17.6	1.0	6.8

Source: Tanno 2006 (45), table 4

The ICERs are shown in table 18 underneath. The ICER includes indirect costs and is therefore relatively small, even though the HRQoL gain per unit change in HAQ is lower than in other studies.

Table A.18 ICERs: Etanercept as 2nd line therapy in a DMARD sequence, compared to a standard DMARD sequence in Japan Base-case results, Tanno 2006

Strategy	Incremental		ICER	
	Costs, JPY million	QALYs	JPY million 2005	NOK 2005
etanercept	6,39	2.56	2.5	145 000

Source: Tanno 2006 (45), table 4

The DMARD bucillamine (ATC M01CC02) is not marketed in Norway. Etanercept monotherapy is only in limited use. The study also points out that Japanese patients are likely to differ from their European counterparts since the former tend to report better state of general health and quality of life than the latter, controlled for disease duration.

Sensitivity analysis

The model was sensitive to the price of etanercept and the rate of HAQ decrease in ACR20-responders

D.7 Welsing 2004

Study background

Welsing 2004 (46) was a cost-utility study from the Netherlands.

Patients

Dutch patients with active RA (DAS 28>3.2,) who had failed two DMARDS, one of which had to be MTX.

Intervention and comparison

1) usual treatment;
2) leflunomide, if non-response after 3 months: usual treatment;
3) TNF-blockers, if non-response after 3 months, usual treatment;
4) leflunomide, if non-response, TNF-blocker, if non-response to this; usual treatment;
5) TNF-blocker, if non-response, leflunomide, if non-response to this; usual treatment.

In the interests of comparison with other studies, only one intervention will be focused upon here:

Intervention: Strategy 3) TNF-blockers, if non.response after 3 months, "usual treatment"

Comparison: Strategy 1) usual treatment

"Usual treatment" is not very well defined. The initial drugs are given as SSZ and MTX, followed by "a range of DMARDs".

Study perspective, time horizon and model type

The study had a third party payer perspective, a 5 year time horizon and employed a Markov model.

Efficacy data and modelled outcomes

The efficacy data used in Welins 2004 is shown below:

Table A.19 Efficacy data: Etanercept, Welsing 2004

Study	Therapy	Study type	Duration	Quality*
Moreland 1999 (14)	Etanercept	RCT	6 months	High
Weinblatt 1999 (15)	etanercept + MTX	RCT	24 weeks	Medium

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2)
Source: Welsing 2004 (46) and Arentz-Hansen 2006 (2), table 5

HRQoL: Utility values were derived using the EQ-5D and assigned to the different Markov states.

Mortality: Any difference in morality between the treatment strategies was not accounted for.

Costs

Direct costs: drugs, other medical costs are incorporated but not specified

Indirect costs: not included

Results

Discounting: Both cost and benefits were discounted at 4 %

Comparison strategy: The comparison strategy costs and outcomes are shown below:

Table A.20 Comparison strategy: Total costs and outcomes for a "usual treatment" sequence in the Netherlands, Welsing 2004

Comparison strategy	Cost euro 2003*	Cost NOK 2005	QALYs gained
Usual treatment	13 212	108 000	2.9

*price year was not stated, so 2003 was assumed

Source: Welsing 2004 (46), table 2

The ICERs are shown in table 21 underneath.

Table A.21 ICERs: Etanercept in mono- or combination therapy as 3rd line therapy in a DMARD sequence, compared to "usual treatment" sequence in the Netherlands. Base-case results, Welsing 2004.

Strategy	Incremental		ICER	
	Costs, euro 2003	QALYs	Costs, euro 2003	NOK 2005
etanercept	45 763	0.14	326 879	2 667 000

*price year is not stated, so 2003 is assumed

Source: Welsing 2004 (46), table 2

Since the DMARD sequence used in the model was not well defined, it is hard to determine whether the study has any relevance for the Norwegian setting. The "tumor necrosis factor-blocking agents" referred to in the title and the strategies turn out to be etanercept in monotherapy and in combination with MTX. The lack of clarity in this regard, along with the poor specification of cots and potential offsets blurs the study results and makes comparison extremely difficult.

Sensitivity analysis

The results were only sensitive to simulated changes in drug effectiveness.

D.8 Jobanputra 2002 and Barton 2004

Study background

Jobanputra 2002 (34) and Barton 2004 (47) were cost-utility studies performed in the first round of appraisal of TNF-inhibitors for RA by NICE in the UK.

Patients

Patients with RA

Intervention and comparison

Intervention: Etanercept with or without MTX in the 3rd position in a UK DMARD sequence (see below).

Comparison: UK DMARD sequence:

1. Sulphasalazine (SSZ)
2. Methotrexate (MTX)
3. Gold (GST)
4. Azathioprine (AZA)
5. Penicillamine (D-Pen)
6. Hydroxychloroquine (HCQ)
7. Leflunomide (LEF)
8. Cyclosporine (CyA)
9. MTX+ CyA (Barton only)
10. Palliation (Barton only)

Study perspective, time horizon and model type

Both studies had a health service perspective, the time horizon was lifetime and the model was of the discrete event simulation type.

Efficacy data and modelled outcomes

The trials underlying the studies are shown in the table below:

Table A.22 Efficacy data: Etanercept (+MTX), Jobanputra 2002 and Barton 2004

Study	Therapy	Study type	Duration	Quality*
Moreland 1996 (12)	Etanercept	RCT	3 months	Medium
Moreland 1997 (13)	Etanercept	RCT	3 months	Medium
Moreland 1999 (14)	Etanercept	RCT	6 months	High
Weinblatt 1999 (15)	etanercept + MTX	RCT	24 weeks	Medium
Bathon 2000 (48)	Etanercept	RCT	1 year	High
Genovese 2000 (49)	Etanercept	RCT	2 years	na
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
Lipsky 2000 (ATTRACT) (22)	infliximab + MTX	RCT	54 weeks	High
Elliott 1994 ((23))	infliximab	RCT	4 weeks	Medium
Kavanaugh 2000 ((24))	infliximab + MTX	RCT	24 weeks	Medium

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), na=not applicable
Sources: Jobanputra 2002, (34) Barton 2004 (47) and Arentz-Hansen 2006 (2), tables 7 and 9

The modelling of HAQ progression was more sophisticated in the Barton 2004 study than in Jobanputra 2002. As in the later Chen 2006 analysis, HAQ was reduced when a patient responded to a DMARD and, conversely, increased when it had to be quit. HAQ was also reduced upon joint replacement surgery.

HRQoL: In Jobanputra 2002, HRQoL was linked to HAQ based on Australian data suggesting a conversion rate of 0,2, such that:

HRQoL =0,2 x HAQ

In Barton 2004, and the later Chen 2006, this formula was updated to:

HRQoL=0,862-0,327 x HAQ

This implied a higher payoff in terms of HRQoL (and therefore QALYs) in Barton 2004 compared to Jobanputra 2002. Both studies assumed an increase and reduction in HRQoL upon respectively starting and quitting a DMARD, but did not specify the level.

Mortality: No relationship was assumed between mortality and HAQ score in Jobanputra, but this had changed in Barton, where relative mortality risk was expected to be associated to HAQ (relative mortality risk=1.33^{HAQ}).

Costs

Direct costs: Direct costs included drugs, monitoring and hospital visits, while Barton 2004 also included costs for joint replacement. (A one-off cost of GBP 5000 was applied at the time of the joint replacement.)

Indirect costs: Indirect costs were not incorporated.

Results

Comparison strategy: The results of the comparison strategy strategies were not presented[2].

Discounting: Costs were discounted at 6% and benefits at 1,5% following NICE guidelines.

Table A.23 ICERs: Etanercept (+MTX) compared to a standard DMARD sequence in the UK. Base-case results from the BPM and BRAM models,

Strategy	Incremental		ICER	
	Cost, GBP	QALYs	GBP 2000	NOK 2005
etanercept, Jobanputra 2002 (34)	19 573	0,24	83 095	1 207 000
etanercept, Barton 2004 (47)	25 257	0,43	59 289	861 000
infliximab, Jobanputra 2002 (34)	14 725	0,13	115 937	1 684 000
infliximab, Barton 2004 (47)	18 957	0,23	81 583	1 185 000

Source: Jobanputra 2002 (34), table 30 and Barton 2004 (47), table 13

[2] The comparison strategy results were presented in Jobanputra 2002, but were discounted to the strart of the programme rather than the point of divergence. ICERs were reported for both versions, but the latter was considered more robust.

The QALY gains in the Barton study were significantly higher than in Jobanputra, although the same underlying trials were used, which the authors ascribe to "improved data sources". (The change in HRQoL over HAQ was higher in the later version of the model). The inclusion of morality effects in Barton will also have increased the total benefits brought about by the TNF-strategies. The effects on joint replacement however, were uncertain since little evidence was available with regard to the association between DMARD use and the incidence of such type of surgery.

Sensitivity analysis

Jobanputra 2002: The results were sensitive to changes in assumptions about treatment effects on utility and HAQ, but not to changes in standardised mortality rate.

Barton 2004: The results were sensitive to assumptions about HAQ progression while on treatment, but not to assumptions about costs of joint replacement.

D.9 Kobelt 2003

Study background

Kobelt 2003 (50) was a cost-utility study sponsored by Schering-Plough that modelled results for both Sweden and the UK,

Patients

The study included RA patients with advanced disease, not adequately controlled on DMARDs (including MTX). The ATTRACT trial that was used for efficacy data input involved patients who had active RA despite MTX therapy.

Intervention and comparison

Intervention: infliximab + MTX

Comparison: MTX alone

No DMARD sequences reflecting clinical practice in the two countries were described.

Study perspective, time horizon and model type

The study perspective was societal. The Markov model had 1-year cycle lengths and extrapolated data for 10 years.

Efficacy data and modelled outcomes

The model utilised the same underlying trial data for both Sweden and the UK, but separate observational and resource-use studies: the Lund Cohort and ERAS, respectively.

Table A.24 Efficacy data: Infliximab + MTX, Kobelt 2003

Study	Therapy	Study type	Duration	Quality*
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
Lipsky 2000 (ATTRACT) (22)	infliximab + MTX	RCT	54 weeks	High
Lund Cohort Study (early RA), Lindqvist 2002 (51)	various	OBS	10 years	na
Early RA Study (ERAS), UK Young 2000 (52)	various	OBS	9 years	na

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), na=not applicable
Sources: Kobelt 2003 and Arentz-Hansen 2006 (2), table 9

HRQoL: The relationship between HAQ and HRQoL was based on the two observational studies mentioned above, both of which used EQ-5D, and which have also been described in an earlier Kobelt study (53). The HRQoL weights – or utilities – by HAQ group are broadly similar between the two countries, except for the HAQ bracket between 1.1 and 1.6. In this group, UK patients are slightly worse off than their Swedish counterparts and would therefore achieve a relative higher HRQoL gain with response, under otherwise equal conditions.

Table A.25 HRQoL by HAQ group in Sweden and the UK

HAQ group	HRQoL-weights	
	Sweden	UK
<0.6	0.73	0.75
0.6 < 1.1	0.64	0.65
1.1 < 1.6	0.61	0.47
1.6 < 2.1	0.42	0.44
2.1 < 2.6	0.24	0.26
2.6-3	0.22	0.25

Source: Kobelt 2002 (53), table 3

Mortality: Separate age and gender-specific mortality risks were used for the two countries, but no relationship with HAQ was established.

Costs

Direct costs: Direct costs comprised the usual drugs and health services cots, including hospitalisation and surgery costs. Cost data were obtained from the different observational studies, and were adjusted for trial compliance (88.75 % of possible treatment months), a method which seems not to have been attempted in other studies reviewed here.

Indirect costs: These were calculated on the basis of the expected productivity loss associated with each health state.

Results

Discounting: Different discount rates were applied to the two countries: In Sweden, both costs and outcomes were discounted at 3 % whereas the NICE norm was followed in the UK with outcomes discounted at 1.5 % and costs at 6 %. Under otherwise equal conditions, this would result in ICERs in the UK being lower than in Sweden.

Comparison strategy: The costs and outcomes related to the comparison strategy (MTX) are shown below:

Table A.26 Comparison strategy: Total costs and outcomes for MTX strategies in Sweden and the UK, Kobelt 2003

Comparison strategy	**Costs, SEK/GBP 2001**		**Costs, NOK 2005**		**QALYs gained**
	Direct	**Total**	**Direct**	**Total**	
MTX, Sweden	191 857	1 121 476	177 000	1 033 000	4.4
MTX, UK	12 666	36 859	174 000	505 000	3.7

Source: Kobelt 2003 (50), table 4

The direct costs in both countries were relatively similar, but the difference in costs resulting from productivity loss was huge. This means that total costs in the UK were about 50% of those in Sweden.

ICER results based on 1 year of treatment (2 year results were also presented in the study) are shown in table A.27 below.

Table A.27 ICER: Infliximab + MTX compared to MTX in Sweden and the UK. Base-case results, Kobelt 2003.

Strategy	Incremental			ICER (based on direct costs)	
	Costs, SEK/GBP 2001		QALYs	SEK/GBP 2001	NOK 2005
	Direct	Total			
infliximab + MTX, Sweden	65 969	8 031	0,25	266 000	231 000
Infliximab + MTX, UK	7 651	6 440	0,29	25 700	333 000

Source: Kobelt 2003 (50), table 4

It is not necessarily surprising that incremental costs differ in the two countries given varying unit costs. Variations on the benefit side may be more interesting: Both infliximab + MTX as well as MTX monotherapy produced more QALYs in Sweden than in the UK, but the increment was lower in the former. This exemplifies the potential caveats in translating results from one clinical practice context to another.

It would have been more appropriate if the intervention and comparison strategies had been sequences rather than two regimens. In the real world, it is likely that MTX non-responders are given another DMARD which would mean that their HAQ progression, and work capacity, would be better than the those in the model. In s review of economic evaluations of TNF-inhibitors, Bansback 2005 (36) criticised Kobelt for combining results from the ATTRACT trial, which included patients with severe RA and an average disease duration 8 years, with the early RA studies Lund and ERAS. (<1 year disease duration.

Sensitivity analysis

The results were sensitive to inclusion of indirect costs, HAQ progression while on treatment and the discount rate

D.10 Barbieri 2005

Study background

Barbieri 2005 (54) was a cost-utility study from the UK, partly funded by Schering-Plough through a research fellowship.

Patients

The study incorporated severe RA patients, inadequately controlled on DMARD treatments and resistant to MTX.

Intervention and comparison

Intervention: Infliximab + MTX

Comparison: MTX alone

No DMARD sequences reflecting clinical practice were described.

Study perspective, time horizon and model type

The study perspective was that of the health services, the time horizon lifetime and the model was of the Markov type with 6-month cycle lengths.

Efficacy data and modelled outcomes

Efficacy data were drawn from the ATTRACT trial and the ARAMIS observational study (data from beyond the first year of treatment).

Table A.28 Efficacy data: Infliximab + MTX, Barbieri 2005

Study	Therapy	Study type	Duration	Quality*
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
ARAMIS (55)	various	OBS	17 085 patent years	na

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), na=not applicable
Sources: Barbieri 2005 (54) and Arentz-Hansen 2006 (2), table 9

The patients' prognosis upon non-response to MTX was better than in the Kobelt 2003 (50) model, given that treatment benefit from other DMARDs were incorporated.

HRQoL: HRQoL-data, based on the VAS, were drawn the above sources,

Mortality: Mortality risk was expected to rise with HAQ, by a factor of 1.77 for each unit increase.

Costs

Direct costs: As opposed to the contemporary Chen et al. study (56), the model included hospitalisation in the direct costs segment.

Indirect costs: Indirect costs were not calculated.

Results

Discounting: Costs were discounted at 6 % at benefits at 1.5 %, in accordance with NICE recommendations.

Comparison strategy: Comparison strategy data were not provided for the lifetime strategy.

The ICER in table 45 was within the bounds of the NICE cost-effectiveness threshold (GBP 30 000), and infliximab + MTX is deemed as a cost-effective intervention for MTX-resistant patients. However, the sensitivity analysis showed that if the discount rate for benefits had been set identical to that of the costs, the ICER would have been GBP 34 680 .(NOK 503 000).

Table A.29 ICERs: Infliximab+ MTX compared to MTX in the UK. Base-case results, Barbieri 2005

Strategy	Incremental		ICER 2000	
	Cost, GBP 2000	QALYs	GBP 2000	NOK 2005
infliximab + MTX	30 147	1.26	23 936	347 000

Source: Barbieri 2005 (54), table IX

Although treatment with other DMARDs was assumed beyond the trial period, no sequence representing clinical proactive was defined. The patient population was described as those with severe RA, but we do not know at which point in the therapy sequence the intervention is to take place (only that it takes place after MTX failure).

Sensitivity analysis

The results did not change substantially whehn sensitivity analyses on assumptions about resource utilisation, mortality risk and the odds ratio of HAQ progression were performed.

D.11 Wong 2002

Study background

Wong 2002 (57) was a cost-utility study from the United States.

Patients

The study included patients with active, refractory RA. The authors defined active RA as a combination of synovitis (minimum 6 swollen or tender joints) and certain other symptoms

Intervention and comparison

Intervention: infliximab + MTX

Comparison: MTX alone

Study perspective, time horizon and model type

The study perspective was societal, the time horizon lifetime and the model was of the Markov kind.

Efficacy data and modelled outcomes

The efficacy data used in the model are shown in table A.30:

Table A.30 Efficacy data: Infliximab + MTX, Wong 2002

Study	Therapy	Study type	Duration	Quality*
Maini 1999 (ATTRACT) (21)	infliximab + MTX	RCT	30 weeks	High
ARAMIS (55)	various	OBS	17 085 patient years	na

*assessed in the NOKC review of clinical trials of TNF-inhibitors (Arentz-Hansen 2006) (2), na=not applicable
Sources: Wong 2002 (57) and Arentz-Hansen 2006 (2), table 9

Mortality: Mortality was linked to HAQ with a 1.77 change in mortality risk per unit HAQ change.

HRQoL: QALYs were extracted from trial data which in turn were derived using the VAS.

Costs

Direct costs: Direct costs included the usual healthcare services, but also home-care costs, non-traditional treatments and nursing home care.

Indirect costs; Indirect costs were included. These were estimated for the first year based on a subgroup of patients from the ATTRACT trial. However, the indirect costs arising in subsequent years were simply assumed to be three times the size of direct costs, as suggested in some studies. This assumption was subjected to sensitivity analysis, where indirect costs were set equal to direct costs and to zero.

Results

Discounting: Costs and benefits were both discounted at 3 %.

Comparison strategy: The costs and outcomes brought about by the comparison strategy (MTX) are shown below:

Table A.31 Comparison strategy: Total costs and outcomes for MTX in the US. Wong 2002

Comparison strategy	Costs, USD 1998		Costs, NOK 2005		QALYs Gained
	Direct	Total	Direct	Total	
MTX	84 100	313 200	714 000	2 659 000	9.1

Sources: Wong 2002 (57), table 4

Wong modelled an incremental *direct* cost of USD 8 900, but an increase in *total* cost of only USD 2 600,. The indirect cost offsets bring the ICER down from USD 30 000 (direct costs only) to approximately USD 9 000 (NOK 76 000, 2005).

Table A.32 ICERs: Infliximab + MTX compared to MTX in the UK. Base-case results, Wong 2002

Strategy	Incremental		ICER 2000	
	Direct cost, USD 1998	QALYs	USD 1998	NOK 2005
infliximab + MTX	8 900	0.29	30 690	295 000

Sources: Wong 2002 (57), based on table 4

If indirect costs offsets were included, the ICER would be USD 8 966 (NOK 76 000, 2005)

Sensitivity analysis

A sensitivity analysis was carried out that demonstrates the effect on the results on changes in disease progression, but the robustness of the results was unclear.

E Study quality

	Chen 2006	Bans-back 2005	Coyle 2006	Kobelt 2005	Brennan 2004	Tanno 2006
1. Was a well defined question posed in answerable form?						
1.1 Did the study examine both costs and effects?	+	+	+	+	+	+
1.2 Did the study include comparison of alternatives?	+	+	+	+	+	+
1.3 Was a viewpoint for the analysis stated?	+	+	+	+	+	+
2. Was a comprehensive description of the alternatives given?						
2.1 Were any important alternatives omitted?	+	+	+	+	+	+
2.2 Was a do-nothing alternative considered?	-	-	-	-	-	-
3. Was the effectiveness of the programmes established?						
3.1 Was this done through a randomised, controlled clinical trial?	+	+	+	+	+	+
3.2 Was effectiveness established through an overview of clinical studies?	+	+	-	-	-	-
3.3 Were observational data or assumptions used to establish effectiveness?	+	+	-	-	-	+
4. Were all the important and relevant costs and consequences identified?				+	**?**	+
4.1 Was the range wide enough for the research question at hand?	+	+	+	+	+	+
4.2 Did it cover all relevant viewpoints?	-	-	-	+	+	-
4.3 Were capital costs, as well as operating costs, included?	-	?	-	?	?	?
5. Were costs and consequences measured accurately in appropriate physical units?				+		+
5.1 Were any of the identified items omitted from measurement?	+	+	+	+	+	+
5.2 Were there any special circumstances that made measurement difficult?	+	+	+	+	+	+
6. Were costs and consequences valued credibly?						+
6.1 Were the sources of all values clearly identified?	+	+	+	-	+	+
6.2 Were market values employed for changes in resources gained or depleted?	+	?	?	?	?	?
6.3 Were adjustments made to approximate market values?	?	?	?	?	?	?
6.4 Was the valuation of consequences appropriate for the question posed?	+	+	+	+	+	+
7. Were costs and consequences adjusted for differential timing?						
7.1 Were costs and consequences discounted?	+	+	+	+	+	+
7.2 Was any justification given for the discount rate used?	?	+	+	-	+	+
8. Was an incremental analysis performed?				+	+	
8.1 Were the additional costs compared with the additional effects?	+	+	+	+	+	+
9. Was allowance made for uncertainty in the estimates?				+	+	+
9.1 Were appropriate statistical analyses performed?	+	+	+	+	+	+
9.2 Was justification provided for the ranges of values?	?	?	+	+	+	+
9.3 Were study results sensitive to changes in the values?	-	-	+	-	+	+
10. Did the study results include all issues of concern		+	**?**	+		

to users?						
10.1 Were the conclusions of the analysis based on some overall index or ratio?	+	+	+	+	+	+
10.2 Were the results compared with those of others?	-	-	-	-	-	+
10.3 Did the study discuss the generalisability of the results?	-	-	-	-	-	+
10.4 Did the study take account of other important factors?	+	+	+	+	+	+
10.5 Did the study discuss issues of implementation?	-	-	-	-	-	-
Number of posittives	**21**	**20**	**19**	**17**	**19**	**21**
Total	**28**	**28**	**28**	**28**	**28**	**28**
Percent	**75 %**	**71 %**	**68 %**	**61 %**	**68 %**	**75 %**

	Welsing 2004	Joban-putra 2002	Barton 2004	Kobelt 2003	Barbieri 2005	Wong 2002
1. Was a well defined question posed in answerable form?						
1.1 Did the study examine both costs and effects?	+	+	+	+	+	+
1.2 Did the study include comparison of alternatives?	+	+	+	+	+	+
1.3 Was a viewpoint for the analysis stated?	+	+	+	+	+	+
2. Was a comprehensive description of the alternatives given?						
2.1 Were any important alternatives omitted?	+	+	+	+	+	+
2.2 Was a do-nothing alternative considered?	-	-	-	-	-	-
3. Was the effectiveness of the programmes established?						
3.1 Was this done through a randomised, controlled clinical trial?	+	+	+	+	+	+
3.2 Was effectiveness established through an overview of clinical studies?	-	+	+	-	-	-
3.3 Were observational data or assumptions used to establish effectiveness?	+	+	+	+	+	+
4. Were all the important and relevant costs and consequences identified?	**+**	**+**	**+**	**+**		
4.1 Was the range wide enough for the research question at hand?	+	+	+	+	+	+
4.2 Did it cover all relevant viewpoints?	-	-	-	+	-	+
4.3 Were capital costs, as well as operating costs, included?	?	?	?	?	?	?
5. Were costs and consequences measured accurately in appropriate physical units?		**+**	**+**	**+**		
5.1 Were any of the identified items omitted from measurement?	+	-	+	+	+	+
5.2 Were there any special circumstances that made measurement difficult?	+	+	+	+	+	+
6. Were costs and consequences valued credibly?	**+**	**+**	**+**	**?**		
6.1 Were the sources of all values clearly identified?	+	+	+	?	+	
6.2 Were market values employed for changes in resources gained or depleted?	?	?	?	?	?	?
6.3 Were adjustments made to approximate market values?	?	?	?	?	?	?
6.4 Was the valuation of consequences appropriate for the question posed?	+	+	+	+	+	+
7. Were costs and consequences adjusted for differential timing?						
7.1 Were costs and consequences discounted?	+	+	+	+	+	+
7.2 Was any justification given for the discount rate used?	-	+	+	+	+	-

8. Was an incremental analysis performed?			+			
8.1 Were the additional costs compared with the additional effects?	+	+	+	+	+	+
9. Was allowance made for uncertainty in the estimates?	+	+	+	+		
9.1 Were appropriate statistical analyses performed?	+	+	+	+	+	+
9.2 Was justification provided for the ranges of values?	+	+	+	+	+	+
9.3 Were study results sensitive to changes in the values?	+	+	+	+	+	+
10. Did the study results include all issues of concern to users?	**?**		+			
10.1 Were the conclusions of the analysis based on some overall index or ratio?	+	+	+	+	+	+
10.2 Were the results compared with those of others?	-	-	+	-	-	-
10.3 Did the study discuss the generalisability of the results?	-	-	+	-	-	-
10.4 Did the study take account of other important factors?	-	-	-	-	-	-
10.5 Did the study discuss issues of implementation?	-	-	-	-	-	-
Number of positives	**17**	**18**	**21**	**18**	**17**	**18**
Total	**28**	**28**	**28**	**28**	**28**	**28**
Percent	**61 %**	**64 %**	**75 %**	**64 %**	**61 %**	**64 %**

Checklist based on Drummond et al. 1997 (58)

F NOR-DMARD analysis (in Norwegian)

Analyser fra NOR-DMARD registeret, juni 2006.

Marte Schrumpf Heiberg/Tore K. Kvien, Revmatologisk avdeling, Diakomhjemmet Sykehus, Oslo

Bakgrunn

Randomiserte kontrollerte undersøkelser er gullstandard for å måle behandlingseffekt.
Den eksterne validiteten begrenses imidlertid av strenge inklusjons- og eksklusjonskriterier. Resultater fra longitudinelle observasjonsstudier kan komplementere kunnskapen om bruk og effekt av behandling i daglig klinisk praksis. Kunnskapssenteret er i ferd med å utarbeide en helseøkonomisk rapport om bruk av tumor nekrose faktor (TNF)-alfa antagonister i behandlingen av revmatoid artritt (RA). Målsettingen med de følgende analysene er å frembringe data fra NOR-DMARD registeret som kan være til nytte for kunnskapssenteret i utarbeidelsen av den helseøkonomiske rapporten.

Materiale og metode

NOR-DMARD registeret
NOR-DMARD studien er en longitudinell observasjonsstudie som gjennomføres på 5 revmatologiske avdelinger i Norge (Tromsø, Trondheim, Lillehammer, Drammen og Diakonhjemmet i Oslo). Pasienter (>18 år) med inflammatoriske leddsykdommer inkluderes når de begynner med ny sykdomsmodifiserende behandling (DMARD (disease modifying anti-rheumatic drug)). Hver "case" representerer et medikamentregime. Inklusjonen startet i desember 2000 og pågår stadig. Pasientene følges regelmessig (comparison strategy, 3 mndr, 6 mndr, 12 mndr, årlig) med registrering av ulike mål på sykdomsaktivitet og helsestatus. Per 01.01.06 var 5281 medikamentregimer inkludert i registeret.

Pasienter
For de aktuelle analysene har vi analysert data for pasienter med RA som ble inkludert før 01.04.05 (mulighet for 6 måneders oppfølging). Vi har sammenliknet følgende regimer: Anti-TNF monoterapi (n=246) og anti-TNF i kombinasjon med methotrexat (MTX) (n=439) versus MTX monoterapi (n=1063) og MTX i kombinasjon med andre DMARDs (MTX combo) (n=331).

Endepunkter
Primære endepunkter var 6 måneders endring i SF-6D score og M-HAQ. SF-6D er en utility score (1) som beregnes på bakgrunn av det generiske instrumentet SF-36 som måler helserelatert livskvalitet. Skalaen går fra 0 (død) til 1(perfekt helse). M-HAQ (2) er en modifisert versjon av HAQ, som måler fysisk funksjon, og har en skala fra 1 (god funksjon) til 4 (dårlig funksjon). Sekundære endepunkter var 6 måneders endring for andre relevante sykdomsvariabler (f.eks DAS-28 og VAS skalaer), "medikamentoverlevelse" og undersøkelse av data vedrørende arbeidssituasjon og

bruk av helsetjenester. DAS-28 er en "disease activity score" som er beregnet på bakgrunn av antall hovne og ømme ledd (av 28 ledd), SR og pasientens globale vurdering av egen helse på en visuell analog skala (VAS) fra 0(bra) - 100(dårlig). VAS skalaer (0-100) er også benyttet til å måle pasientens selvrapporterte tretthet, leddsmerte og undersøkers globale vurdering.

Statistikk

Sammenlikninger av 6 måneders endringer mellom gruppene ble gjort parvis (hhv TNF mono og TNF + MTX versus MTX mono og MTX combo). Ujusterte endringer ble sammenliknet med two-sample t-test. For å justere for "channeling bias"/"confounding by indication" benyttet vi oss av propensity modellering (3), der propensity scorer ble beregnet for hver sammenlikning. I en logistisk regresjonsanalyse identifiseres comparison strategyvariabler som predikerer hvilken behandling pasientene får. Kun statistisk signifikante variabler ble beholdt i modellen. Alder og kjønn ble beholdt uavhengig av statistisk signifikans for å balansere gruppene ift disse. For hver sammenlikning får den enkelte pasient en score som indikerer sannsynligheten for at denne pasienten mottar den ene behandlingen versus den andre. Endringene ble deretter sammenliknet i en covarians-analyse (ANCOVA) med justering for propensity score og comparison strategy verdien for den avhengige variablen. Ujusterte rater for "medikamentoverlevelse" ble undersøkt i Kaplan-Meier analyser, med log rank tester for parvise sammenlikninger. Risiko for å avslutte terapi ble sammenliknet med Cox Regresjonsanalyser med justering for propensity score. Kun deskriptive analyser ble gjort vedr arbeidssituasjon og bruk av helsetjenester. Alle analyser ble gjort med "last observation carried forward" (LOCF). Signifikansnivå ble satt til 5%.

Resultater

Comparison strategy

Demografiske variabler og gjennomsnittlig sykdomsaktivitet - og alvorlighet ved comparison strategy er vist for de ulike gruppene i tabell 1 (kontinuerlige variabler) og tabell 2-5 (kategoriske variabler).

Generelt har pasienter som mottar TNF-alfa antagonister mer aktiv og alvorlig sykdom, lengre sykdomsvarighet og brukt flere DMARDs tidligere enn pasienter som mottar MTX (mono eller i kombinasjon med andre DMARDs)

Fordelingen av ulike DMARDs innen hver gruppe sees i tabell 6

		anti tnf	anti tnf + mtx	mtx	mtx combo
Alder	N	244	437	1060	328
	Mean	55,60	51,70	56,75	53,54
	Std. Deviation	12,82	13,02	13,49	14,32
Sykdomsvarighet	N	244	435	1057	325
	Mean	12,54	10,40	5,88	7,21
	Std. Deviation	9,29	8,92	8,53	8,00
Antall tidligere DMARDs	N	246	439	1063	331
	Mean	4,47	3,63	1,12	1,83
	Std. Deviation	2,22	2,48	1,84	1,51
Antall hovne ledd	N	243	435	1059	328
	Mean	8,84	9,09	7,95	8,26
	Std. Deviation	6,25	5,96	5,93	5,65
Antall ømme ledd	N	242	433	1054	328
	Mean	10,45	9,47	8,52	8,33
	Std. Deviation	7,63	7,16	6,84	6,92
SR	N	230	421	999	318
	Mean	32,40	33,45	30,25	28,24
	Std. Deviation	23,70	25,56	23,38	23,40
CRP	N	239	419	1008	317
	Mean	27,01	33,18	24,98	26,06
	Std. Deviation	28,29	38,40	28,66	31,75
M-HAQ score	N	243	429	1051	327
	Mean	1,92	1,86	1,71	1,68
	Std. Deviation	,57	,50	,52	,52
DAS-28	N	226	406	977	314
	Mean	5,52	5,38	5,08	5,00
	Std. Deviation	1,29	1,35	1,31	1,41
SF6DV1	N	222	391	897	286
	Mean	,55	,56	,56	,57
	Std. Deviation	,10	,10	,10	,10
VAS smerte	N	244	429	1048	329
	Mean	53,34	53,21	47,75	48,36
	Std. Deviation	24,81	23,31	23,86	23,45
VAS fatigue	N	243	428	1045	328
	Mean	56,91	54,86	44,98	49,91
	Std. Deviation	26,89	26,38	28,63	28,08
VAS pasientens globale vurd.	N	244	428	1045	329
	Mean	57,31	57,76	50,25	52,55
	Std. Deviation	24,27	22,11	23,97	23,19
VAS undersøkers globale vurd.	N	244	432	1050	329
	Mean	48,20	49,20	41,41	43,94
	Std. Deviation	20,08	19,18	17,10	17,02

Tabell 1

			Kjønn		
			Mann	Kvinne	Total
Treatment group	anti tnf	Count	50	196	246
		% within Treatment group	20,3%	79,7%	100,0%
	anti tnf + mtx	Count	128	311	439
		% within Treatment group	29,2%	70,8%	100,0%
	mtx	Count	282	779	1061
		% within Treatment group	26,6%	73,4%	100,0%
	mtx combo	Count	96	235	331
		% within Treatment group	29,0%	71,0%	100,0%
Total		Count	556	1521	2077
		% within Treatment group	26,8%	73,2%	100,0%

Tabell 2. Kjønnsfordeling i gruppene.

			Revma faktor		
			Nei	Ja	Total
Treatment group	anti tnf	Count	51	193	244
		% within Treatment group	20,9%	79,1%	100,0%
	anti tnf + mtx	Count	105	332	437
		% within Treatment group	24,0%	76,0%	100,0%
	mtx	Count	418	639	1057
		% within Treatment group	39,5%	60,5%	100,0%
	mtx combo	Count	113	217	330
		% within Treatment group	34,2%	65,8%	100,0%
Total		Count	687	1381	2068
		% within Treatment group	33,2%	66,8%	100,0%

Tabell 3. Andel revmatoid faktor positive pasienter.

			Erosiv sykdom		
			Nei	Ja	Total
Treatment group	anti tnf	Count	47	193	240
		% within Treatment group	19,6%	80,4%	100,0%
	anti tnf + mtx	Count	117	316	433
		% within Treatment group	27,0%	73,0%	100,0%
	mtx	Count	614	424	1038
		% within Treatment group	59,2%	40,8%	100,0%
	mtx combo	Count	149	180	329
		% within Treatment group	45,3%	54,7%	100,0%
Total		Count	927	1113	2040
		% within Treatment group	45,4%	54,6%	100,0%

Tabell 4. Andel pasienter med erosiv sykdom.

			steroider		
			Nei	Ja	Total
Treatment group	anti tnf	Count	80	166	246
		% within Treatment group	32,5%	67,5%	100,0%
	anti tnf + mtx	Count	183	256	439
		% within Treatment group	41,7%	58,3%	100,0%
	mtx	Count	509	554	1063
		% within Treatment group	47,9%	52,1%	100,0%
	mtx combo	Count	162	169	331
		% within Treatment group	48,9%	51,1%	100,0%
Total		Count	934	1145	2079
		% within Treatment group	44,9%	55,1%	100,0%

Tabell 5. Andel pasienter som bruker steroider ved comparison strategy.

			Treatment regimen											
			etanercept	infliximab	mtx	mtx+am	mtx+am+sulf	mtx+sulf	mtx+cyclo	mtx+etanercept	mtx+infliximab	mtx+leflunomide	adalimumab	
Treatment group	anti tnf	Count	127	29	0	0	0	0	0	0	0	0	90	
		% within Treatment gr	51,6%	11,8%	,0%	,0%	,0%	,0%	,0%	,0%	,0%	,0%	36,6%	,
	anti tnf + mt	Count	0	0	0	0	0	0	0	153	161	0	0	1
		% within Treatment gr	,0%	,0%	,0%	,0%	,0%	,0%	,0%	34,9%	36,7%	,0%	,0%	28,
	mtx	Count	0	0	1063	0	0	0	0	0	0	0	0	
		% within Treatment gr	,0%	,0%	00,0%	,0%	,0%	,0%	,0%	,0%	,0%	,0%	,0%	,
	mtx combo	Count	0	0	0	73	85	143	2	0	0	28	0	
		% within Treatment gr	,0%	,0%	,0%	22,1%	25,7%	43,2%	,6%	,0%	,0%	8,5%	,0%	,
Total		Count	127	28	1063	73	85	143	2	153	162	28	90	1
		% within Treatment gr	6,1%	1,3%	51,1%	3,5%	4,1%	6,9%	,1%	7,4%	7,8%	1,3%	4,3%	6,

Tabell 5. Fordeling av DMARDs innen hver gruppe

<u>Propensity scorer</u>

Følgende variabler ble vurdert i univariate analyser for inklusjon i den multivariate analysen:

Alder, kjønn, sykdomsvarighet, antall tidligere DMARDs, erosiv sykdom, revmatoid faktor, VAS pasientens globale vurdering, VAS smerte, VAS fatigue VAS undersøkers globale vurdering, antall hovne ledd, antall ømme ledd, SR, CRP, M-HAQ score.

For sammenlikninger med anti-TNF monoterapi ble tidligere bivirkninger av MTX tatt med i modellen.

Logistiske regresjonsanalyser resulterte i propensity-modeller som vist i tabellene nedenfor (5a-8a). En høy propensity score angir større sjanse for å motta regimer med anti-TNF versus konvensjonelle DMARDs. I tabellene 5b-8b vises andelen i hver gruppe pr propensity-kvartil.

TNF monoterapi versus MTX monoterapi

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
								Lower	Uppe
Step 1[a]	Alder	-,018	,007	5,800	1	,016	,983	,968	,9
	Kjønn	-,113	,227	,246	1	,620	,893	,572	1,3
	Antall tidligere DMARDs	,429	,044	93,077	1	,000	1,535	1,407	1,6
	Erosiv sykdom	,678	,216	9,860	1	,002	1,970	1,290	3,0
	M-HAQ score	,420	,182	5,318	1	,021	1,522	1,065	2,1
	Tidl MTX- bivirkninger	1,685	,209	64,784	1	,000	5,393	3,578	8,1
	VAS undersøkers globale vurd.	,009	,006	2,732	1	,098	1,009	,998	1,0
	Constant	-3,455	,523	43,609	1	,000	,032		

a. Variable(s) entered on step 1: Age, Sex, numbdmar, EroDis, V1MHAQsc, MTXtolerability, V1VASTot.

Tabell 5a

tnf mono vs mtx * Predicted probability (Banded) Crosstabulation

			Predicted probability (Banded)				
			1	2	3	4	Total
tnf mono vs mtx	mtx	Count	309	308	274	123	101
		% within tnf mono vs mtx	30,5%	30,4%	27,0%	12,1%	100,0
	tnf mono	Count	4	5	38	190	23
		% within tnf mono vs mtx	1,7%	2,1%	16,0%	80,2%	100,0
Total		Count	313	313	312	313	125
		% within tnf mono vs mtx	25,0%	25,0%	24,9%	25,0%	100,0

Tabell 5b

TNF monoterapi versus MTX + andre DMARDs

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Alder	-,006	,009	,455	1	,500	,994	,977	1,0
	Kjønn	,303	,273	1,228	1	,268	1,354	,792	2,3
	antall tidligere DMARDs	,599	,067	80,253	1	,000	1,820	1,597	2,0
	VAS smerte	-,019	,006	9,186	1	,002	,981	,968	,9
	M-HAQ score	,929	,273	11,546	1	,001	2,532	1,482	4,3
	Tidl. MTX- bivirkninger	2,496	,314	63,236	1	,000	12,137	6,560	22,4
	Constant	-3,210	,622	26,640	1	,000	,040		

a. Variable(s) entered on step 1: Age, Sex, numbdmar, V1JntPn, V1MHAQsc, MTXtolerability.

Tabell 6a

tnf mono vs mtx+DMARD * Predicted probability (Banded) Crosstabulation

			Predicted probability (Banded)				
			1	2	3	4	Total
tnf mono vs mtx+DMARD	mtx + dmard	Count	132	119	56	14	3
		% within tnf mono vs mtx+DMARD	41,1%	37,1%	17,4%	4,4%	100,0
	tnf mono	Count	9	23	85	128	2
		% within tnf mono vs mtx+DMARD	3,7%	9,4%	34,7%	52,2%	100,0
Total		Count	141	142	141	142	5
		% within tnf mono vs mtx+DMARD	24,9%	25,1%	24,9%	25,1%	100,0

Tabell 6b

TNF + MTX versus MTX monoterapi

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Alder	-,043	,006	56,130	1	,000	,958	,947	,9
	Kjønn	-,628	,165	14,478	1	,000	,534	,386	,7
	Antall tidligere DMARDs	,458	,039	140,932	1	,000	1,580	1,465	1,7
	Erosiv sykdom	,759	,166	21,006	1	,000	2,136	1,544	2,9
	Revmatoid faktor	,378	,167	5,104	1	,024	1,459	1,051	2,0
	VAS fatigue	,009	,003	11,138	1	,001	1,009	1,004	1,0
	VAS undersøkers globale vurd.	,013	,004	9,376	1	,002	1,014	1,005	1,0
	CRP	,009	,002	15,340	1	,000	1,009	1,005	1,0
	Constant	-1,161	,391	8,813	1	,003	,313		

a. Variable(s) entered on step 1: Age, Sex, numbdmar, EroDis, RhmFact, V1Fatig, V1VASTot, V1CRP.

Tabell 7a

tnf+mtx vs mtx * Predicted probability (Banded) Crosstabulation

			Predicted probability (Banded)				
			1	2	3	4	Total
tnf+mtx vs mtx	mtx	Count	331	305	217	102	95
		% within tnf+mtx vs mtx	34,7%	31,9%	22,7%	10,7%	100,0
	tnf+mtx	Count	6	32	119	235	39
		% within tnf+mtx vs mtx	1,5%	8,2%	30,4%	59,9%	100,0
Total		Count	337	337	336	337	134
		% within tnf+mtx vs mtx	25,0%	25,0%	24,9%	25,0%	100,0

Tabell 7b

TNF + MTX versus MTX + DMARDs

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95,0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Alder	-,032	,007	21,211	1	,000	,969	,956	,9
	Kjønn	-,532	,192	7,666	1	,006	,588	,403	,8
	Antall tidligere DMARDs	,464	,053	75,526	1	,000	1,590	1,432	1,7
	Erosiv sykdom	,484	,187	6,724	1	,010	1,623	1,125	2,3
	SR	,011	,004	8,651	1	,003	1,011	1,004	1,0
	M-HAQ score	,469	,177	7,043	1	,008	1,599	1,131	2,2
	Constant	-,369	,459	,645	1	,422	,692		

a. Variable(s) entered on step 1: Age, Sex, numbdmar, EroDis, V1SR, V1MHAQsc.

Tabell 8a

tnf+mtx vs mtx+DMARD * Predicted probability (Banded) Crosstabulation

			Predicted probability (Banded)				
			1	2	3	4	Total
tnf+mtx vs mtx+DMARD	mtx + dmard	Count	135	88	59	26	3
		% within tnf+mtx vs mtx+DMARD	43,8%	28,6%	19,2%	8,4%	100,0
	tnf+mtx	Count	42	90	119	151	4
		% within tnf+mtx vs mtx+DMARD	10,4%	22,4%	29,6%	37,6%	100,0
Total		Count	177	178	178	177	7
		% within tnf+mtx vs mtx+DMARD	24,9%	25,1%	25,1%	24,9%	100,0

Tabell 8b

6 måneders endringer, parvise sammenlikninger

Ujusterte endringer

TNF monoterapi versus MTX monoterapi

Group Statistics

	tnf mono vs mtx	N	Mean	Std. Deviation	p-value
SF-6D	mtx	730	,05	,10	,00
	tnf mono	174	,02	,11	
M-HAQ	mtx	984	-,19	,48	,10
	tnf mono	216	-,13	,49	
DAS-28	mtx	875	-1,18	1,53	,09
	tnf mono	182	-,97	1,53	
SR	mtx	902	-10,11	20,28	,00
	tnf mono	188	-4,14	17,98	
CRP	mtx	909	-10,63	30,30	,00
	tnf mono	207	-3,76	31,11	
VAS pain	mtx	980	-12,13	25,61	,49
	tnf mono	217	-10,76	29,59	
VAS fatigue	mtx	977	-3,63	28,52	,02
	tnf mono	217	-8,78	28,84	
VAS patient	mtx	979	-11,89	26,08	,90
	tnf mono	217	-11,65	30,94	
VAS investigator	mtx	984	-17,56	20,99	,68
	tnf mono	217	-18,22	23,41	

Tabell 9

TNF monoterapi versus MTX + andre DMARDs

Group Statistics

	tnf mono vs mtx+DMARD	N	Mean	Std. Deviation	p-value
SF-6D	mtx + dmard	241	,04	,10	,05
	tnf mono	174	,02	,11	
M-HAQ	mtx + dmard	304	-,17	,47	,38
	tnf mono	216	-,13	,49	
DAS-28	mtx + dmard	284	-,85	1,44	,37
	tnf mono	182	-,97	1,53	

SR	mtx + dmard	293	-6,72	17,69	,12
	tnf mono	188	-4,14	17,98	
CRP	mtx + dmard	284	-9,76	29,04	,03
	tnf mono	207	-3,76	31,11	
VAS pain	mtx + dmard	304	-10,87	25,82	,97
	tnf mono	217	-10,76	29,59	
VAS fatigue	mtx + dmard	303	-6,87	27,56	,45
	tnf mono	217	-8,78	28,84	
VAS patient	mtx + dmard	304	-12,51	26,18	,73
	tnf mono	217	-11,65	30,94	
VAS investigator	mtx + dmard	308	-15,34	20,91	,14
	tnf mono	217	-18,22	23,41	

Tabell 10

TNF + MTX versus MTX monoterapi

	TNF + MTX vs mtx	N	Mean	Std. Deviation	p-value
SF-6D	mtx	730	,05	,10	,10
	TNF + MTX	319	,06	,12	
M-HAQ	mtx	984	-,19	,48	,00
	TNF + MTX	393	-,28	,52	
DAS-28	mtx	875	-1,18	1,53	,00
	TNF + MTX	355	-1,52	1,51	
SR	mtx	902	-10,11	20,28	,25
	TNF + MTX	375	-11,60	22,46	
CRP	mtx	909	-10,63	30,30	,00
	TNF + MTX	373	-17,58	34,07	
VAS pain	mtx	980	-12,13	25,61	,00
	TNF + MTX	394	-19,06	28,70	
VAS fatigue	mtx	977	-3,63	28,52	,00
	TNF + MTX	393	-13,33	29,17	
VAS patient	mtx	979	-11,89	26,08	,00
	TNF + MTX	394	-19,91	27,25	
VAS investigator	mtx	984	-17,56	20,99	,00
	TNF + MTX	397	-23,23	22,90	

Tabell 11

TNF + MTX versus MTX + DMARDs

Group Statistics

	TNF + MTX vs mtx+DMARD	N	Mean	Std. Deviation	p-value
SF-6D	mtx + dmard	241	,04	,10	,08
	TNF + MTX	319	,06	,12	
M-HAQ	mtx + dmard	304	-,17	,47	,00
	TNF + MTX	393	-,28	,52	
DAS-28	mtx + dmard	284	-,85	1,44	,00
	TNF + MTX	355	-1,52	1,51	

SR	mtx + dmard	293	-6,72	17,69	,00
	TNF + MTX	375	-11,60	22,46	
CRP	mtx + dmard	284	-9,76	29,04	,00
	TNF + MTX	373	-17,58	34,07	
VAS pain	mtx + dmard	304	-10,87	25,82	,00
	TNF + MTX	394	-19,06	28,70	
VAS fatigue	mtx + dmard	303	-6,87	27,56	,00
	TNF + MTX	393	-13,33	29,17	
VAS patient	mtx + dmard	304	-12,51	26,18	,00
	TNF + MTX	394	-19,91	27,25	
VAS investigator	mtx + dmard	308	-15,34	20,91	,00
	TNF + MTX	397	-23,23	22,90	

Tabell 12

Endringer justert for propensityscore og comparison strategy verdi for den avhengige variabelen

Justerte endringer (estimated marginal means) er beregnet på bakgrunn av covariatene i modellen (ANCOVA).
I tabellene nedenfor presenteres gjennomsnittlige endringer i SF-6D og M-HAQ og p-verdi for forskjellen mellom disse.

TNF monoterapi versus MTX monoterapi

SF-6D

Dependent Variable: sf6d3i_1

tnf mono vs mtx	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
Mtx	710	,047(a)	,003	,041	,054	0.19
tnf mono	161	,034(a)	,008	,018	,051	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,1915727, SF6DV1 = ,5545.

Tabell 13a

M-HAQ

tnf mono vs mtx	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
Mtx	953	-,190(a)	,014	-,217	-,163	0.80
tnf mono	206	-,179(a)	,035	-,248	-,111	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,1851519, V1MHAQsc = 1,73.

Tabell 13b

Andre sykdomsvarabler.
6 måneders endring i SR var signifikant bedre i MTX-gruppen enn i TNF-gruppen med justering for SR ved comparison strategy og propensity score. For CRP, DAS-28 og VAS skalaer fant vi ingen signifikante forskjeller mellom gruppene (output vedlagt)

TNF monoterapi versus MTX + andre DMARDs

Group Statistics

SF-6D

tnf mono vs mtx+DMARD	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx + dmard	236	,042(a)	,007	,029	,055	0.16
tnf mono	169	,025(a)	,008	,008	,041	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,4261342, SF6DV1 = ,5529.

Tabell 14a

M-HAQ

tnf mono vs mtx+DMARD	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx + dmard	301	-,183(a)	,028	-,239	-,127	0.20
tnf mono	214	-,116(a)	,036	-,186	-,046	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,4259402, V1MHAQsc = 1,78.

Tabell 14b

Andre sykdomsvarabler.
For SR, CRP, DAS-28 og VAS skalaer fant vi ingen signifikante forskjeller mellom gruppene (output vedlagt).

TNF + MTX versus MTX monoterapi

SF-6D

TNF + MTX vs mtx	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx	679	,046(a)	,004	,039	,053	0.004
Tnf + mtx	298	,068(a)	,006	,056	,081	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,3017153, SF6DV1 = ,5570.

Tabell 15a

M-HAQ

TNF + MTX vs mtx	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx	898	-,199(a)	,015	,228	,170	0.007
Tnf + mtx	364	-,284(a)	,025	,333	,235	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,2896691, V1MHAQsc = 1,75.

Tabell 15b

Andre sykdomsvarabler.
For CRP, DAS-28 og VAS skalaer fant vi signifikant større forbedring fra comparison strategy i TNF + MTX-gruppen enn i MTX-gruppen etter justering for comparison strategy verdi og propensity score (output vedlagt). For SR var det ingen statistisk signifikant forskjell mellom gruppene.

TNF + MTX versus MTX + DMARDs

SF-6D

TNF + MTX vs mtx+ dmard	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx + dmard	228	,037(a)	,007	,024	,050	0.002
Tnf + mtx	301	,066(a)	,006	,055	,077	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,5731776, SF6DV1 = ,5567.

Tabell 16a

M-HAQ

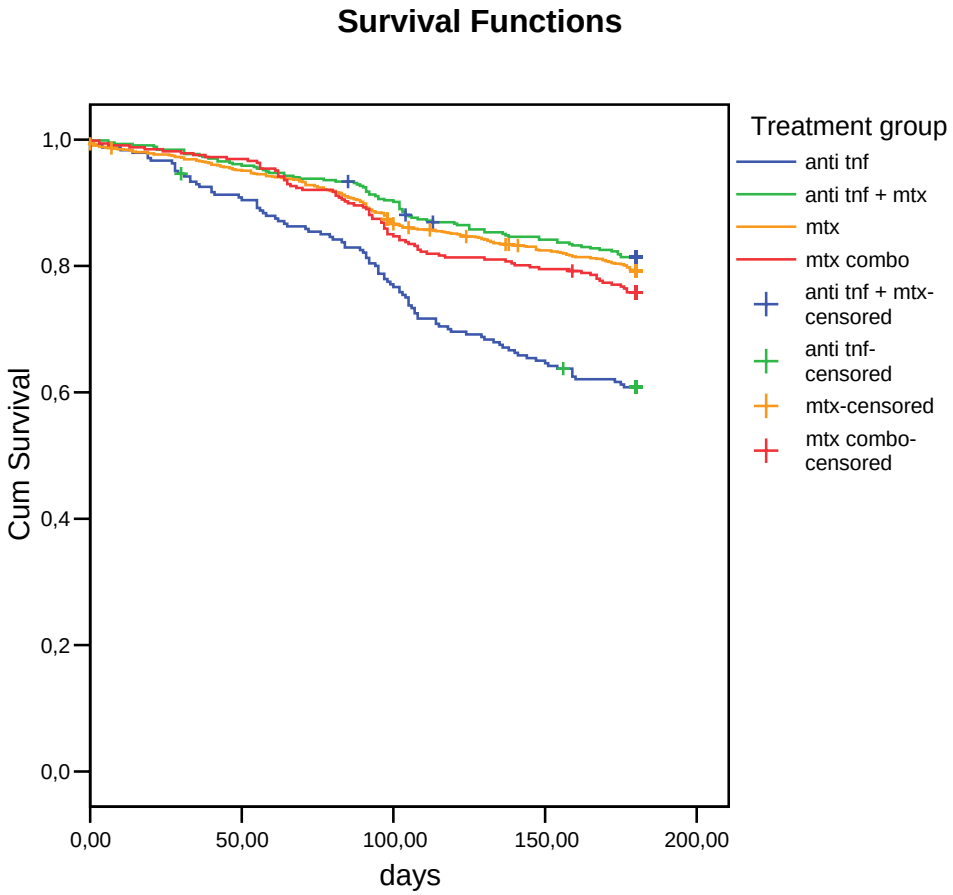
TNF + MTX vs mtx+ dmard	N	Mean	Std. Error	95% Confidence Interval		p-value
				Lower Bound	Upper Bound	
mtx + dmard	290	,203(a)	,026	,254	,152	0.20
Tnf + mtx	372	,249(a)	,023	,294	,205	

a Covariates appearing in the model are evaluated at the following values: Predicted probability = ,5635128, V1MHAQsc = 1,79.

Tabell 16b

Andre sykdomsvarabler.
For SR, CRP, DAS-28 og VAS skalaer fant vi signifikant større forbedring fra comparison strategy i TNF + MTX-gruppen enn i MTX + DMARD -gruppen etter justering for comparison strategy verdi og propensity score (output vedlagt).

<u>6 måneders "medikament-overlevelse"</u>



Etter 6 måneder var det hhv 39,0%, 24,2%, 20,7% og 18,5% av behandlingen med TNF mono, MTX+DMARD, MTX og TNF + MTX som var avsluttet. Det var statistisk signifikant forskjell for MTX og MTX+DMARD vs TNF mono og for TNF + MTX vs MTX+DMARD.

Parvise sammenlikninger av risiko for å avslutte behandling ble også undersøkt i en Cox regresjonsanalyse med justering for propensity scorer.

TNF monoterapi versus MTX monoterapi

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
Tnf vs mtx	,428	,168	6,450	1	,011	1,534	1,103	2,134
Prop sc	,776	,259	8,993	1	,003	2,172	1,308	3,607

Tabell 17

Det var fortsatt signifikant større risiko for å avslutte behandling med anti-TNF monoterapi enn MTX monoterapi

TNF monoterapi versus MTX+DMARD

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
Tnf vs combo	,426	,190	5,052	1	,025	1,531	1,056	2,221
Prop sc	,573	,403	2,014	1	,156	1,773	,804	3,909

Tabell 18

Det var fortsatt signifikant større risiko for å avslutte behandling med anti-TNF monoterapi enn MTX+ DMARD

TNF + MTX versus MTX

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
TNF + MTX vs mtx	-,390	,169	5,324	1	,021	,677	,486	,943
Prop sc	,676	,273	6,116	1	,013	1,965	1,150	3,357

Tabell 19

Det var nå signifikant større risiko for å avslutte behandling med MTX enn TNF + MTX

TNF + MTX versus MTX+DMARD

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
TNF + MTX vs combo	-,349	,188	3,471	1	,062	,705	,488	1,018
Prop sc	,152	,409	,138	1	,711	1,164	,522	2,596

Tabell 20

Det var nå grensesignifikant større risiko for å avslutte behandling med MTX+DMARD enn TNF + MTX

<u>Arbeidsituasjon</u>

I tabellene 21 a og b finner man andelen av pasienter som er i mer eller mindre enn 50% arbeid ved comparison strategy og etter 6 mndr. Pensjonister er ekskludert fra analysene. Vi brukte LOCF ved 6 måneder.

baseline

			i arbeid		
			< 50%	>= 50%	Total
	anti tnf	Count	138	62	200
		% within Treatment group	69,0%	31,0%	100,0%
	anti tnf + mtx	Count	255	128	383
		% within Treatment group	66,6%	33,4%	100,0%
	mtx	Count	487	294	781
		% within Treatment group	62,4%	37,6%	100,0%
	mtx combo	Count	163	106	269
		% within Treatment group	60,6%	39,4%	100,0%
Total		Count	1043	590	1633
		% within Treatment group	63,9%	36,1%	100,0%

Tabell 21a

6 måneder

			i arbeid		
			< 50%	>= 50%	Total
	anti tnf	Count	137	63	200
		% within Treatment group	68,5%	31,5%	100,0%
	anti tnf + mtx	Count	252	131	383
		% within Treatment group	65,8%	34,2%	100,0%
	mtx	Count	463	318	781
		% within Treatment group	59,3%	40,7%	100,0%
	mtx combo	Count	156	113	269
		% within Treatment group	58,0%	42,0%	100,0%
Total		Count	1008	625	1633
		% within Treatment group	61,7%	38,3%	100,0%

Tabell 21b

Kommentarer

Vedrørende propensity modellering

Propensity modellering er en stadig hyppigere brukt metode for å justere for forskjeller mellom grupper som medfører ulik behandling. Dette er et velkjent problem i observasjonsstudier. Man skal likevel være klar over at propensity modellering bare delvis kan veie opp for disse forskjellene. Det er dessuten flere ulike måter å beregne propensity scorer på, og mange er uenige om hvordan dette skal gjøres på best mulig måte. Vi har, i samarbeid med statistiker, valgt en metode for propensity modellering. Med denne metoden blir resultatene sannsynligvis underjustert i noen grad snarere enn overjustert.

Vedrørende SF-6D
SF-6D er en av flere verktøy for å beregne utilities. I forhold til f.eks EQ-5D, som er et mye brukt verktøy er SF-6D mer konservativt. Det har en mindre skala, som gir mindre utslag i form av endringer i utilities enn EQ-5D.

Vedrørende missing verdier
Missing verdier er et vanlig problem i observasjonstudier. Spesielt for variabler som er beregnet på bakgrunn av mange enkeltvariabler vil man kunne få mye missing, slik som er tilfelle for spesielt SF-6D i disse analysene.

Vedrørende resultatene
Alle resultatene er nokså konsistente. Methotrexate er i utgangspunktet en meget god medisin og medfører minst like store forbedringer som TNF-blokkere før man justerer for forskjellene disse gruppene imellom. Etter justering derimot kommer TNF + MTX signifikant bedre ut i forhold til nesten alle endepunkter. Anti-TNF som monoterapi kommer klart dårligst ut, både før og etter justering. Men man bør være klar over at det kan være en selektert gruppe som blir behandlet med anti-TNF som monoterapi, bl.a. ved at disse pasientene er intolerante for MTX og derfor i en klinisk situasjon ikke har noe reelt behandlingsalternativ. Man kan således argumentere for at en direkte sammenlikning ikke er klinisk relevant.

Vedrørende bruk av helsetjenester
Dataene var såpass mangelfulle/uoversiktlige og vanskelige å tolke at det var vanskelig å gjøre analyser som ga meningsfull informasjon.

Vedrørende fravær av radiologiske data
Av gjennomførbarhets-/ressursmessige grunner innebefatter ikke NOR-DMARD registeret radiologiske data (røntgen). Dette er en svakhet ved studien. Imidlertid har flere studier vist at den relative gevinsten ved bruk av anti-TNF behandling i forhold til MTX er større når det gjelder radiologisk progresjon enn kliniske endepunkter.

Vedrørende bruk av data
Kunnskapssenteret står fritt til å velge å benytte alle eller de av analysene som er relevante for deres rapport, men Diakonhjemmet (v/ Heiberg og Kvien) forbeholder seg retten til å vurdere og kommentere hvordan dataene blir presentert og fortolket.

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