Economic evaluation of a tight-control treatment strategy using an imaging device (handscan) for monitoring joint inflammation in early rheumatoid arthritis

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Abstract

Objective

To evaluate the cost-effectiveness of a tight-control treatment strategy using the handscan (TCHS) compared to using only clinical assessments (TC) and compared to a general non-tight-control treatment strategy (usual care; UC) in early rheumatoid arthritis (RA).

Methods

Data from 299 early RA patients from the CAMERA trial were used. Clinical outcomes were extrapolated to Quality Adjusted Life Years (QALYs) and costs using a Markov model. Costs and QALYs were compared between the TC and UC treatment strategy arm of the CAMERA trial and a simulated tight-control treatment strategy using the handscan (TCHS). Incremental Cost-Effectiveness Ratios (ICERs) were calculated and several scenario analyses performed. All analyses were performed probabilistically to obtain confidence intervals and costs-effectiveness planes and acceptability curves.

Results

In TCHS, €4,660 (95% CI -€11,516 to €2,045) was saved and 0.06 (95% CI 0.01 to 0.11) QALYs were gained when compared to UC, with an ICER of €77,670 saved per QALY gained. Ninety-one percent (91%) of simulations resulted in less costs and more QALYs. TCHS resulted in comparable costs or even limited savings €642 (95% CI -€6,903 to €5,601)) and comparable QALYs to TC. In all scenario analyses, TCHS and TC were found to be cost effective as compared to UC.

Conclusion

A tight-control treatment strategy is highly cost-effective compared to a non-tight-control approach in early RA. Using the handscan as a monitoring device might facilitate implementation of tight-control treatment strategy at comparable costs and with comparable effects. This approach should be investigated further.

Key words

rheumatoid arthritis, tight control, economic evaluation, cost effectiveness

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Introduction

Rheumatoid arthritis (RA), being a chronic inflammatory disease, requires long-term treatment starting from the early phase. Treatment is aimed at controlling inflammation to prevent or stop joint damage, as such preventing functional disability in later stages of the disease. Nowadays tight-control with treat-to-target is accepted as the gold standard treatment principle in early RA (1). Tight-control can be defined as a treatment strategy with dose and drug adjustments tailored to the disease activity of the individual patient (2). In this approach the activity of the disease is monitored and treatment intensified until a predefined level of disease activity (the 'treatment target') is reached. Several tight-control studies like TICORA (3), CAMERA (2), FINRA-Co (4, 5) and CIMESTRA (6, 7) have shown that this intensive approach in early RA results in more improvement in disease activity on average and in more patients reaching low disease activity or even remission, compared to non-tight-control strategies.

RA leads to high costs for society including (expensive, biological) medication, costs due to physician's investigations and hospital attendances (8) and also loss of productivity of patients (9). Although the clinical effectiveness of a tight-control strategy has been shown, there is a need for evidence for this treatment approach to be cost effective as well, especially when drug treatment involves expensive biological drugs (10, 11). However, only one recent cohort study (12) has investigated the cost-effectiveness of a tight-control approach and found it to be cost-effective compared to a usual care approach.

RA treatment recommendations include regular disease activity measurements, as frequently as monthly for patients early in the disease and those with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission (13). The frequent visits in early disease, including detailed clinical measurement of disease activity are often not feasible in rheumatology outpatient clinics in daily practice. To bridge this gap between evidence based guidelines and daily clinical practice, assessments of diseases activity need to be quick, inexpensive, objective and easy to perform. New advanced technologies like magnetic resonance imaging (MRI) and ultrasound (US) offer assessment of bone damage and improved sensitivity to detect low level inflammation (14), but are costly (MRI) and need considerable training of assessors (US), and are time consuming. Considering the need for optimal treatment for this disease, given its high burden to patients and society and the above mentioned practical issues, new tools to monitor disease activity could better enable rheumatology centres to implement a tight-control treatment strategy for their patients.

The 'handscan', developed by Hemics, is the first non-invasive imaging system for monitoring RA inflammation. The device is an optical spectral transmission device and measurements have shown to correlate well with clinical assessment of joint inflammation (15). The prototype predicted absence of inflammation on US and showed good agreement with US and MRI assessed joint inflammation especially in case of low disease activity and remission (16). Patients need to place their hands in the instrument and within minutes the measurement is available. Therefore, the 'handscan' is considered promising in monitoring RA inflammation in daily clinical practice (16). However, its applicability in terms of its expected clinical effects as well as costs for regular use in practice has not been established. The objective of this study was therefore to evaluate the cost-effectiveness of a tight-control treatment strategy using the handscan compared to using only clinical assessments and a general non-tight-control treatment strategy in patients with early RA.

Methods

Trial data used for the economic evaluation

The data from two hundred and ninety-nine (299) patients with early RA who participated in the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) trial, a two-year multicenter open-label strategy trial (2)

from the Utrecht Rheumatoid Arthritis Cohort (URAC) study group was used. Patients were randomly assigned to an intensive strategy or a conventional strategy, both groups received MTX and the aim was remission. Patients in the intensive treatment group came to the outpatient clinic once every month; adjustment of MTX dosage was tailored to the individual patient on the basis of predefined response criteria, using a computerised decision program. Patients in the conventional strategy group came to the outpatient clinic once every three months; they were treated according to common practice. The clinical effect of the intensive strategy was better than the conventional strategy with 76 (50%) patients in the intensive strategy achieving at least one period of remission during the two year trial, versus 55 patients (37%) in the conventional strategy (p=0.03). Further details of the trial can be found elsewhere (2).

Treatment strategy arms used in the economic evaluation

Three treatment strategies were defined and compared in the economic evaluation. 1) A usual care strategy (UC) that was directly based on the conventional strategy arm of CAMERA. 2) The intensive- or tight-control strategy group (TC), directly based on the intensive strategy group of CAMERA. 3) A tight-control strategy group using the 'handscan' (TCHS). This last strategy was based on a modification of the tight control strategy group from the CAMERA trial. In this modified (*i.e.* not directly observed) treatment arm patients were assumed to visit the hospital every month, as in the TC strategy. However, instead of visiting a rheumatologist every month, 2 out of 3 evaluations were replaced with evaluation of disease activity using the 'handscan'. No rheumatologist visits are assumed to be required during the visits with the 'handscan' measurements, except when the outcome of the measurement dictates a change in treatment. In that case a limited consult at the rheumatologist was assumed, since no extensive examination of the patient would be needed. The frequency of these 'handscan' visits which needed rheumatologist interference was based on the observed treatment changes over the duration of the trial in the intensive strategy group of CAMERA (TC group). The clinical effectiveness of this treatment strategy was assumed to be the same as for the TC group.

Health economic model

In order to translate the clinical results, as observed in the trial, to general health outcomes (*i.e.* quality adjusted life years, QALYs) and costs, a Markov (or Health state) model was used. Health states were based on disease activity, defined as remission (according to ACR 2011 (17)), remission based on the DAS28, low-, moderate- and high DAS28 (13). A cycle length of 3 months and a time horizon of 2 years was used for the analysis, in line with the duration of the CAMERA trial. DAS28 as observed every 3 months in the treatment strategy arms of the trial was used in the model. Markov models with a comparable structure are often used in RA (18). To account for progression of the disease next to current disease activity functional disability (Health Assessment Questionnaire: HAQ) over time was simulated using the relation between (cumulative) disease activity and progression of functional limitations according to a regression function estimated in follow up data of URAC (n=1034 patients with RA) and the baseline HAQ in the CAMERA trial (19).

Costs

Since no data on costs were collected in the observed trial, individual patient data from the URAC study group (20) ('external data') on direct medical costs and costs of productivity loss per 3 months stratified by DAS28 and HAQ were used to calculate the costs for patients in the model. Direct costs included costs of hospitalisations (including surgical procedures), rehabilitation, nursing home admittance, purchase of adaptations in/around the house and devices needed to perform activities of daily living, consultations with healthcare workers, and costs for alternative therapies (20). In the model direct medical costs and costs due to productivity loss were sampled from these data according to the DAS28 state and HAQ values (<0.5, 05–1, 1–1.5, 1.5–2, ≥2) of patients in the model per cycle.

Costs for the extra visits (*i.e.* monthly versus 3 monthly visits) and drug treatment (based on observed treatment in the treatment strategy arms) were added separately per cycle. The costs values used for clinical visits using the 'handscan' are presented in Appendix I.

Utility

Utility (EQ5D), which was also not directly measured in the trial, was sampled from the same external data (see under costs) which also included data on utility, similar to the sampling of costs. Quality Adjusted Life Years (QALYs) were calculated by weighing the life years in the model by the utility they were spent in.

Analysis

Mean differences in costs and QALYs with 95% confidence limits and the Incremental Cost Effectiveness Ratio (ICER) were calculated from a societal perspective (*i.e.* including direct costs and costs due to productivity loss) and a health care perspective (*i.e.* excluding costs due to productivity loss). The ICER is defined as the difference in costs between two treatment strategies divided by the difference in QALYs between these two treatment strategies. Results were also graphically presented in cost-effectiveness planes and cost-effectiveness acceptability curves. Costs and QALYs were discounted at 4% and 1.5%, respectively, according to the Dutch guidelines for pharmacoeconomic research (21).

All analyses were performed using 5000 simulations (*i.e.* a probabilistic analysis) in which cost and utility value was sampled for each patient cycle and population uncertainty was taken into account by resampling (with replacement) from the observed trial patient groups.

Scenario analysis

To account for various uncertainties, several scenario analyses were performed making specific changes to the (assumptions in the) base case.

1. Consider the costs of a full rheumatologist visit (instead of half the cost

Table I. Expected costs and QALYs and differences over 2 years per patient for the treatment strategies.

	Usual Care (UC)	Tight-control (TC)	Tight-control using handscan (TCHS)	TC compared to UC	Differences TCHS compared to UC	TCHS compared to TC
	Mean (2.5 to 97.5 percentile)	Mean (2.5 to 97.5 percentile)	Mean (2.5 to 97.5 percentile)	Mean (2.5- 97.5 percentile)	Mean (2.5- 97.5 percentile)	Mean (2.5- 97.5 percentile)
Direct costs	€ 24,382 (€ 19,648 to € 29,953)	€ 21,987 (€ 18,012 to € 26,756)	€ 21,332 (€ 17,421 to € 26,018)	-€ 2,395 (-€ 8,380 to € 3,232)	-€ 3,050 (-€ 9,080 to € 2,566)	-€ 655 (-€ 5,887 to € 4,561)
Productivity loss	€ 13,055 (€ 10,866 to € 15,382)	€ 10,862 (€ 8,923 to € 12,967)	€ 10,876 (€ 9,021 to € 12,858)	-€ 2,193 (-€ 4,983 to € 515)	-€ 2.179 (-€ 4,953 to € 568)	€14 (-€ 2,548 to € 2,653)
Drug costs	€ 121 (€ 82 to € 169)	€ 690 (€ 585 to € 801)	€ 690 (€ 583 to € 799)	€ 570 (€456 to € 687)	€ 569 (€ 453 to € 686)	-€ 1 (-€ 159 to € 148)
Total costs	€ 37,558 (€ 32,095 to € 43,846)	€ 33,540 (€ 28,967 to € 38,850)	€ 32,897 (€ 28,290 to € 38,117)	-€ 4,018 (-€ 10,884 to € 2,549)	-€ 4,660 (-€ 11,516 to € 2,045)	-€ 642 (-€ 6,903 to € 5,601)
Mean DAS28	4.21 (4.05 to 4.37)	3.65 (3.50 to 3.81)	3.65 (3.50 to 3.81)	-0.56 (-0.79 to -0.34)	-0.56 (-0.78 to -0.34)	0.00 (-0.21 to 0.21)
Mean HAQ	0.95 (0.88 to 1.02)	0.89 (0.82 to 0.96)	0.89 (0.82 to 0.96)	-0.06 (-0.16 to 0.03)	-0.06 (-0.16 to 0.03)	0.00 (-0.09 to 0.09)
QALYs	1.31 (1.28 to 1.35)	1.37 (1.34 to 1.41)	1.37 (1.34 to 1.41)	0.06 (0.01 to 0.11)	0.06 (0.01 to 0.11)	0.00 (-0.05 to 0.05)
ICER				66,970 saved /QALY gained	77,670 saved /QALY gained	undefined

UC: usual care; TC: tight-control; TCHS: tight-control with handscan. Represented values are discounted for costs and effects at 4% and 1.5% respectively. The results represent mean and 2.5th and 97.5th percentiles of 5,000 simulations, ICER for TCHS compared to TC is undefined since denominator is zero.

for in between visits) when a treatment change is needed in TCHS.

2. Use adalimumab instead of cyclosporine as a second line drug treatment to make the drug treatment strategies more comparable to the current situation. Disease activity was assumed to be 19% further improved after starting adalimumab instead of cyclosporine, based on a comparison of the change in disease activity at 3 months after starting cyclosporine in CAMERA with this change after starting adalimumab in a recent trial with a comparable treatment strategy and design: CAMERA II (22).

3. Assume lower costs (€25 instead of €50) for a 'handscan' visit.

4. Assume higher costs (€75 instead of €50) for a 'handscan' visit.

5. Add the cost of measuring the erythrocyte sedimentation rate (ESR; €8) to all 'handscan' visits. This would make disease activity measurements more in line with a clinical disease activity index.

6. Increase the effectiveness of TCHS with 10% (*i.e.* 10% lower DAS28 values from 3 months onward as compared to base case). This is based on the superior relation of the prototype 'handscan' with US (r=0.63) compared to the DAS28 (r=0.41) (16).

7. Decrease the effectiveness of TCHS with 10% (*i.e.* 10% higher DAS28 values from 3 months onward as compared to base case).

8. Increase effectiveness of UC with 10% (decreasing DAS28 value by 10%), reflecting general improved care for patients with RA during recent years, irrespective of a formal TC protocol.

Apart from these scenario analyses an analysis considering only expenses in

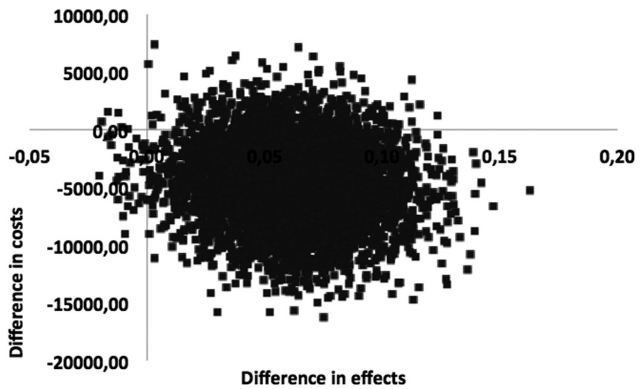

Fig. 1 A. Cost effectiveness plane for TCHS compared to UC

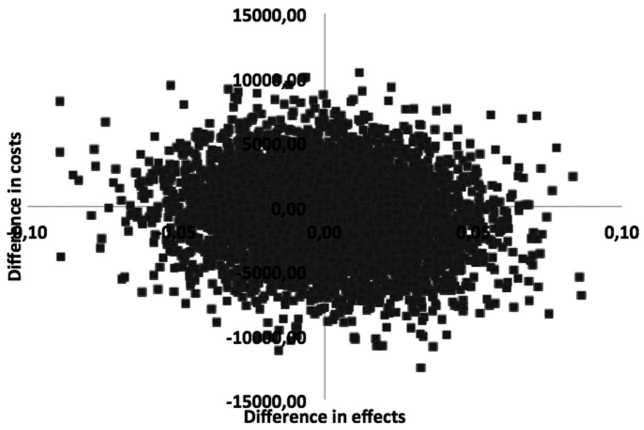

Fig. 1 B. Cost effectiveness plane for TCHS compared to TC

Table II. Results of scenario analyses from societal perspective and healthcare perspective representing mean differences in costs and QALY with distribution in cost effectiveness plane.

Scenario	TCHS compared to UC (2.5% - 97.5% percentile)		TCHS compared to TC (2.5% - 97.5% percentile)	
	Societal	Healthcare	Societal	Healthcare
1. Full rheumatologist visit				
Cost diff	-€ 4,451	-€ 2,282	-€ 431	-€ 433
(2.5- 97.5 percentile)	(-€ 11,027 to €1,992)	(-€ 7,971 to €3,379)	(-€ 6,904 to €5,918)	(-€ 5,751 to €4,970)
QALY diff	0.06	0.06	0	0
(2.5- 97.5 percentile)	(0.01 to 0.11)	(0.1 to 0.11)	(-0.05 to 0.05)	(-0.05 to 0.05)
% (SE,SW,NW,NE)	91,1,0,8	78,1, 0, 21	29, 26, 26,19	29,27,24,19
2. ADA instead of ciclo				
Cost diff	-€ 1,024	€ 1,062	NA	NA
(2.5- 97.5 percentile)	(-€ 7,364 to €4,989)	(-€ 4,434 to €6,259)		
QALY diff	0.06	0.06		
(2.5- 97.5 percentile)	(0.01 to 0.10)	(0.01 to 0.10)		
% (SE,SW,NW,NE)	62,1,0,37	34,0,1,65		
3. €25 instead €50 for handscan visit				
Cost diff	-€ 5,138	-€ 2,989	-€ 1,106	-€ 1,105
(2.5- 97.5 percentile)	(-€ 11,879 to €1,552)	(-€ 8,586 to €2,816)	(-€ 7,518 to €5,219)	(-€ 6,463 to €4,237)
QALY diff	0.06	0.06	0	0
(2.5- 97.5 percentile)	(0.01 to 0.11)	(0.01 to 0.11)	(-0.05 to 0.05)	(-0.05 to 0.05)
% (SE,SW,NW,NE)	93, 1,0,6	85,1,0,14	34,29,21,16	35, 31,19,15
4. €75 instead €50 for handscan visit				
Cost diff	-€ 4,374	-€ 2,221	-€ 335	-€ 321
(2.5- 97.5 percentile)	(-€ 11,040 to €2,134)	(-€ 8,003 to €3,431)	(-€ 6,422 to €5,975)	(-€ 5,644 to €4,901)
QALY diff	0.06	0.06	0	0
(2.5- 97.5 percentile)	(0.01 to 0.11)	(0.01 to 0.11)	(-0.05 to 0.05)	(-0.05 to 0.05)
% (SE,SW,NW,NE)	90,1,0,9	78,0,0,22	28,26,26,21	28,27,24,21
5. add ESR to handscan visit				
Cost diff	-€ 4,541	-€ 2,413	-€ 519	-€ 523
(2.5- 97.5 percentile)	(-€ 11,112 to €2,297)	(-€ 8,142 to €3,335)	(-€ 6,681 to €5,725)	(-€ 5,923 to €4,707)
QALY diff	0.06	0.06	0	0
(2.5- 97.5 percentile)	(0.01 to 0.11)	(0.01 to 0.11)	(-0.05 to 0.05)	(-0.05 to 0.05)
% (SE,SW,NW,NE)	90,1,0,9	79,1,0,20	31,26,24,19	31,27,23,19
6. 10% ↑ effect of TCHS				
Cost diff	-€ 7,852	-€ 4,488	-€ 3,805	-€ 2,608
(2.5- 97.5 percentile)	(-€ 14,278to -€1,483)	(-€ 10,185 to €820)	(-€ 9,832 to €2,158)	(-€ 7,626 to €2,350)
QALY diff	0.09	0.09	0.03	0.03
(2.5- 97.5 percentile)	(0.04 to 0.14)	(0.04 to 0.14)	(-0.02 to 0.08)	(-0.02 to 0.08)
% (SE,SW,NW,NE)	99, 0,0,1	95,0,0,5	78,11,2,9	74,10,3,13
7. 10% ↓ effect TCHS				
Cost diff	-€ 2,018	-€ 956	€ 1,789	€ 737
(2.5- 97.5 percentile)	(-€ 8,450 to €4,462)	(-€ 6,440 to €4,754)	(-€ 4,199 to €8,209)	(-€ 4,335 to €6,233)
QALY diff	0.04	0.04	-0.02	-0.02
(2.5- 97.5 percentile)	(-0.01 to 0.09)	(-0.01 to 0.09)	(-0.07 to 0.03)	(-0.07 to 0.03)
% (SE,SW,NW,NE)	69,4,2,25	60,3,2,35	6,20,62,12	6,29,54,11
8. 10% ↑ effect of UC				
Cost diff	-€ 1,702	-€ 644	NA	NA
(2.5- 97.5 percentile)	(-€ 8,405 to €4,475)	(-€ 6,380 to €4,950)		
QALY diff	0.03	0.03		
(2.5- 97.5 percentile)	(-0.02 to 0.08)	(-0.02 to 0.08)		
% (SE,SW,NW,NE)	62,8,5,25	53,6,6,35		
		Hospital perspective		
9. no cost biological				
Cost diff	€ 390		-€ 680	
(2.5- 97.5 percentile)	(-€ 1,478 to €1,948)		(-€ 2,064 to €737)	
QALY diff	0.06		0	
(2.5- 97.5 percentile)	(0.01 to 0.11)		(-0.05 to 0.05)	
% (SE,SW,NW,NE)	29, 0,0,71		43,41,8,8	
10. with costs of biological				
Cost diff	€ 3,858		NA	NA
(2.5- 97.5 percentile)	(€ 1,809 to €5,622)			
QALY diff	0.06			
(2.5- 97.5 percentile)	(0.01 to 0.11)			
% (SE,SW,NW,NE)	0,0,1,99			

1: full rheumatologist visit in case of treatment switch in handscan group instead of half visit, 2: adalimumab as treatment instead of cyclosporine with a 19% extra decrease in DAS28 with this treatment, 3: handscan cost 25 euro instead of 50 euro, 4: handscan cost €75 instead of €50, 5: include an ESR assessment with handscan visit, 6: increase efectiveness TCHS by 10% , 7: decrease effectiveness TCHS by 10% , 8: increase efectiveness UC by 10%, 9: Only in hospital cost with no drug cost, 10: Only in hospital cost with biological cost

SE: gain in QALY, less espensive; SW: loss in QALY, less expensive; NW: loss in QALY, more expensive; NE: gain in QALY, more expensive.

NA: not applicable because by definition the effectiveness of UC and drug use (assumed equal in both TC groups) cannot influence the comparison of TCHS with TC these scenarios are not applicable.

the hospital reflecting an analysis from a hospital perspective was performed to estimate cost borne by the hospital. As an extension to this, the cost of biological treatment was also added (nowadays sometimes paid by the hospital budget) assuming a biological being used instead of cyclosporine.

Results

Baseline characteristics of patients in the CAMERA treatment groups are presented in Appendix II.

Cost effectiveness result

Table I presents the difference in mean costs and QALYs over 2 years per patient for the three treatment strategies. TC and TCHS both resulted in significant cost savings and gain in QALYs when compared with UC (*i.e.* the tight-control treatment strategies dominated UC). Costs were saved in direct as well as costs due to productivity loss. Direct costs in TCHS were saved due to less frequent clinic visit (compared to TC). Both TC and TCHS resulted in less medical consumption based on better DAS28/HAQ, however drug costs were higher. TCHS resulted in the same number of QALYs and same costs due to productivity loss and comparable or slightly lower direct costs compared to TC. The ICER for TC and TCHS compared to UC were €66,970 and €77,670 saved per QALY gained from the societal perspective.

The cost effectiveness planes (Fig. 1A-B) represent the 5,000 simulations in the analyses. On the x-axis the difference in costs is shown and on the y-axis the difference in QALYs. For the comparison of TCHS with UC, 91% of the simulations fall in the lower right quadrant (*i.e.* cost-savings with QALY gain; implying the strategy to be positively dominant) and 8% in the upper right quadrant (*i.e.* higher costs with QALY gain). The probability of cost effectiveness was above 99% at a willingness to pay (WTP) of €20,000 per QALY. When compared with TC, TCHS was found to be dominant in 31% of simulations, in 19% more expensive and more effective, in 27% less expensive but also less effective, and in 23% inferior (*i.e.* more expensive and less effective).

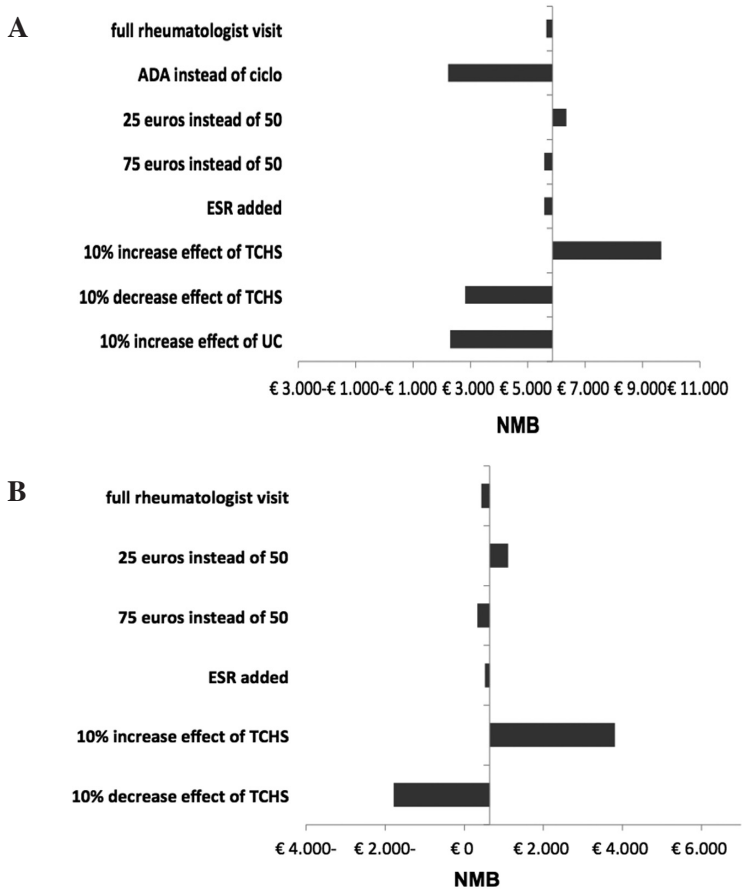

Fig. 2A. Tornado diagram representing the influence on cost effectiveness results comparing TCHS and UC expressed as the net monetary benefit (NMB) with a willingness to pay of €20,000.
2B. Tornado diagram representing the influence on cost effectiveness results comparing TCHS and TC expressed as the net monetary benefit (NMB) with a willingness to pay of €20,000.

Scenario analysis

Cost-effectiveness results for the different scenarios are presented in Table II. Almost all scenarios on average seem to result in cost saving and QALY gain when TCHS/TC was compared with UC. A high proportion of simulations indicate dominance of TCHS/TC from a societal perspective. For the comparison of TCHS with TC, on average savings in the costs were observed, however the simulations are evenly spread over the different quadrants indicating a small uncertain difference in costs and effects. Changing the drug treatment step with cyclosporine to the more expensive adalimumab resulted in higher extra drug costs for TCHS and TC compared to UC. When the effectiveness of the 'handscan' strategy was increased, high cost savings along with QALY gains as compared to UC as well as TC was observed with 78% and 74% of simulations in the positive dominant quadrant from the societal and healthcare perspective, respectively. Reducing effectiveness in TCHS resulted in a loss of QALYs and extra costs when TCHS was compared to TC with 62% and 54% in the inferior quadrant from the societal and healthcare perspective. From the hospital perspective overall no savings in costs were observed for TC/TCHS, especially with the use of biological. When TCHS was compared to TC there were some savings in costs, €680 (-€2,064 to €737) observed from the hospital perspective, clearly with extra gain in case of 10% improved effectiveness of the 'handscan' strategy (not shown).

In Figure 2A-B, the relative importance of the assumptions varied in the scenario analyses for the costs effectiveness results are shown in a tornado diagram. The assumptions regarding the clinical effectiveness of TCHS, UC and the use of adalimumab had the largest influence

Appendix I

Cost considerations

The costs for a rheumatologist visit were taken from the Dutch costing manual (specialist visit: €72) (27). The costs for a visit using the handscan were considered to be €50 (including time for a nurse performing the measurement and the costs for use as well as maintenance of the handscan machine). This cost value was based on manufacturers calculation based on estimated cost of the device, number of patients visiting the rheumatologists in the Netherlands and requiring handscan per visit (including usage and maintenance for 5 years). When a rheumatologist was needed at a handscan visit because a treatment adjustment was indicated, these costs were considered to be half the cost of a full rheumatologist's visit (€36; since disease activity was already measured) and these costs were added to the handscan visit costs.

Appendix II

Table I. Baseline characteristics of CAMERA I trial patients.

	Tight-control group, n=151	Usual care group, n=148
Women (%)	104 (69)	97 (66)
Age, years mean (SD)	54 (14)	53 (15)
Rheumatoid factor positive (%)	89 (59)	77 (52)
Functional ability, HAQ mean (SD)	1.2 (0.7)	1.2 (0.7)
Disease activity score (DAS28) mean (SD)	5.6 (1.1)	5.7 (1.0)
Radiographic damage score mean (SD)	1.6 (4.2)	2.2 (5.3)

on costs-effectiveness results when comparing TCHS and UC. For the comparison of TCHS and TC clinical effectiveness of TCHS had the largest influence on costs effectiveness results.

Discussion

We evaluated the influence on health outcomes and costs of a tight-control treatment strategy using the 'handscan' as compared to a non-tight-control strategy (usual care) and a regular tight-control treatment strategy using validated clinical measurements for disease activity in RA. We showed as one of the first that a tight-control treatment strategy is highly cost-effective compared to a regular non-tight-control treatment strategy and for the first time based on a randomised controlled trial. Comparing the tight-control treatment strategy using the 'handscan' with a tight-control treatment strategy using only clinical measurements for disease activity, we present that these strategies result in comparable or slightly lower costs for the tight-control strategy using the 'handscan'. This suggests that the 'handscan' might be an efficient tool for monitoring patients in a tight-control treatment strategy that could be easy to implement in daily clinical practice compared to a strategy using clinical measurements only. This conclusion seems robust against different assumptions.

One recently published paper (12) investigated the cost-effectiveness of a tight-control treatment strategy as compared to usual care and also found the tight-control treatment strategy to be cost-effective in early RA. They presented an ICER of €3,591/QALY which is less favourable than our results, although they are in the range of the results of our scenario analyses. Differences could also be due to specific differences in the tight-control approach as compared to our study. Also, the comparison of treatment strategies was not based on a randomised comparison as it was in our analysis.

A tight-control treatment approach focuses on lowering disease activity or even reaching (sustained) remission in a large part of patients and has been found to be effective also regarding remission even if applying strict remission criteria and quality of life outcomes (2, 4, 7, 22-24). In such a treatment approach regular disease activity assessment are needed. An ideal measurement for doing this in daily clinical practice is an easy to use, inexpensive, and validated measure, with no need for extensive training of assessors and defined disease activity levels (*i.e.* treatment targets). As comparator for the tight-control treatment strategy using the 'handscan' we used a tight- control treatment strategy using well validated and accepted clinical measurements of disease activity performed by the rheumatologist which could be considered as a gold standard. The 'handscan' has been shown to correlate highly with clinical assessment of joint inflammation (15, 16) especially in the low disease activity and remission ranges (using ultrasound and MRI as reference standard). However, it is not yet studied in a tight-control treatment strategy trial. Although a positive role for ultrasound (US) assisted tight control treatment has been described in patients with early psoriatic arthritis (25), cost-effectiveness of the techniques like MRI and US poses challenges (26) and using it in daily practice is probably not feasible since it requires trained assessor which also adds to the costs. Also these are not studied in a tight-control treatment strategy trial yet. Patient self-evaluation measures (like SDAI) might also be used in a TC approach; however the validity is questionable and has never been studied in a TC approach.

As no empirical ('real') data were available using 'handscan' as a monitoring tool in daily clinical practice yet, effectiveness of this treatment strategy was assumed to be equal to the tight-control strategy as studied in a clinical trial. We also tested this assumption in several scenario analyses. Given the above described association of this optical spectral transmission device with other disease activity measures, this assumption is reasonable. It is considered to be more sensitive in the low disease activity and remission (16). Therefore in the scenario analyses we also assumed a better effectiveness of the TC approach using the 'handscan'. However, measurements are performed only in the hand joints (which add to the feasibility of the measurement) which may counteract the increased sensitivity and might decrease effectiveness of the TC approach using the 'handscan' as assumed in another scenario analyses with still acceptable cost-effectiveness outcomes. Development of a 'footscan' would be worthwhile to consider and study.

CAMERA is a relatively old trial with a drug treatment strategy including cyclosporine when high dose MTX did not result in adequate reduction of

disease activity. Nowadays, probably a biological would be used instead of cyclosporine. Also, patients in the usual care arm would probably be treated more intensively with the advancement in the knowledge of treatment regimens even when no formal tight-control treatment strategy was implemented. However, since randomised controlled trials are the gold standard to compare treatments (strategies) we directly based our base case scenario on the CAMERA trial and accounted for probable advancements in drug treatment and in general intensity of treatment in current daily practice in our scenario analyses.

Overall the proven clinical effectiveness of a tight-control (with treat to target) approach appeared highly cost-effective. However, implementing a tight-control treatment strategy in general practice might be challenging. A tight-control treatment strategy using the 'handscan', usually without the need for a rheumatologist may facilitate implementation with equal cost-effectiveness results compared to such an approach using only clinical disease activity measurements. The clinical effectiveness of this measurement tool in a tight-control treatment strategy needs to be validated, but the present results warrant further investigation of this device and its use in clinical practice.

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