CHAPTER 6

Cost-effectiveness of internet-based self-management compared with usual care in asthma

Victor van der Meer, Wilbert B. van den Hout, Moira J. Bakker, Klaus F. Rabe, Peter J. Sterk, Willem J.J. Assendelft, Job Kievit, Jacob K. Sont

Submitted
ABSTRACT

Background
Effectiveness of internet-based self-management in patients with asthma has been shown, but its cost-effectiveness is unknown. We conducted a cost-effectiveness analysis of internet-based asthma self-management compared with usual care.

Methods
Cost-effectiveness analysis alongside a randomized controlled trial, with 12 months follow-up. Patients were aged 18 to 50 year and had physician diagnosed asthma. The internet-based self-management program involved weekly on-line monitoring of asthma control with self-treatment advice, remote Web communications, and internet-based information. We determined quality adjusted life years (QALYs) as measured by the EuroQol-5D and costs for health care use and absenteeism. We performed a detailed cost price analysis for the primary intervention.

Results
QALYs improved for internet-based self-management compared with usual care with 0.024 (-0.016 to 0.065). Costs of the internet-based intervention were $254 ($243 to $265) during the period of 1 year. From a societal perspective, costs were $641 (95% CI, $-1957 to $3240) higher in the intervention group, with a cost-utility ratio of $26700 per QALY. From a health care perspective, total costs were $37 (95% CI, $-874 to $950) higher in the intervention group, with a cost-utility ratio of $1500 per QALY. At a willingness-to-pay of $50000 per QALY, the probability that internet-based self-management was cost-effective compared with usual care was 62% and 82% from a societal and health care perspective, respectively.

Conclusions
The results suggest that internet-based self-management in asthma is cost-effective compared with usual care, even more so from a health care perspective than from a societal perspective.
INTRODUCTION

Asthma is a chronic, inflammatory disorder of the airways clinically characterized by respiratory symptoms such as wheeze, cough, dyspnoea, chest tightness and impaired lung function (1, 2). Treatment for asthma is aimed at improving asthma control, i.e. reducing current symptoms and need for short-acting bronchodilation, improving lung function and preventing future exacerbations (1-3).

In the past decade, the care for asthma patients has shifted from physician-managed care to guided self-management. Guided self-management includes asthma education, self-monitoring of symptoms and/or lung function and adjustment of treatment according to an action plan guided by a health care professional (not necessarily a physician). Self-management has been shown to improve asthma control and quality of life and reduce health care utilization and sometimes improve lung function (4).

Besides clinical effectiveness, the implementation of new disease management strategies requires an economic evaluation to determine whether the clinical benefits are gained at reasonable costs. Several cost evaluations have compared paper-and-pencil self-management plans to usual care in asthma (5-11), but only a few compared costs to quality of life (10-11). Most of these economic evaluations found that written self-management plans for asthma were likely to be cost-effective compared with usual physician provided care. However, the implementation of paper-and-pencil self-management plans is hampered by patients’ and doctors’ reluctance to use written diaries (12).

Implementation of guided self-management programs may be enhanced by the use of internet-based technologies, particularly in remote and underserved areas. In a recently conducted randomized controlled trial we have shown that internet-based self-management is feasible and provides better clinical outcomes compared with usual physician provided care with regard to asthma related quality of life, asthma control, symptom-free days and lung function (13). Although previous trials have also evaluated the clinical effects of internet-based self-management in adults (14) and children (15, 16), so far, no economic evaluations have been conducted. We therefore carried out a cost-utility analysis, comparing quality of life with societal and health care costs during one year, to determine whether the clinical benefits gained with internet-based self-management are attained at reasonable costs.

METHODS

Setting and participants

Two hundred patients participated in a 12-month multicenter, non-blinded, randomized controlled trial. Patients were recruited from 37 general practices (69 general practitio-
ners) in the Leiden and The Hague area and the Outpatient Clinic of the Department of Pulmonology at the Leiden University Medical Center, The Netherlands over the period from September 2005 to September 2006 (13). We included patients with physician diagnosed asthma as coded according to the International Classification of Primary Care in the electronic medical record (17), aged 18-50 years, with a prescription of inhaled corticosteroids for at least three months in the previous year, access to internet at home, mastery of the Dutch language and without serious co-morbid conditions that interfered with asthma treatment. Patients on maintenance oral glucocorticosteroid treatment were excluded. All participants gave their written consent. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Details of the randomization and intervention have been described previously (13). Briefly, the 200 patients were randomly assigned to internet-based self-management as an adjunct to usual care (internet group: 101 patients) or to usual physician-provided care alone (usual care group: 99 patients). Allocation took place by computer after collection of the baseline data, ensuring concealment of allocation. The internet-based self-management program included weekly monitoring of asthma control and lung function, immediate treatment advice according to a computerized personal action plan after completing the validated Asthma Control Questionnaire on the internet (18), on-line education and group-based education, and remote Web communication with a specialized asthma nurse. After one year, asthma related quality of life (Asthma Quality of Life Questionnaire (19)), asthma control and lung function showed a clinically relevant and statistically significant improvement in the internet group compared to the usual care group (13).

Utilities and QALYs
Utilities express the valuation of health-related quality of life on a scale from zero (death) to one (perfect health). Patients described their health-related quality of life using the EuroQol classification system (EQ-5D) (20), from which we calculated their utilities over time using the British tariff (21). The area under the utility curve is known as quality-adjusted life years (QALY) and was used as the primary outcome measure for the cost-effectiveness analysis. Patients additionally valued their own health status on a visual analogue scale (VAS). This scale from the patient perspective is potentially more responsive to change than other generic quality of life instruments, but is not the best choice for economic evaluations from a societal perspective (22). The VAS scale was transformed to a utility scale using the power transformation $1 - (1-VAS/100)^{1.61}$ (23).

We obtained utility measurements at baseline, 3 and 12 months. For EQ-5D measurements 6.5%, 10% and 8.5% were missing and for visual analogue measurements 7%, 10% and 9% were missing at 0, 3 and 12 months, respectively. To correct for possibly selective non-response, missing measurements were replaced by 5 imputed values.
based on switching regression (24, 25) with regression variables randomisation group, age, sex, asthma control at baseline and available utility measures at all time points. We estimated the intervention effect for each of the 5 data sets by a linear regression model with randomisation group as only independent variable, combining the multiple imputation sets using Rubin’s rules (26).

Costs

We distinguished three major cost categories: intervention costs, other health care costs and productivity costs (10, 11). Intervention costs consisted of materials (software support, electronic spirometer), personnel and patient costs (travel, time, internet and text messaging costs). Other health care costs included contacts (including face-to-face, telephonic and home contacts) with health care professionals (general practitioners, chest physician, other specialists, physiotherapists, psychologists, complementary care and other paramedical professionals), emergency room visits, hospital admissions and both asthma and non-asthma medication.

Patients reported their use of health care resources and the hours of absence from work using a quarterly cost-questionnaire. Details of the drugs used were derived from pharmacy records. We used standard prices for units of resource use and hours of absenteeism (27, 28), which were converted to the price level of 2007 according to the general Dutch consumer price index (29) and converted to US dollars using the purchasing power parity index (€1 = $1.131) (30). Because of the one-year time horizon, costs were not discounted.

Cost-questionnaires were scheduled to be handed in at 3, 6, 9 and 12 months. Of these quarterly questionnaires, 10%, 14%, 19% and 9% were missing, respectively. Pharmacy records were available for 182 patients (91%). Missing cost-questionnaire and pharmacy record were imputed using multiple imputation, as previously described under ‘Utilities and QALYs’.

Statistical analysis

The base case cost-effectiveness analysis compared societal costs with QALYs gained based on the British EQ-5D over the period of one year. Because of the limited degree of modelling in this cost utility analysis, we carried out sensitivity analyses only on the use of different utility measures (British EQ-5D or Visual Analogue Scale) and on the included cost categories (societal or health care perspective).

Differences and statistical uncertainty of QALYs and costs were calculated using non-parametric bootstrap estimation with 5000 random samples (1000 from each of the 5 imputations). Statistical uncertainty of the cost-effectiveness was analyzed using the net benefit approach (31). The net benefit (NB) is defined as WTP x ΔQALY – Δcosts, where WTP is the willingness to pay for a QALY gained. This approach reformulates the QALY
difference into a monetary difference. In a cost-effectiveness acceptability curve we graphed the probability that the internet-based self-management program was cost-effective compared with usual care as a function of WTP and reported this probability at commonly cited WTP values of $50000 and $100000 per QALY (32).

Analyses were carried out with Stata 9.0 (StataCorp, College Station, TX).

RESULTS

The internet group and usual care group consisted of 101 and 99 participants, respectively. Mean age of the sample was 37 years and 70% of the participants were women (table 1). At baseline, asthma related quality of life, asthma control and medication use were similar for the two randomization groups.

Table 1. Baseline characteristics

|                          | Usual care group (n=99) | Internet group (n=101) |
|--------------------------|------------------------|------------------------|
| Women                    | 71%                    | 68%                    |
| Age, years               | 37 (18-50)             | 36 (19-50)             |
| Asthma duration, years   | 18 (0-47)              | 15 (1-47)              |
| Education level          |                        |                        |
| Low                      | 14%                    | 11%                    |
| Middle                   | 33%                    | 37%                    |
| High                     | 53%                    | 52%                    |
| Care provider            |                        |                        |
| General practitioner     | 80%                    | 79%                    |
| Chest physician          | 20%                    | 21%                    |
| FEV1 (pre-bronchodilator), L | 3.13 (1.56-5.23)     | 3.08 (1.14-5.19)     |
| FEV1 (pre-bronchodilator), % predicted | 90 (53-118)    | 88 (34-133)            |
| Inhaled corticosteroid dose, μg/day | 517 (0-2000)   | 494 (0-1000)           |
| Inhaled long-acting β2-agonist, % of patients | 60%              | 59%                    |
| Leukotriene modifier, % of patients | 2%                | 3%                     |
| Clinical outcomes        |                        |                        |
| Asthma Quality of Life Questionnaire * | 5.79 (3.03-7.00) | 5.73 (3.66-6.94) |
| Asthma Control Questionnaire † | 1.11 (0-3.86)       | 1.12 (0.07-3.22)       |
| Patient utilities ‡      |                        |                        |
| EQ-5D utility            | 0.89 (-0.06-1.00)     | 0.91 (0.49-1.00)       |
| EQ-5D visual analogue scale | 74 (35-100)     | 73 (20-100)            |

Data are mean (range) unless otherwise indicated. * Range 1 (worst) – 7 (best) (19). † Range 0 (best) – 6 (worst) (18). ‡ EQ-5D = EuroQol questionnaire, 5 dimensions (20). Parts of this table were published previously (13).
Utilities and QALYs

At baseline, the utilities according to the EQ-5D were non-statistically significantly higher for the internet group than for the usual care group. EQ-5D utilities did not reach a statistical significant difference throughout the study. At 3 months and 12 months the difference in EQ-5D utility was 0.037 (-0.007 to 0.081) and 0.006 (-0.042 to 0.054), respectively, in favour of the internet group. Quality adjusted life years gained in the internet group were estimated to be 0.024 (-0.016 to 0.065) compared to the usual care group (table 2).

Similarly, visual analogue scale utilities were not statistically significantly different throughout the study. At 3 and 12 months the difference in visual analogue scale utility was 0.012 (-0.026 to 0.050) and 0.013 (-0.015 to 0.040), respectively, in favour of the internet group. Quality of life years gained based on the visual analogue scale were estimated to be 0.007 (-0.017 to 0.032) in favour of the internet group (table 2).

Table 2. Utilities at 0, 3 and 12 months and QALYs *

| Variable     | Usual care group | Internet group | Difference (95% CI) | P value |
|--------------|------------------|----------------|---------------------|---------|
| EQ-5D        |                  |                |                     |         |
| 0 months     | 0.89             | 0.91           | 0.026 (-0.024 to 0.076) | 0.31    |
| 3 months     | 0.89             | 0.93           | 0.037 (-0.007 to 0.081) | 0.099   |
| 12 months    | 0.91             | 0.92           | 0.006 (-0.042 to 0.054) | 0.80    |
| QALYs        | 0.90             | 0.92           | 0.024 (-0.016 to 0.065) | 0.25    |
| Visual analogue scale † |                  |                |                     |         |
| 0 months     | 0.87             | 0.86           | -0.013 (-0.045 to 0.019) | 0.43    |
| 3 months     | 0.87             | 0.89           | 0.012 (-0.026 to 0.050) | 0.54    |
| 12 months    | 0.88             | 0.89           | 0.013 (-0.015 to 0.040) | 0.37    |
| QALYs        | 0.88             | 0.88           | 0.007 (-0.017 to 0.032) | 0.57    |

* Values are summary estimates of the 5 data sets obtained by multiple imputation, combined using Rubin’s rules. † Transformed using the power transformation 1 – (1-VAS/100)^1.61 (23)

Costs

The total intervention costs were estimated at $25675, which is $254 (95% CI, $243 to $265) per patient (table 3). The highest cost components of the internet-based intervention were software support ($7917) and the patients’ time costs ($5380 for monitoring time and $5106 for attending the education sessions).

The difference in other health care costs amounted to $-217 (95% CI, $-1117 to $682) per patient indicating (non-significant) cost savings for the internet group (table 4). Patients in the internet group had fewer contacts with health care providers than patients in the usual care group. Particularly, reductions in contacts with physiotherapists ($-120,
p=0.03) and contacts with general practitioners ($-69, p=0.18) resulted in cost reductions for the internet group. In contrast, costs for medication were higher in the internet group due to increased use of inhaled corticosteroid/long-acting β₂ agonist combinations ($82, p=0.09) and leukotriene antagonists ($25, p=0.12). The difference in other health care costs was similar in size to the opposite difference in intervention costs, resulting in a negligible difference in health care costs of $37 (95% CI, $-874 to $950), slightly in favour of usual care.

Patients in the internet group reported 114 hours of absence from work compared to 98 hours for patients in the usual care group. The 16 hours difference in absenteeism was estimated to be equivalent to $604 (95% CI, $-1430 to $2637) in monetary terms. The difference in societal costs (i.e. health care costs plus costs due to absenteeism) was therefore estimated at $641 (95% CI, $-1957 to $3240) in favour of usual care.

### Cost-utility analysis

From a societal perspective, costs were in favour of usual care and QALYs, based on the EQ-5D, were in favour of internet-based self-management. According to this base case analysis, the cost-utility ratio was $26700 per QALY. Due to statistical uncertainty of both costs and QALYs, the probability that internet-based self-management is cost-effective compared with usual care depends on the willingness-to-pay per QALY. This probability was 62% at $50000 per QALY and 74% at $100000 per QALY (figure 1). From a health care perspective, the lower health care costs result in a cost-utility ratio of $1500 per QALY.

---

**Table 3. Implementation costs ($) of internet-based self-management intervention**

| Component of cost                   | Cost per unit | Number of units | Total cost |
|-------------------------------------|---------------|-----------------|------------|
| **Materials**                       |               |                 |            |
| software support                    | 7917 / yr     | 1               | 7917       |
| electronic spirometer               | 19.22 / device| 101             | 1942       |
| **Personnel**                       |               |                 |            |
| development educational aids        | 26 / hr       | 16              | 412        |
| education sessions                  | 26 / hr       | 30              | 780        |
| data review and patient communication| 26 / hr       | 91              | 2351       |
| **Patient costs**                   |               |                 |            |
| travel costs for sessions           | 6 / session   | 258             | 1465       |
| time costs for sessions (incl. travel time) | 20 / session | 258             | 5106       |
| time costs for monitoring *         | 0.50 / log in | 10873           | 5380       |
| internet log in costs †            | 0.0016 / log in | 9374          | 15         |
| mobile phone costs ‡               | 0.20 / message| 1499            | 305        |
| **Total implementation costs**      |               |                 | 25675      |
| **Total implementation costs per patient** |               |                 | 254        |

* Monitoring time was estimated at 3 minutes per log in and valued at $10 per hour, i.e. the Dutch standard price for unpaid labour (27). Number of units was obtained from internet log files. † Internet costs were valued at $23 per month. ‡ Mobile phone costs were valued at $0.20 per message.
The probability that internet-based self-management is cost-effective from a health care perspective was 82% at $50000 per QALY and 86% at $100000 per QALY (figure 1). QALYs gained, based on the visual analogue scale, were less than those based on the EQ-5D. In this case cost-utility ratios were $91600 per QALY and $5300 per QALY from a societal and health care perspective, respectively.

**DISCUSSION**

In this study we evaluated the cost-effectiveness of a new disease management strategy, internet-based self-management, for patients with asthma. The internet group non-statistically significantly gained 0.024 QALY during a follow-up period of 1 year compared with usual care. Costs were $641 higher from a societal perspective, with an estimated
cost-utility ratio of $26700 per QALY, which is generally considered acceptable. Both the estimation of QALYS gained and the calculated expenses showed considerable uncertainty, which is displayed by the probability curves. At a commonly cited willingness-to-pay threshold of $50000 per QALY (32) the internet-based self-management intervention had a probability of 62% and 82% to be cost-effective compared with usual care from a societal perspective and health care perspective, respectively.

We have previously shown substantial and statistically significant clinical effects in favour of internet-based self-management with regard to asthma related quality of life, asthma control and lung function (13). Although the utility outcomes presented in the current study point in the same direction (i.e. in favor of internet-based self-management) as the clinical outcomes, their statistical significance is less evident. There are two main reasons that may explain this finding. First, generic quality of life measures, such as the EQ-5D, must be distinguished from disease-specific quality of life measures, such as the Asthma Quality of Life Questionnaire (19). The latter is well known to be responsive to change (22). However, generic preference-based instruments may differentiate between the highest and lowest levels of asthma control, but are less able to discriminate between moderate levels (33, 34). The baseline asthma control scores found in our primary care study population can be classified as moderately or partly controlled asthma and substantial improvements in disease-specific quality of life may have been missed by the generic instruments. Second, the absence of a statistically significant difference in our primary utility measure may reflect a lack of statistical power, since our trial was powered to detect a statistical difference in the primary outcome.
measure, asthma related quality of life, and not explicitly to detect differences in generic preference-based utility measures (13, 35).

The intervention costs of $254 per patient were similar to intervention costs of a paper-and-pencil asthma self-management program (10), but were half of the costs of intensive nurse-led telemonitoring in asthma reported by others (11). The costs of the technological innovation (software support, electronic spirometer, internet and mobile phone costs) were only about 40% of the total intervention costs. The fixed technological costs of software support constituted about one third of the intervention costs, so a considerable increase in the number of users could reduce the cost per user by one third. Moreover, the calculations were based on costs during the one-year randomized controlled trial. Asthma self-management cost-effectiveness studies with a longer time horizon have shown that intervention costs decrease after the first year (10, 36). In our study, costs for education sessions only apply to the first year, thus reducing costs in later years by about a quarter.

The other health care costs show a reduction of contacts with health care providers in the internet group. Although this reduction is consistently observed in 9 out of 10 health care providers, only the reduction in contacts with physiotherapists were statistically significant, suggesting that patients with better asthma control are less in need for physiotherapy. The cost of drugs for asthma show small decreases in short-acting β2-agonists and inhaled corticosteroids along, but increases in combination therapy (inhaled corticosteroids plus long-acting β2-agonists) and leukotriene antagonists in the self-management group. This finding, in combination with favorable clinical outcomes of the internet-based self-management group, suggests that asthma medication was used more efficiently by those in the internet group.

Our study had several limitations. First, quality adjusted life year estimates were calculated from only two follow-up measurements. More measurements would possibly have resulted in more accurate QALY estimates, but we limited the number of follow-up measures in order to minimize the awareness of participating in a clinical trial among patients in the usual care group. Second, patients were inevitably aware of the allocated group, which may have influenced their utility ratings. Third, our economic evaluation was limited to one year. As pointed out above a longer duration would probably have resulted in reduced intervention cost estimates after one year. It is, however, unknown how EQ-5D utility scores will progress after one year.

New cost-effective disease management strategies for asthma are required to face up to the global burden of asthma. Internet-based self-management is an innovative and effective management strategy in adults with asthma that improves clinical outcome. The results of the current study suggest that internet-based self-management is cost-effective compared with usual care, even more so from a health care perspective than from a societal perspective.
REFERENCES

1. National Institutes of Health. Global initiative for asthma. Global strategy for asthma management and prevention. NIH Publication No 02-3659. Issued: January 1995 (Updated 2006).
2. National Heart Lung and Blood Institute. National Asthma Education and Prevention Program (NAEPP). Expert panel report 3: guidelines for the Diagnosis and Management of Asthma, 2007.
3. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Eur Respir J 2008;32(3):545-54.
4. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma (Cochrane review). In: The Cochrane Library, Issue 1. Oxford: Update Software, 2003.
5. Willems DC, Joore MA, Hendriks JJ, Wouters EF, Severens JL. Cost-effectiveness of self-management in asthma: a systematic review of peak flow monitoring interventions. Int J Technol Assess Health Care 2006;22(4):436-42.
6. Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. Chest 1997;112(6):1534-8.
7. Ghosh CS, Ravindran P, Joshi M, Stearns SC. Reductions in hospital use from self-management training for chronic asthmatics. Soc Sci Med 1998;46(8):1087-93.
8. Lahdensuo A, Haahateia T, Herrala J, Kava T, Kiviranta K, Kuusisto P, et al. Randomised comparison of cost effectiveness of guided self management and traditional treatment of asthma in Finland. BMJ 1998;316(7138):1138-9.
9. Gallefoss F, Bakke PS. Cost-effectiveness of self-management in asthmatics: A 1-yr follow-up randomised, controlled trial. Eur Respir J 2001;17(2):206-13.
10. Schermer TR, Thoonen BP, Van den Boom G, Akkermans RP, Grof RP, Figlering HT, et al. Randomized controlled economic evaluation of asthma self-management in primary health care. Am J Respir Crit Care Med 2002;166(8):1062-72.
11. Willems DCM, Joore MA, Hendriks JJE, Wouters EFM, Severens JL. Cost-effectiveness of a nurse-led telemonitoring intervention base on peak expiratory flow measurements in asthmatics: results of a randomised controlled trial. Cost Eff Resour Alloc 2007;5:10.
12. Jones A, Pill R, Adams S. Qualitative study of views of health professionals and patients on guided self management plans for asthma. BMJ 2000;321(7275):1507-10.
13. Van der Meer V, Bakker MJ, Van den Hout WB, Rabe KF, Sterk PJ, Kievit J, et al. Internet-based self-management plus education compared with usual care in asthma: a randomized controlled trial. Ann Intern Med 2009;151(2):110-20.
14. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: a long-term, randomized clinical study of 300 asthmatic subjects. J Allergy Clin Immunol 2005;115(6):1137-42.
15. Chan DS, Callahan CW, Hatch-Pigott VB, Lawless A, Proffitt L, Manning NE, et al. Internet-based home monitoring and education of children with asthma is comparable to ideal office-based care: results of a 1-year asthma in-home monitoring trial. Pediatrics 2007;119(3):569-78.
16. Jan RL, Wang JY, Huang MC, Tseng SM, Su HJ, Liu LF. An Internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. Telemed J E Health 2007;13(3):257-68.
17. Lamberts H, Wood M: International Classification of Primary Care. Oxford: Oxford University Press;1987.
18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-7.
19. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147(4):832-8.
20. The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.
21. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-1108.
22. Rutten-van Móelken MPMH, Custers F, Van Doorslaer EKA, Jansen CCM, Heurman L, Maesen FPV, et al. Comparison of performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. Eur Respir J 1995;8(6):888-98.
23. Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, Haes JFD. The ‘utility’of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? Int J Technol Assess Health Care 1996;12(2):291-98.
24. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing… presumed at random: cost-analysis of incomplete data. Health Econ 2003;12(5):377-92.
25. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med 1999;18(6):681-94.
26. Rubin DB. Multiple imputation for non response in surveys. New York: J Wiley; 1987
27. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Manual for cost analyses, methods and standard prices for economic evaluations in health care. [In Dutch] Amstelveen: Dutch Health Insurance Executive Board, 2004.
28. Dutch Health Insurance Executive Board. Pharmacotherapeutic Compass. [in Dutch] www.fk.cvz.nl; November 2007.
29. Statistics Netherlands. Consumer price index (accessed July 2, 2008 at www.cbs.nl). 2008.
30. OECD. Purchasing Power Parities (PPPs) for OECD Countries 1980-2006 (accessed July 2, 2008 at www.oecd.org/dataoecd/61/56/39653523.xls).
31. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S68-S80.
32. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in healthcare resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004;7(5):518-28.
33. McTaggart-Cowan HM, Marra CA, Yang Y, Brazier JE, Kopec JA, FitzGerald JM, et al. The validity of generic and condition-specific preference-based instruments: the ability to discriminate asthma control status. Qual Life Res 2008;17(3):453-62.
34. Szende A, Svensson K, Ståhl E, Mészáros A, Berta GY. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level. Pharmacoeconomics 2004;22(8):537-47.
35. Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JPA. Reporting and interpretation of SF-36 outcomes in randomised trials: systematic review. BMJ 2009;338:a3006.
36. Kauppinen R, Vilka V, Sintonen H, Klaukka T, Tukiainen H. Long-term economic evaluation of intensive patient education during the first treatment year in newly diagnosed adult asthma. Respir Med 2001;95(1):56-63.
