ERJ Express. Published on August 28, 2009 as doi: 10.1183/09031936.00153108

Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study

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Financial Support: GlaxoSmithKline

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ABSTRACT

TORCH was a 3 year multi-centre trial of 6112 patients randomized to: salmeterol (SAL), fluticasone propionate (FP), the FP + SAL combination (SFC) , or placebo (PL). Here we assess the cost-effectiveness of treatments evaluated in the TORCH study.

Three year all-cause hospitalization, medication, and outpatient care costs were calculated for four regions. The sample was restricted to the 21 countries (n=4237) for which EQ-5D data were collected to estimate quality-adjusted life years (QALYs). Regression models were fitted to survival, study medication cost, other medication cost and EQ-5D data to estimate total cost, QALYs and cost-per-QALY adjusted for missing data and region.

SFC had a trial-wide estimate of $43,600 cost per QALY compared with PL (95% CI: 21,400 to 123,500). Estimates for SAL vs. PL ($197,000) and FP vs. PL ($78,000) were less favorable. The US estimates were greater than other regions: for SFC vs. PL the cost-per QALY was $77,100 (46,200 to 241,700) compared to $24,200 (15,200 to 56,100) in Western Europe.

Compared with PL, SFC has a lower incremental cost-effectiveness ratio than either FP or SAL used alone and is therefore preferred to these monotherapies on the grounds of cost-effectiveness.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an incurable, debilitating and progressive disease that can be fatal. Patients typically suffer a prolonged respiratory and systemic functional decline punctuated by acute exacerbations often requiring hospital treatment.[1] The incidence of COPD is increasing world wide, making it one of the greatest disease burdens in many countries.[2] Pharmacological treatments that can extend life and improve the quality of life of COPD patients have the potential to offset this burden. Nevertheless, if they are to become routinely available, health systems around the world need evidence not only of effectiveness but also the cost-effectiveness of such interventions.

Despite the importance of COPD as a major disease burden, there is a paucity of high quality cost-effectiveness data concerning potential treatments. The Towards a Revolution in COPD Health (TORCH) study has recently reported[3] its clinical findings. This multinational 3-year study was the first trial of pharmacotherapy to adopt mortality as a primary endpoint in COPD and included a rigorous tracking of deaths to ensure complete follow-up. Furthermore, the TORCH study prospectively collected data on medical resource use and health-related quality of life for patients in the trial. This provides an opportunity to assess the impact of study treatments on health economic outcomes in order to judge whether they are worthwhile from the perspective of the health care system.

The aim of this paper is to report the analysis of the economic data from the TORCH study in order to inform decision makers of the potential cost-effectiveness of alternative treatments for COPD. Special consideration is given to the need to estimate cost-effectiveness results that are relevant to decision makers in particular jurisdictions covered by this multinational trial.

METHODS

The Trial

The TORCH study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to investigate the long term effects of the long-acting β_2-agonist salmeterol 50µg (SAL) and the inhaled corticosteroid fluticasone propionate 500µg (FP), individually and as a fixed-dose combination (SFC), relative to placebo (PL), on the survival of participants with COPD during 3 years of treatment. Recruited patients had a diagnosis of COPD with a forced expiratory volume in one second (FEV_1) of less than 60% of the predicted value,[4] had at least 10-years pack history of smoking, and were aged between 40 and 80 years. The study was conducted in 42 countries in five regions (the US, Eastern Europe, Western Europe, Asia/Pacific, and Other).

Endpoints

The primary endpoint was all-cause mortality. Data were also collected on health status and medical resource use. Health status was measured with the EQ-5D[5] at baseline, every 24 weeks during the study and at the final visit after three years of follow-up. Preference weights ('utilities') for EQ-5D health states were derived using the

recommended tariffs derived from a UK population survey.[6] EQ-5D data were only collected in the 21 of the 42 participating countries for which validated translations of the instrument were available, so the cost-effectiveness analysis was limited to trial participants in these 21 countries (which enrolled 4237 of the total 6112 study participants). Because none of seven Asia/Pacific countries collected EQ-5D data, this region was excluded from the cost-effectiveness analysis.

Recorded medical resource use included: study medication, COPD hospitalization (days in intensive care units / routine care), non-COPD hospitalization (number of admissions), physician visits for COPD (including outpatient and general practitioner appointments), telephone contacts for COPD, long term oxygen therapy and concomitant medications (both COPD and non-COPD related). Non-COPD-related physician visits and any rehabilitation services were not recorded. Costs borne by patients or their careers and productivity losses to society were considered outside of the scope of the health service/third party payer perspective of the analysis.

Price Weights

Price weights (i.e., unit costs) for the 3 study medications were compiled from the IMS Health database[7] for all 21 of the countries that were included in the analysis. Price weights for COPD hospitalizations, outpatient care, and concomitant medications were obtained for 12 of the 21 countries and weights for non-COPD hospitalizations were obtained for 11 countries. These countries were chosen so as to include representatives from the four main regions that participated in the trial. For the remaining countries, the

mean price weights from countries with a similar level of development (e.g., developed or developing) were used. Price weights were translated to a common currency (US$) by use of purchasing power parity (PPP) statistics reported by the Organization for Economic Co-operation and Development (OECD) for 2006.[8] The exceptions were Argentina and South Africa where no OECD PPP was available, and for which other sources were used.[9,10] Where necessary, costs were inflated to the 2007 base year.

Other Explanatory Variables

Other explanatory variables included in statistical models were age, body mass index, race, gender, count of items in medical history at baseline (as an indicator of high medical resource use), count of pre-randomization exacerbations requiring hospitalization, baseline FEV_1 % predicted, Medical Research Council (MRC) Dyspnoea score,[11] disease-specific health status (St George's Respiratory Questionnaire[12]) and region. As 10-pack years of smoking was an inclusion criterion for the trial, all participants were current or previous smokers at study entry and this baseline smoking status was also included.

Analysis

Figure 1 provides an overview of the methods used to estimate the components of the cost-effectiveness calculation. In the first stage, multivariate regression models were fitted separately for survival, study medication cost, other medical cost and preference data. In the second stage, estimates of these four components were combined to give total cost, QALY and cost-per-QALY estimates. This approach is described in more

detail below, with particular emphasis on the methods for handling missing data due to attrition which affected the secondary endpoints of medical resource use and health status, and the adjustment of the estimates to the regions of the study.

Missing data - There were no missing survival data except for one year of follow up in one subject.[3] Withdrawal from the study or missed follow-up visits resulted in 22.6% of the medical service use data and 26.1% of the EQ-5D data being missing. This missingness was addressed by use of inverse probability weighting (IPW).[13,14] Weights were defined as the reciprocal of the estimated probability of being observed (generated from a logistic regression with missingness status as the dependent variable) and then utilized in weighted regression models to estimate study medication cost, other medical cost, and preference scores adjusted for the missing values. Further details relating to the modeling of each component of the cost-effectiveness calculation are given below.

Survival - Mortality was estimated as a function of explanatory prognostic factors and treatment allocation by use of a parametric Weibull survival model. Life years associated with each treatment arm (overall and as a function of other important prognostic factors, including geographical region) were estimated as the area under the Weibull curve.

Cost - Separate estimates of the cost of study medication and other costs were made, recognizing that the treatment cost was part of the trial protocol, whereas other costs relate to the health system. Generalized linear models (GLM) were used to estimate

study medication cost and other costs utilizing separate link functions and families guided by the fit to the data.[15]

Preferences - Ordinary least squares regression was employed to model the EQ-5D scores. Quality-adjusted life years (QALYs) in each treatment arm were calculated by weighting the per-period estimates of preference scores by the probability of surviving at the corresponding visit.

Regional estimates – The TORCH study included participants from five geographic/economic regions of the world: the US, Western Europe, Eastern Europe, Asia-Pacific, and all other countries. As no validated EQ-5D instrument was available for the languages in the Asia-Pacific region, the economic analysis presented here relates only to the remaining four regions. Regional estimates of costs and QALYs for each of the four arms in TORCH were generated by including regional main effect terms alongside the treatment indicators and other explanatory variables in each of the four regression models described above. Treatment-by-region interaction terms were evaluated for each regression, but these terms were only included in the final regression model if the joint test of significance was $p<0.05$. Treatment, region and treatment-by-region interaction terms were estimated taking into account the baseline characteristics of subjects in that region. Note that the economic results are aggregated and presented at the regional rather than the country level since the number of patients recruited by individual countries was low, with the exception of the US which is considered as a region in its own right.

Cost-effectiveness – Trial-wide cost-effectiveness ratios are reported as are region-specific ratios that are calculated by use of the region-specific estimates of costs and QALYs described above. The method of recycled predictions[15] was employed to estimate costs and QALYs and these were discounted at a rate of 3% per year. Cost and QALY results are presented on the cost-effectiveness plane[16] for the US and Western European regions. The US region was chosen as this is the region with the highest health care costs and the Western European region was chosen as the region where the majority of formal reimbursement authorities who make use of cost-effectiveness data reside. Incremental cost-effectiveness ratios are presented in detail for the primary comparison of SFC versus PL (the regulatory comparison) and for SFC versus SAL (since SAL is likely to be standard of care in most countries).

Uncertainty – Standard errors were estimated by use of a nonparametric bootstrap and 95% confidence intervals for incremental cost-effectiveness ratios were based on the bootstrap percentiles.[17] Cost effectiveness acceptability curves[18] are employed to represent the joint uncertainty across all four treatment options included in the TORCH trial, for the US and Western European regions. In common with the majority of cost-effectiveness studies reported alongside clinical trials, prices in our analysis are treated as fixed weights. As a result, statistical measures of uncertainty in the cost of each treatment option relate to the sampling variability associated with the observed resource use in the study.

RESULTS

Study Population

Table 1 shows characteristics of the 4237 participants in TORCH who were enrolled in the 21 countries for which validated translations of the EQ-5D instrument were available. The characteristics of this sample do not differ substantially from the characteristics of the full 6112 patients reported in the TORCH study[3] except for the expected difference in racial mix associated with excluding the Asia/Pacific region and a lower proportion of males in the remaining four regions. The percentage of data points with missing information on resource use and EQ-5D indicates that the problem of attrition was related to treatment group with PL having the greatest quantity of missing data points and SFC the least. Also shown is the number of deaths over the study period for the 4237 participants. SFC has the lowest number of deaths over the study period, although the reduction compared with PL is not significant at the 5% level.

Cost and QALYs

Table 2 shows trial-wide estimates of mean cost and QALYs for PL, SAL, FP, and SFC from the regression models, as well as estimates for each region. The mean cost for all 3 active treatment arms was greater than the mean cost for placebo, with SFC having significantly higher cost overall. Excluding study medications, COPD-related hospitalizations accounted for 47% of the remaining total cost, COPD medications 22%, non-COPD-related hospitalizations 22%, and non-COPD related medications the final 9%. SFC-treated patients also gained significantly more QALYs than those receiving PL ($p = 0.002$), SAL ($p=0.003$), and FP ($p=0.03$). There were no significant QALY

differences between any of the other 3 therapy comparisons (p-values ranging between 0.30 and 0.75).

Table 2 also shows regional estimates. Joint tests of significance for treatment by region interactions in each of the four models revealed no evidence of heterogeneity across regions for treatment effects in the survival, EQ-5D or 'other cost' (i.e. non-medication) regressions ($p>0.1$ for each test)). However, evidence of heterogeneity in study medication cost was significant ($p<0.0001$), with the costs in the US being higher than those for other regions.

Cost-Effectiveness

The trial-wide estimate of cost per QALY gained for the comparisons of SFC versus PL and for SFC versus SAL is shown in Table 3, together with the cost-effectiveness estimates by region. SFC had a trial-wide point estimate of $43,600 compared with PL (95% CI, 21,400 to 123,500). The trial-wide point estimates for SAL vs. PL ($197,000) and FP vs. PL ($78,000, data not shown) were less favorable, whereas the trial-wide cost per QALY estimates for SFC vs SAL ($26,500) and SFC vs FP ($27,000, data not shown) were necessarily more favorable. The cost-effectiveness estimates for all therapies in US were greater than those in other regions, reflecting the higher cost structure in the US. In the US, the point estimate for SFC versus PL was $77,100, which was again less than the US point estimates for SAL vs. PL ($291,000) and FP vs. PL ($124,000).

Ratios for the comparison of SFC versus SAL were lower than those for the comparison of SFC vs. PL because SAL produces fewer additional QALYs than does SFC at a higher cost per QALY and the same was true for the SFC vs. FP comparison (results not shown but available from the authors on request). This relationship is illustrated in Figure 2, which plots the incremental cost and QALYs for the three active treatments compared to placebo in the Western European region and in the US. In these plots, the gradient of the line from the origin to the plotted points represents the point estimate for the cost-effectiveness ratios for the therapies compared to placebo. The gradient of the line between the different active therapies represents the incremental cost-effectiveness ratios for the relevant therapy comparison. In both regions, SAL and FP produce fewer QALYs than SFC at a higher cost-per QALY ratio compared to PL and this same pattern was apparent in the Eastern European and 'Other' regions (data not shown but available from the authors on request).

Figure 3 shows the cost-effectiveness acceptability curves for the simultaneous comparison of uncertainty between the four arms of TORCH in the Western European and US regions. These show the likelihood that each treatment arm is cost-effective for a given willingness to pay for an additional QALY. At a threshold willingness to pay for a QALY of $50,000, the (one-tailed) likelihood for each of SFC, PL, SAL and FP being cost-effective are approximately 0.93, 0.04, 0.01, and 0.03 respectively in the Western European region. Assuming a threshold willingness to pay in the US of $100,000 per QALY gained the corresponding values are 0.65, 0.21, 0.04, and 0.10. Results for the

Eastern European and ‘Other’ regions are similar to the Western European region (data not shown but available from the authors on request).

DISCUSSION

In this paper we report on the cost-effectiveness of ICS and LABA , alone or in combination, for the treatment of COPD based on an economic analysis of the recently reported TORCH study.[3] The trial wide point estimate for the cost/QALY ratio was $43,600 for combination therapy versus placebo (95% CI, 21,400 to 123,500), but there was clear evidence of heterogeneity in study medication costs across regions, which limits the applicability of this 'overall' result to individual regions and countries that participated in the trial. When we estimated cost-effectiveness ratios for each region we found that in the US the incremental cost/QALY ratios for SAL, FP and SFC were all higher than the ratios observed in other regions reflecting the higher cost structure in the US.

There is currently no single agreed methodology for estimation of regional cost-effectiveness estimates.[19] A recent suggestion[20] has been to use a formal heterogeneity test of cost-effectiveness to choose between use of a single pooled estimate across the trial versus splitting the data and calculating region-specific cost-effectiveness ratios. Comparison of the pooled estimate reported here with four region-specific estimates based on splitting the data, failed to reject the null hypothesis of homogeneity across regions (results not reported but available from the authors on request). However, such an approach suffers from an acknowledged lack of power[20] which makes such negative test results difficult to interpret. The method reported here represents a variation on the approach suggested by Cook and colleagues with heterogeneity tests conducted on

individual components of the cost-effectiveness calculation. Although the potential problem of lack of power remains, our preferred approach has the advantage that known differences in prices of medication between regions are not masked by high levels of uncertainty in other components of cost-effectiveness.

One of the challenges of interpretation of the economic evaluation of TORCH is the simultaneous comparison of four arms of the trial, as shown on the cost-effectiveness plane of Figure 2. Incremental cost-per-QALY ratios involve the comparison of two alternatives. Since the incremental cost-per-QALY of SFC vs. PL is lower than for SAL vs. PL or FP vs. PL, the appropriate summary cost-effectiveness value for SFC comes from the comparison with PL (this is an example of what is known as the principle of 'extended dominance'[21]). While this is straightforward for point estimates, the analysis of uncertainty in cost-effectiveness results is less straightforward. The policy decision is to choose between all four options: withhold treatment, or use either FP or SAL alone or in combination. One approach to expressing the uncertainty in this decision is represented by the multiple cost-effectiveness acceptability curves of Figure 3. Such presentations encourage the reader to think about the appropriate level of evidence that is sufficient to recommend adoption of a particular treatment rather than relying on arbitrary p-value thresholds.[22]

Another challenge faced in this analysis was the high levels of missing data for medical service costs (22.6%) and preference scores (26.1%) due to attrition in the study. The approach taken here was to use the inverse proportional weighting technique in

combination with a set of multivariate regression models for the estimation of the components of the cost-effectiveness calculation. This approach gives greater weight to the observed values of patients who have similar characteristics to those patients that have dropped out of the study. Since this approach is based on the observed data, it is unable to account for situations where the propensity to be missing is directly related to the unobserved values (called 'non-ignorable missingness'). Nevertheless, if it is assumed that attrition in the study is associated with poor outcomes and higher cost, and that the placebo group suffered the highest rates of attrition, the approach used in this study is likely to be conservative with respect to estimating the value of treatment (versus placebo).

The scope of the resource use data collection in the TORCH study was limited by practical necessity. COPD related costs were collected for medication, primary and secondary care resource categories. For non-COPD related resource use, only secondary care (hopitalisations) were recorded. No rehabilitation data were collected, nor were any data collected on the costs borne by patients or carers, nor productivity losses to society. In practice, this limitation in scope is conservative with respect to the estimation of the cost-effectiveness of active treatment. Active treatments in TORCH were shown to reduce COPD-exacerbation rates compared to PL with SFC achieving the greatest reduction. The analysis of all costs other than those related to study medication showed nonsignificant trends in favour of active treatment and broadening the scope of cost data collection (particularly patient costs and productivity losses which might be expected to

be strongly correlated with exacerbations of COPD) would most likely have reinforced the study results in favour of active therapy.

The TORCH study has two great strengths. Firstly, it is the first randomized controlled trial to be powered to examine mortality as a primary endpoint. Secondly, it collected economic data prospectively within the trial, which allows the prospective assessment of value in terms of cost-per-QALY. Previous analyses of cost-effectiveness alongside clinical trials in COPD have only been able to report results in terms of cost per exacerbation avoided[23,24] which does not facilitate comparisons of the results across disease areas (required for reimbursement decisions). QALY results have previously been presented for COPD treatments, but based on economic modeling studies which typically project treatment effects from short-term randomized controlled trials over the lifetime of patients.[25,26] The cost-per-QALY results reported in this paper relate to the observed three-year duration of follow-up of the TORCH study. Relatively simple models projecting experience beyond the three-year results suggest that cost-effectiveness ratios for long term therapy are likely to fall by approximately 50% after 6 years of projection (i.e., after the ninth year of therapy) in line with other studies where the benefits have been reported first over the period of the trial and then extrapolated to patient lifetimes.[27-30.] Therefore, the within-trial results presented here are likely to represent a conservative estimate of the true cost-effectiveness of long-term COPD treatment.

Ultimately, it will be for individual countries to judge whether the combined ICS and LABA therapy represents a cost-effective use of resources in their own jurisdiction, given the point estimates of cost-effectiveness and associated uncertainty. In the UK, for example, it is commonly considered that treatments falling below £20,000 per QALY are likely to be considered cost-effective, while those above £30,000 are unlikely to be acceptable on cost-effectiveness grounds alone.[31] In the US there is no single reimbursement authority, nevertheless a threshold of $50,000 per QALY is commonly quoted and more recently commentators have suggested that a contemporary threshold is likely to be $100,000 or greater.[32] In comparison to other disease areas, the cost-effectiveness of SFC combination therapy falls somewhere between primary prevention of CVD with statins[33] and secondary prevention with implantable defibrillators[34], both of which have received positive recommendations from NICE in the UK.

To summarise, based on the analysis of data from the TORCH study, SFC is more effective and has a lower incremental cost-effectiveness ratio (compared with PL) than either FP or SAL used alone and therefore this combination therapy is preferred to existing use of monotherapy on efficiency grounds. For patients who are treatment naïve, whether combination therapy offers good value for money is a judgment for the decision makers in each jurisdiction. Nevertheless, this economic analysis of TORCH provides a strong empirical basis for those decisions to be made.

ACKNOWLEDGEMENTS

This study was funded by GlaxoSmithKline under a contract that allowed the analysis and reporting of the results independently of the sponsor. The sponsor received and commented on the manuscript prior to submission.

REFERENCES

1. Soler JJ, Martinez-Garcia MA, Roman P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005; 60(11):925-31.

2. Petty TL. Definition, epidemiology, course, and prognosis of COPD. Clin Cornerstone 2003; 5(1):1-10.

3. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.

4. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: official statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5-40.

5. The EuroQol Group. EuroQol a new facility for the measurement of health related quality of life. Health Policy 1990;16:199-208.

6. Dolan P. Modeling valuations for EuroQol health states. Medical Care 1997; 35(11):1095-108.

7. Wolters Kluwer Health, Inc; Facts and Comparisons 2007, Master Drug Database.

8. Organization for Economic Co-operation and Development (OECD). Purchasing power parities. Main Economic Indicators, July 2007. pp. 278-9. http://www.oecd.org/document/47 /0,3343,en_2649_34347_36202863_1_1_1_1,00.html. Last accessed March 6, 2008.

9. World Health Organization. Purchasing power parity 2000. http://www.who.int /choice/costs/ppp/en/. Last accessed March 6, 2008.

10. The Big Mac index. The Economist. February 1, 2007. http://www.economist.com/markets/indicators/displaystory.cfm?story_id=8649005&CFID=13546391&CFTOKEN=b6489205ba0e3306-85B21FBD-B27C-BB00-01296499DCFD7106. Last accessed March 6, 2008.

11. Fletcher CM (Chairman). Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ 1960;2:1665.

12. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St George's Respiratory Questionnaire. Am Rev Respir Dis 1992;145:1321-7.

13. Lin DY. Linear regression analysis of censored medical costs. Biostatistics 2000;1:35-47.

14. Lin DY. Regression analysis of incomplete medical cost data. Stat Med 2003;22:1181-200.

15. Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. Oxford: Oxford University Press, 2007.

16. Black WC. The cost-effectiveness plane: a graphical representation of cost-effectiveness. Med Decis Making 1990; 10: 212-4.

17. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Economics 1997; 6(4):327-40.

18. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001;10(8):779-87.

19. Reed SD, Anstrom KJ, Bakhai A, et al. Conducting economic evaluations alongside multinational clinical trials: Toward a research consensus. Am Heart J 2005;149:434-43.

20. Cook JR, Drummond MR, Glick H, Heyse JF. Assessing the appropriateness of combining economic data from multinational clinical trials. Statist. Med. 2003; 22:1955-76.

21. Cantor S. Cost-effectiveness analysis, extended dominance, and ethics: a quantitative assessment. Med Decis Making 1994;14:259-65

22. Claxton K, Sculpher MJ, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). The Lancet 2002; 360:711-5.

23. Oostenbrink JB, Rutten-van Mölken MP, Al MJ, Van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. Eur Respir J. 2004;23(2):241-9.

24. Rutten-van Mölken MP, van Nooten FE, Lindemann M, Caeser M, Calverley PM. A 1-year prospective cost-effectiveness analysis of roflumilast for the treatment of patients with severe chronic obstructive pulmonary disease. Pharmacoeconomics 2007;25(8):695-711.

25. Oostenbrink JB, Rutten-van Mölken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health 2005;8(1):32-46.

26. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.

27. Kim LG, Thompson SG, Briggs AH et al. How cost-effective is screening for abdominal aortic aneurysms? J Med Screen 2007;14:46-52.

28. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R for the Heart Protection Study Collaborative Group. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: a randomised trial in 20 536 high-risk individuals. The Lancet 2005; 365: 1779-85.

29. Mihaylova BN. Using clinical trial evidence for economic evaluation of health care interventions, 2006, DPhil thesis, Oxford, 56-3334 (BL: DN101189).

30. Glick H, Cook J, Kinosian B, Pitt B, Bourassa MG, Pouleur H, Gerth W. Costs and Effects of Enalapril Therapy in Patients with Symptomatic Heart Failure: An Economic Analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial. Journal of Cardiac Failure. 1995;1:371-80.

31. Rawlins MD & Culyer AJ. National Institute for Clinical Excellence and its value Judgments. BMJ 2004;329;224-227.

32. Braithwaite SR, Meltzer D, King J, Leslie D, Roberts M. What Does the Value of Modern Medicine Say About the $50,000 per Quality-Adjusted Life-Year Decision Rule? Medical Care 2008; 46(4):349-56.

33. National Institute for Health & Clinical Excellence. Statins for the prevention of cardiovascular events. Technology Appraisal 94. NICE: London, January 2006. (Available: www.nice.org.uk/TA094)

34. National Institute for Health & Clinical Excellence. Implantable cardioverter defibrillators for arrhythmias: Review of Technology Appraisal 11. Technology Appraisal 95. NICE: London, July 2007. (Available: www.nice.org.uk/TA095)

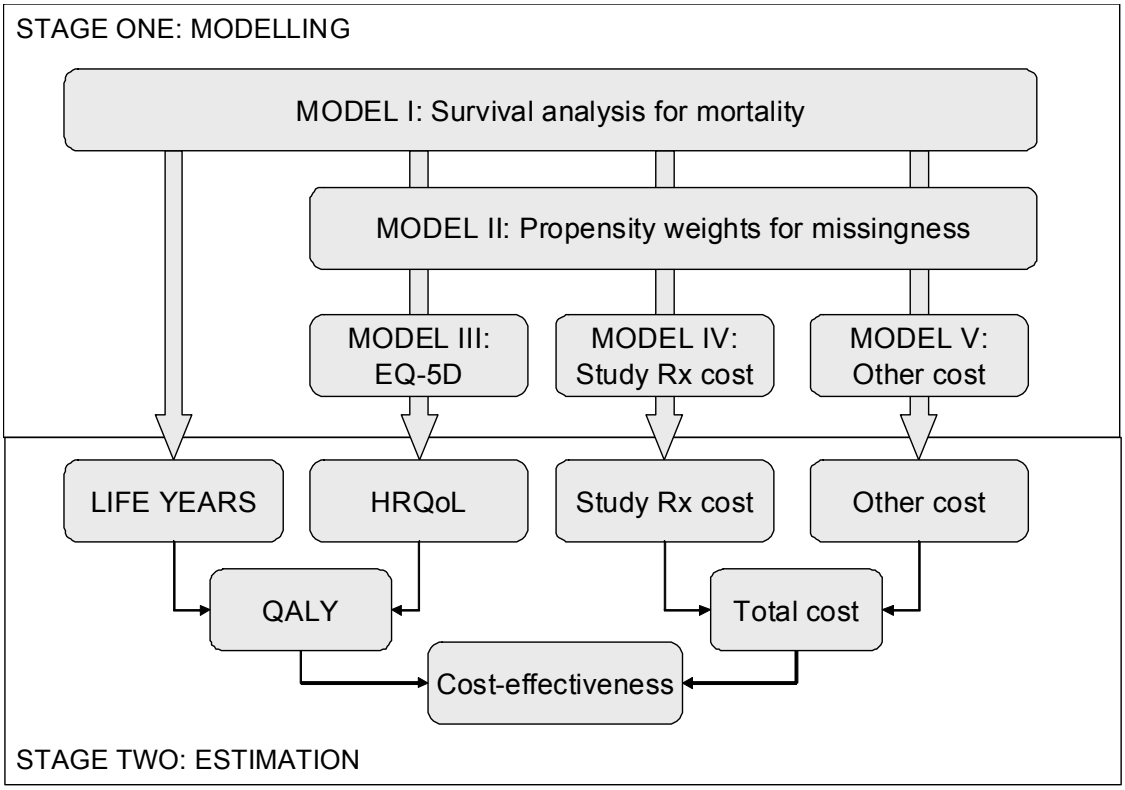
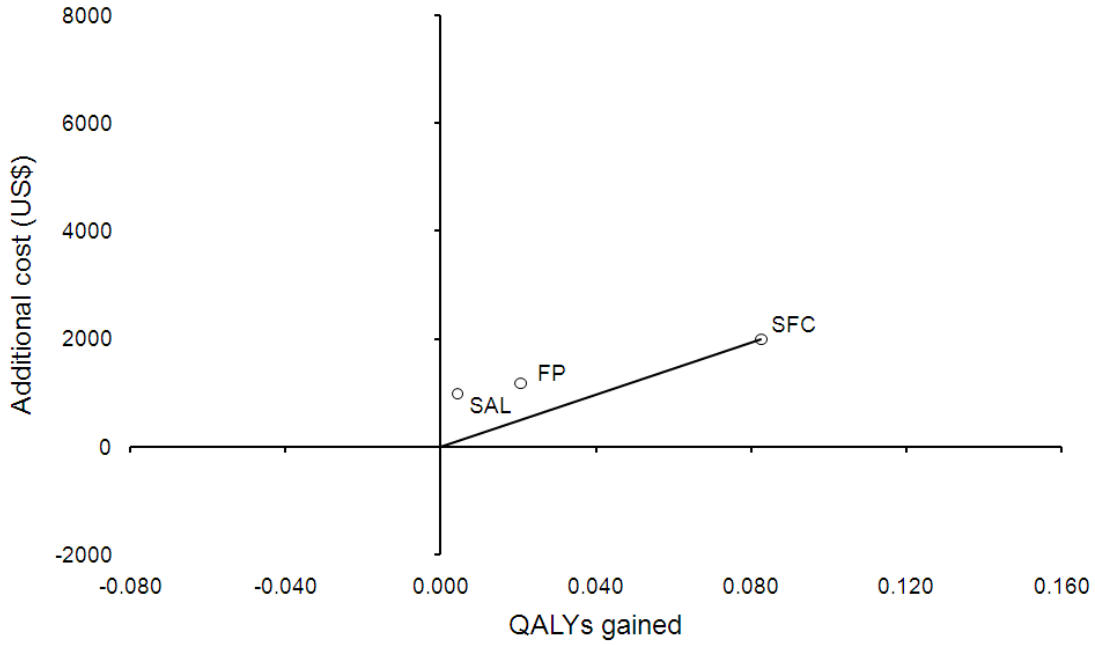
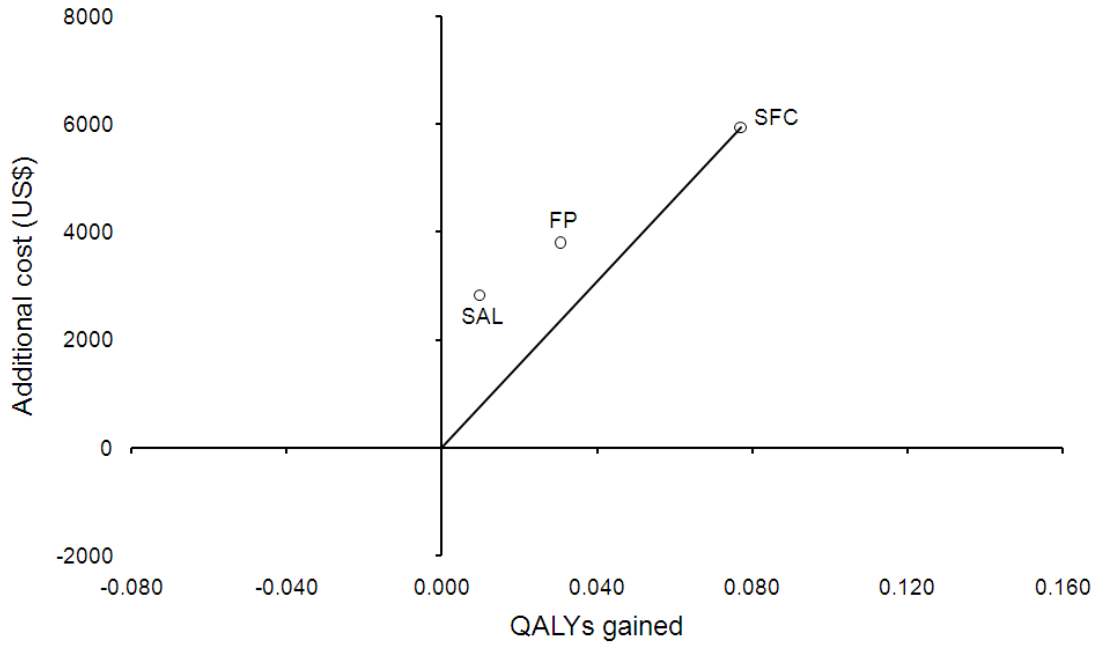

STAGE ONE: MODELLING
MODEL I: Survival analysis for mortality
MODEL II: Propensity weights for missingness
MODEL III: EQ-5D
MODEL IV: Study Rx cost
MODEL V: Other cost
LIFE YEARS
HRQoL
Study Rx cost
Other cost
QALY
Total cost
Cost-effectiveness
STAGE TWO: ESTIMATION

Figure 1. Schematic of Analyses

In the first stage, multivariate regression models are fitted to the TORCH data, with treatment and region as covariates (alongside other prognostic factors). In the first model, a parametric (Weibull) time to event model is fitted to the mortality data directly since these data are complete. Due to attrition there is missing data in the preference (EQ-5D) and cost data, therefore the second model estimates a set of weights based on the estimated propensity for observations to be missing via logistic regression. These weights are then used in weighted regression analyses of the preference and cost data in models III, IV and V. In the second stage, the fitted models are used to estimate the components of the cost-effectiveness calculation. The health related quality of life (HRQoL) preference estimates are combined with life-years to estimate QALYs and the study medication and other medical service use costs are combined to estimate total cost.



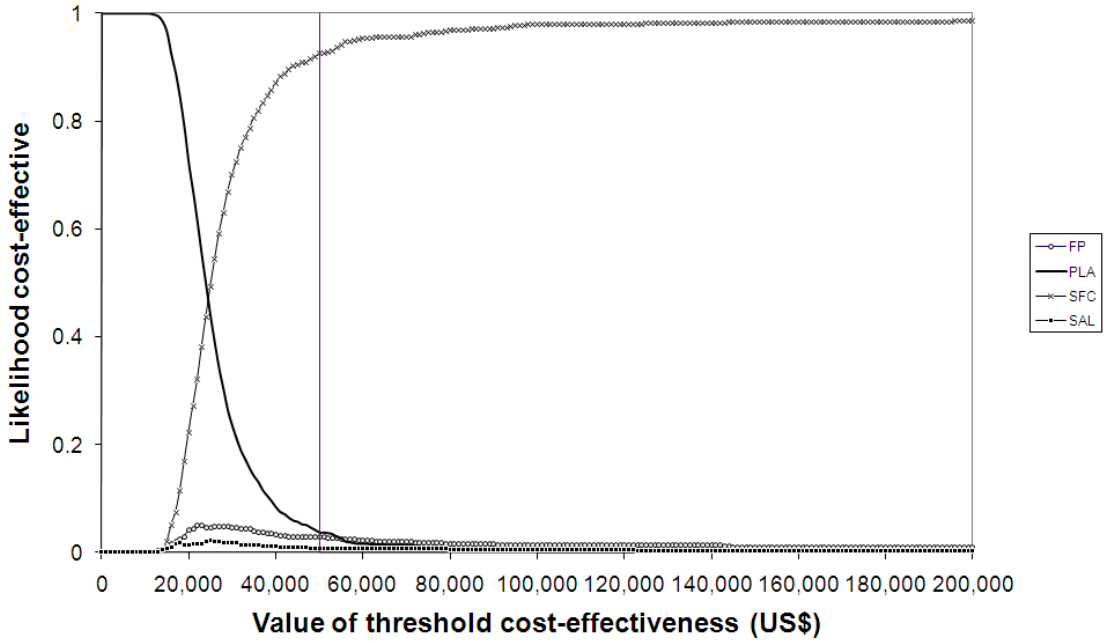
(a) Western European estimates



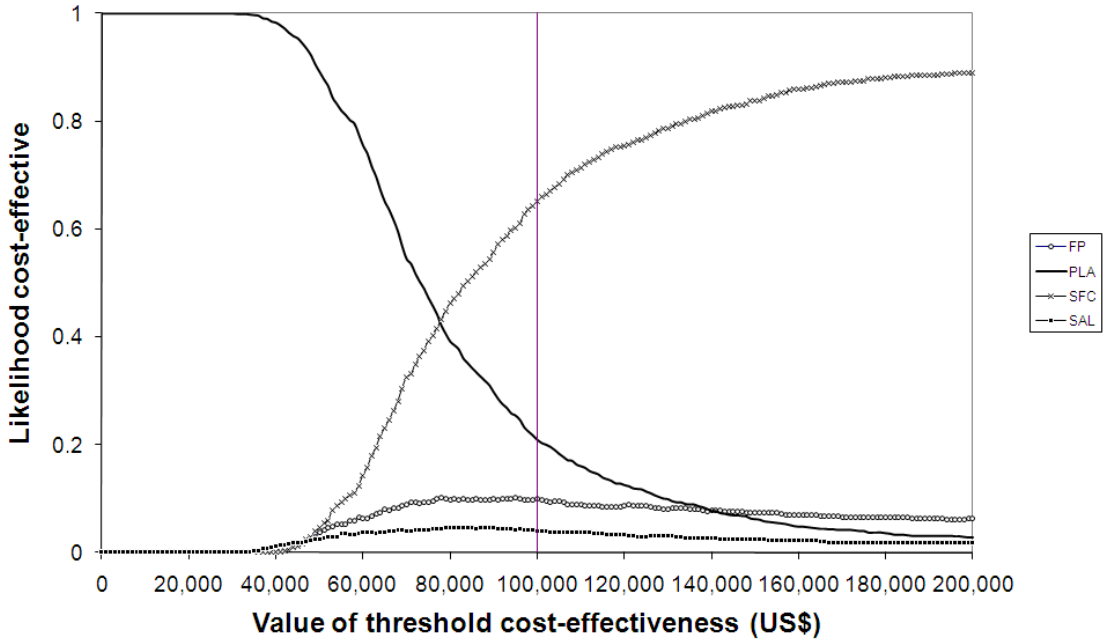
(b) US estimates

Figure 2. Cost-effectiveness plane for treatment compared to placebo

The additional QALY gains and additional costs over placebo are plotted on the cost-effectiveness plane for all three treatments (SFC, FP, SAL) separately for the (a) Western European and (b) US regions. The gradient of the line connecting SFC to the origin (placebo) represents the incremental cost-effectiveness of SFC. SAL and FP point estimates lie above and to the left of this line indicating that whilst these options have lower cost than SFC, the proportional increase in QALY per (extra) dollar spent was less than for SFC. They are both, therefore, less efficient than SFC in producing QALYs given their cost.



(a) Western Europe



(b) US estimates

Figure 3. Cost-effectiveness acceptability curves for all treatment arms

Each curve represents the proportion of times in 1,000 bootstrap replications of the data that a treatment is preferred as a function of the threshold value for cost-effectiveness (ceiling cost-per-QALY ratio). The graph should be read vertically, a given threshold cost-effectiveness value being represented as a vertical line. For each bootstrap replication at a particular threshold value, one treatment is preferred. The proportion of times (across 1000 replications) that each treatment is preferred is given by the y-axis value for the intersection of the vertical line and the therapy curve. The sum of the four intersection values is 1.0. Results are presented separately for the (a) Western European and (b) US regions. Vertical lines represent possible decision thresholds of $50,000 (approx. £26,300) in Western Europe and $100,000 in the US.

Table 1. Characteristics of Participants

	All, N=4,237		PL, N=1,052		SAL, N=1,055		FP, N=1,065		SFC, N=1,065	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	64.7	8.4	64.8	8.5	64.8	8.4	64.8	8.5	64.6	8.6
Male, %	70.7		71.3		71.3		69.6		70.5	
White, %	93.8		93.9		94.1		93.6		93.5	
Body mass index	25.9	5.2	26.0	5.2	25.9	5.2	25.9	5.2	26.0	5.2
Geographic region, %										
United States	32.8		32.8		32.8		32.7		32.8	
Asia-Pacific	0.0		0.0		0.0		0.0		0.0	
Eastern Europe	10.7		10.7		10.9		10.7		10.4	
Western Europe	38.2		38.3		38.2		38.3		38.1	
Other	18.3		18.2		18.1		18.3		18.7	
Predicted pre-bronchodilator FEV1	40.8	11.9	41.0	11.7	39.9	12.1	41.0	11.8	41.3	12.0
Baseline SGRQ questionnaire	49.0	16.9	48.7	17.2	49.6	16.5	49.5	17.0	48.0	16.9

Number exacerbations requiring antibiotics / oral corticosteroids	0.9	1.1	0.9	1.1	0.9	1.1	0.9	1.1	0.9	1.1
Number exacerbations requiring hospitalization	0.2	0.4	0.2	0.4	0.2	0.5	0.2	0.5	0.2	0.4
Current smoker, %	43.6		44.1		43.6		43.4		43.5	
Missing data on resource use, %	22.6		28.7		22.8		21.3		17.9	
Missing data on EQ-5D, %	26.1		31.0		26.2		25.5		22.3	
Died during study period, %	12.8		13.8		12.6		14.6		11.6	
(no. deaths)	(555)		(145)		(133)		(155)		(122)	

Table 2. Adjusted costs* and QALYs for each arm of TORCH by region and pooled across the whole trial

	PL				SAL				FP				SFC			
	Cost	SE	QALY	SE	Cost	SE	QALY	SE	Cost	SE	QALY	SE	Cost	SE	QALY	SE
US	18,891	1012	1.880	0.027	21,717	1019	1.890	0.026	22,692	1010	1.911	0.024	24,830	1026	1.957	0.023
EE	4455	287	1.863	0.040	5815	294	1.869	0.037	6437	286	1.904	0.037	7710	300	1.974	0.034
WE	5623	324	2.026	0.025	6603	323	2.030	0.024	6797	318	2.047	0.025	7619	328	2.109	0.023
Other	4490	354	1.909	0.034	5404	360	1.919	0.032	5726	350	1.923	0.035	6511	364	2.003	0.032
Pooled	9456	575	1.941	0.020	11,035	546	1.949	0.019	11,486	598	1.967	0.019	12,967	595	2.022	0.018

*Costs translated into $2007 US by use of purchasing power parity statistics

Table 3. Regional Cost/QALY Results for SFC vs. PL and SFC vs. SAL

	Difference In Cost (US$ 2007)	Difference In QALYs	Cost/QALY (US$ 2007)	95% CI
		SFC vs. PL		
U.S.	5940	0.077	77,100	46,200 to 241,700
E.E.	3255	0.112	29,100	18,800 to 58,700
W.E.	1996	0.083	24,200	15,200 to 56,100
Other	2021	0.094	21,500	13,400 to 60,000
Pooled	3511	0.081	43,600	21,400 to 123,500
		SFC vs. SAL		
U.S.	3114	0.067	46,300	28,300 to 201,300
E.E.	1895	0.105	18,000	12,200 to 37,700
W.E.	1017	0.078	13,000	8500 to 33,100
Other	1107	0.084	13,200	8200 to 47,000
Pooled	1932	0.073	26,500	7600 to 88,800