Value in Health, Volume 9, Number 4, 2006 , pp. 227-235

ESTIMATING THE COST-EFFECTIVENESS OF FLUTICASONE PROPIONATE FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN THE PRESENCE OF MISSING DATA

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Financial support: Funding was provided by GlaxoSmithKline Pharmaceuticals. The contract allowed the authors full freedom to examine the data, report and publish the results independently of the sponsor.

Keywords: COPD, cost-effectiveness, missing data, ICER.

Running title: Cost-Effectiveness of Fluticasone Propionate for COPD

Value in Health, Volume 9, Number 4, 2006 , pp. 227-235

ABSTRACT

Objectives: To explore the cost-effectiveness of fluticasone propionate (FP) for the treatment of chronic obstructive pulmonary disease (COPD), we estimated costs and quality adjusted life years (QALYs) over 3-years, based on an economic appraisal of a previously reported clinical trial (ISOLDE).

Methods: 742 patients enrolled in the ISOLDE trial who received either FP or placebo had data available on health care costs and quality of life over the period of the study. The SF-36 based utility scores for quality of life were used to calculate QALYs. A combined imputation and bootstrapping procedure was employed in order to handle missing data and to estimate statistical uncertainty in the estimated cumulative costs and QALYs over the study period. The imputation approach was based on propensity scoring and nesting this approach within the bootstrap ensured that multiple imputations were performed such that statistical estimates included imputation uncertainty.

Results: Complete data were available on mortality within the follow up period of the study and a non significant trend towards improved survival of 0.06 (95% CI:-0.02 to 0.14) life years was observed. In an analysis based on a propensity scoring approach to missing data we estimated the incremental costs of FP versus placebo to be £974 (95% confidence interval (CI): £655 to 1,344) with an additional effect of 0.14 QALYs (CI: 0.05 to 0.24). Cost-effectiveness estimates for the within-trial period of £15,555 per life-year gained (£6,347 to ∞) and £7,199 per QALY gained (CI: £3,556 to £19,540) were generated that include uncertainty due to the imputation process. An alternative imputation approach did not materially affect these estimates.

Conclusions: Previous analyses of the ISOLDE study showed significant improvement on disease specific health status measures and a trend towards a survival advantage for treatment with FP. This analysis shows that joint considerations of quality of life and survival result in a substantial increase in QALYs favouring treatment with FP. Based on these data, the inhaled corticosteroid FP appears cost-effective for the treatment of COPD. Confirmation or refutation of this result may be achieved once the TOwards a Revolution in COPD Health (TORCH) study reports, a large randomized controlled trial powered to detect mortality changes associated with the use FP alone, or in combination with salmeterol, which is also collecting resource use and utility data suitable for estimating cost-effectiveness.

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a chronic disease characterized by non-reversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lungs to particles and gases, and particularly tobacco smoke (1). The symptoms of COPD, due to airway irritation and altered lung function, include coughing, sputum production, breathlessness, wheezing and chest pain (2). In addition to chronic symptoms, subjects with COPD may also experience episodes of acute exacerbations, commonly triggered by respiratory infection (3) that frequently require intense medical follow-up in hospital, sometimes including respiratory therapy (4). The impact of COPD on health related quality of life is well-documented; worse health is associated with an increased likelihood of hospitalization (5), more frequent exacerbations (6) and increased mortality (7). A recent study has shown that frequent exacerbations are associated with a more rapid decline in health status (8).

With an approximate global prevalence of 600 million and 2.5 million deaths recorded worldwide annually, COPD was estimated to be the 11th leading cause of disability and the 5th leading cause of mortality in 2000 (9). Due to ageing populations, air pollution (10) and rapid increases in the rate of cigarette smoking in some (mostly developing) countries (11-15) and among specific subgroups (16), it is projected that, by 2020, COPD will become the fifth leading cause of disability and third leading cause of death in the world (17).

Available treatments for moderate to severe COPD mostly comprise single agent or combination bronchodilator therapy (i.e. short or long acting β_2-agonists, inhaled anticholinergics and theophyllines), and oral corticosteroids to manage COPD exacerbations (18,19). Few long-term studies have investigated the effect of inhaled corticosteroids on lung function and exacerbations. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study was a randomized, placebo controlled clinical trial comparing inhaled fluticasone propionate (FP) versus placebo in 751 subjects with moderate to severe COPD (20,21). The objective was to determine the effect of treatment on lung function, exacerbations and health status over the three year follow-up of the trial. The results showed that, while FP did not reduce the annual rate of decline in lung function compared to placebo, significant benefits

were achieved in terms of reduced frequency of exacerbations and a reduction in the decline of health status (22,23). Because of their strong association with prolonged hospitalization and death (24), COPD exacerbations are often interpreted as a pertinent health outcome. In that regard, the ISOLDE study showed that inhaled corticosteroids could potentially yield important benefits.

Although a main focus of the original clinical trial was deterioration of health status as measured by the disease-specific St George's Respiratory Questionnaire (SGRQ) (25), the generic SF-36 health status measure was also included in ISOLDE (26). The reduction in rate of health status deterioration associated with FP treatment occurred over all domains of the SGRQ and the Physical Function, Physical Role, Energy/Vitality and Mental Health domains of the SF-36 (27). The recent publication of an algorithm to translate SF-36 scores into utility scores (28) offers, for the first time, the potential for the improvement in health status associated with treatment already observed in ISOLDE to be translated into a gain in Quality Adjusted Life Years (QALYs). QALYs explicitly combine length and quality of life in a single measure and are the preferred metric in health economic evaluations for bodies such as the National Institute for Clinical Excellence (NICE) in the UK (29), as they allow the direct comparison of treatment cost-effectiveness between disease areas.

METHODS

Following the early withdrawal of nine patients prior to double-blind randomization in the ISOLDE trial, 742 patients were available for analysis. The economic analysis was conducted from a UK public sector (Health and Personal Social Services) perspective over the three years of the clinical study. Costs and effects were discounted at the rate of 3.5% per annum, the rate currently recommended in the most recent guidance from NICE in the UK (29).

Calculation of utility scores

In the ISOLDE study, the generic SF-36 instrument was administered every six months for the three years of follow-up, generating a maximum of six possible observations for patients enrolled in the trial. Brazier and colleagues have reported work on deriving a reduced health status index from the SF-36 that they term the SF-6D (30) and more recently, they have published an algorithm that allows the estimation of

utility scores for all states of the SF-6D index (31). Following this published algorithm, the SF-36 scores observed in the trial were converted to utility scores. Accumulating these scores over the maximum of six visits (three years) of the study allowed the estimation of per patient QALYs for ISOLDE.

Estimation of costs

In addition to the cost of treatment, six categories of resource were collected as part of ISOLDE: rescue medication use; concomitant medication use; visits to the general practitioner; visits to outpatient clinics; visits to the emergency room and inpatient hospital stays. Unit costs for medications were obtained from the British National Formulary (32), and the unit costs of health service contacts from a published compendium of unit cost figures (33). For the purposes of this analysis, costs were accrued for the same six month periods relating to the visits at which health status was measured. Accumulating these costs over the maximum six periods (three years) gave the per-patient total cost for the study. The costing employs a base year of 1998-99, corresponding to the year in which trial ended.

Missing data due to attrition

One important issue observed in the ISOLDE clinical trial was the high rate of withdrawals over the three years of follow-up. Experiencing COPD-related adverse events was also stated as one of the main reasons for dropping out and the overall rate of dropout was higher in the placebo group at 53% of subjects compared to 43% in the FP group (34). Consequently, a large amount of data on periodic costs and utilities had missing values over the three years of the clinical study. Although the original clinical study reported 36 deaths during the study period in the placebo group compared to 32 among those allocated to FP, these represented only deaths prior to dropout from the study. Retrospective examination of death records revealed that there were in fact 58 deaths among those allocated placebo within the three year period of the study compared to just 45 in the FP arm of the study. Having adjusted for data known to be unavailable due to death, the rate of missing data observations was estimated to be 20% for costs and 34% for SF-36 information at scheduled visit dates (see Table 1).

A preliminary analysis of QALYs and cost was conducted based only on the complete cases for each category of data (complete information was available for the life-year analysis as described above). This provides a useful reference point for comparison with the full imputation analysis described below. When combining complete cases of cost and QALYs (and life years) to estimate cost-effectiveness the full set of complete case information was retained, however, covariance information for confidence interval calculation could only be estimated from patients that had both cost and effect information available.

Imputation of missing information

For cost and utility information that was missing after dropout from the study but before death/end of the three year follow-up period the values of the missing observations were imputed. Following Oostenbrink and colleagues (35), an imputation approach based on propensity scoring was employed with baseline variables including age, smoking status, gender, pulmonary function (forced expiratory volume in one second), body mass index categories and disease-specific SGRQ score entered into a logistic regression to predict the chance of a missing value. In addition, one-period lagged values of the relevant cost or utility score were included as explanatory variables. The predicted probability from this regression is the propensity score and on the basis of this predicted probability, the available data were arranged into quintiles. Where cost data or a utility score were missing, a replacement value was selected at random from the available data points within the same quintile. By choosing a value at random within the same quintile the principle of multiple imputation could be employed (36). Multiple imputation procedures are considered more valid than single imputation methods because instead of filling in a single value and treating it as known (as would be the case if a single value based on the closest propensity match was used), in each imputation uncertainty in the imputation process is taken into account such that the imputed data points represent a random sample of the missing values (37).

Although the standard approach is to use a small number of imputed datasets in a multiple imputation process, the recent ISPOR Task Force on CEA alongside clinical trials suggested that both statistical and imputation uncertainty could be combined by bootstrapping the whole imputation/estimation process (38).

Therefore, the existing data set was first bootstrapped including the missing data and then the imputation process was employed to fill in the missing values. The whole bootstrap/imputation procedure was then repeated 1,000 times in order to generate an overall estimate of uncertainty that includes uncertainty in the imputation process.

In a more qualitative sensitivity analysis of the imputation procedure a best and worst case analysis was also performed. For the best case, imputed values for the costs and utilities in the FP group were based on the mean cost and utility in the first period for all completers, and for the placebo group the mean cost and utility in the last available period for subjects that eventually dropped out (when costs were generally higher and utilities lower). For the worst case scenario, we applied the reverse logic by imputing values for FP that were based on mean cost and utility for the last period prior to subjects dropping out and for the placebo group we used the mean costs and utility in the first period for all completers. These alternative imputation approaches allowed the importance of the chosen imputation method to be assessed.

Economic Analysis

The three outcomes estimated for the economic analysis were cumulative costs, life expectancy and quality-adjusted life expectancy over three years. To determine cost-effectiveness, we calculated the incremental cost-effectiveness ratio (ICER) as the ratio of the difference in costs between FP and placebo to the difference in effects. Lower values of the ratio suggest that the benefits of treatment come at lower cost and therefore indicate better value for money. Feiller's theorem (39,40) was employed to generate confidence intervals for cost-effectiveness estimates based on complete data, whereas the non parametric bootstrap was used to represent the combination of statistical/imputation uncertainty where multiple imputation was employed. Uncertainty surrounding the ICER was also presented on the cost-effectiveness plane (41,42).

RESULTS

The mortality curves for FP and placebo are presented in Figure 1. The difference in survival was estimated to be 23 days or 0.06 life years over the study period, although this difference did not reach statistical significance at conventional levels (p=0.11). No imputation was necessary for mortality as the data were complete. The extent of missing information relating to cost and utility is summarized in Table 1 and shows that approximately 20% of the observations relating to cost and 34% of the observations relating to utility were missing. Furthermore, data were more likely to be missing from the placebo than the treatment group. These missing observations have a more profound effect on complete cases with just 69% of patients having a complete set of cost data and only 41% of patients having complete information on utilities.

A complete case analysis based only on those patients that had full and complete data for the three year follow-up of the study is reported in Table 2, with all confidence intervals calculated using standard parametric methods. These results show that FP is associated with a significantly increased cost, but also a significant benefit in terms of QALYs gained over the three year study period. These results are presented on the cost-effectiveness plane in terms of both life-years and QALYs gained in Figure 2. Despite these promising results there are two concerns with the complete case analysis presented in Table 2 and Figure 2. Firstly, the reduced sample size as a basis for this analysis is wasteful of information (due to excluding patients with some information, but who are missing at least one data point) with consequent loss of power. Secondly, the results may be biased if the data are not missing completely at random.

The imputation results for the propensity scoring method are reported in Table 3 and Figure 3 where confidence intervals are now calculated non-parametrically and include both sampling and imputation uncertainty by nesting the imputation within the bootstrap. The incremental costs of FP versus placebo was estimated to be £974 (95% confidence interval: £655 to 1,344) with an additional effect of 0.14 QALYs (0.05 to 0.24). Cost-effectiveness for the within-trial period was estimated to be £15,555 per life-year gained (£6,347 to ∞) and £7,199 per QALY gained (£3,556 to £19,540). The results of the

sensitivity analysis for the best case scenario resulted in an ICER point estimate of £5,170 while the worst case scenario yielded an ICER of £13,220.

The confidence ellipses of Figure 2 based on complete case analysis are overlaid in Figure 3 and show how the imputation approach changes the location of the joint distribution slightly, but that the main effect is to reduce the variance of the estimates, particularly for QALYs gained where missing data observations were greatest.

DISCUSSION

In this study, we have estimated the cost-effectiveness of fluticasone propionate versus placebo using data from the previously published ISOLDE study. It is only following the publication of an algorithm for converting data on the SF-36 instrument to utility scores suitable for calculating QALYs that it has been possible to directly estimate cost-utility results from ISOLDE. ISOLDE was not designed to have sufficient power to detect differences between groups for mortality, but nevertheless showed a trend towards reduced mortality. The results of the analysis reported here show that combining that trend with the significant improvement previously reported in health status resulted in a highly significant QALY gain. However, given the retrospective nature of the analysis and the fact that the study was not powered for mortality differences, these results should be considered as hypothesis generating.

The high rate of withdrawal in the clinical study required the use of imputation techniques to handle missing data. Of particular concern was that there was a strong indication that the attrition was related to adverse outcomes with those experiencing COPD-related adverse events representing the majority of patients dropping out of the study. This means that the underlying pattern of missingness was certainly not completely at random and may be informative. Informative missingness is problematic in that any use of statistical techniques based on observed data are potentially misleading, while modeling unobserved data requires assumptions that are difficult to verify. Our solution was to use propensity scoring as the base case analysis, since this at least imputes from the group of patients that had a similar propensity to have missing values and might, therefore, account for some of the informative nature of those missing

values. In addition, a more qualitative analysis of replacing missing values examined 'best case' and 'worst case' scenarios (from the perspective of the intervention under study) and revealed that even if missing values were deliberately stacked against the intervention, the estimate of cost-effectiveness was still within acceptable limits. That the estimated cost-effectiveness was insensitive to the choice of imputation method used (even under extreme assumptions) suggests that the level of missingness in ISOLDE does not invalidate the results.

The original costing of ISOLDE was undertaken using a cost base year corresponding to the year that the trial closed. While this may seem to be out of date for a current analysis, we have not attempted to update the costing for two main reasons. First, for some resource use categories (such as concomitant medications) the individual resource use quantities are not available, and so any updating of costs could only be achieved through the use of a health service inflation index. Secondly, the price of FP has not changed since the trial was undertaken. Therefore, the analysis presented here is conservative, since the cost of FP is effectively the current price, while any cost-savings from the reduction in other health service resource use associated with treatment are currently valued using 1998/99 unit costs.

The results of this study suggest that inhaled fluticasone propionate is associated with increased quality-adjusted survival when compared with placebo. This adds support to the need to account for the quality-of-life considerations when evaluating treatments for COPD. These benefits came at relatively small overall incremental costs resulting in a favourable cost-effectiveness ratio for FP compared to placebo. For example, while NICE have strenuously denied the existence of a single cost-per-QALY threshold, they have indicated that they would be unlikely to reject a treatment in the range of £5,000-15000 per QALY purely on cost-effectiveness grounds (43). The effect of inhaled corticosteroids alone or in combination with a long acting beta-agonist on survival is currently being investigated in TORCH (TOwards a Revolution in COPD Health), a large randomized controlled trial involving over 6,000 patients comparing the effects of FP alone, or in combination with salmeterol, with placebo (44). This study should provide further evidence on the effectiveness and cost-effectiveness of inhaled corticosteroids

alone and in combination and could provide the definitive analysis to confirm or refute the ISOLDE results presented here.

Reference List

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. 2001.

2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. 2001.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. 2001.

4. Soto FJ, Varkey B. Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 2003;9:117-24.

5. Osman IM, Godden DJ, Friend JA, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. Thorax 1997;52:67-71.

6. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-22.

7. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Felez M, Khalaf A, Marrades RM, Monso E, Serra-Batlles J, Anto JM. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:680-5.

8. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. Eur Respir J 2004;23:698-702.

9. Murray CJ, Lopez AD, and Mathers CD. The global burden of disease 2000 project: aims, methods and data sources. Global Programme on Evidence for Health Policy Discussion Paper No. 36. 2001. World Health Organization.

10. Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: a review. Eur Respir J 2001;17:1024-33.

11. Women and the tobacco epidemic: Challenges for the 21st Century. 2001. Canada, World Health Organization.

12. Mackay J and Eriksen M. The tobacco Atlas. 2002. Geneva, Switzerland, World Health Organization.

13. Niu SR, Yang GH, Chen ZM, Wang JL, Wang GH, He XZ, Schoepff H, Boreham J, Pan HC, Peto R. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. BMJ 1998;317:1423-4.

14. Yang G, Fan L, Tan J, Qi G, Zhang Y, Samet JM, Taylor CE, Becker K, Xu J. Smoking in China: findings of the 1996 National Prevalence Survey. JAMA 1999;282:1247-53.

15. Yang G, Ma J, Chen A, Zhang Y, Samet JM, Taylor CE, Becker K. Smoking cessation in China: findings from the 1996 national prevalence survey. Tob Control 2001;10:170-4.

16. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest 2002;121:121S-6S.

17. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349:1498-504.

18. Calverley PM. Modern treatment of chronic obstructive pulmonary disease. Eur Respir J Suppl 2001;34:60s-6s.

19. MacNee W, Calverley PM. Chronic obstructive pulmonary disease . 7: Management of COPD. Thorax 2003;58:261-5.

20. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

21. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:122-8.

22. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

23. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:122-8.

24. Soto FJ, Varkey B. Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 2003;9:117-24.

25. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

26. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:122-8.

27. Spencer S, Calverley PM, Sherwood BP, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:122-8.

28. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271-92.

29. National Institute for Clinical Excellence (NICE). Guide to the methods of technology assessment. 2004. London, NICE.

30. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. J Clin Epidemiol 1998;51:1115-28.

31. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271-92.

32. Joint Formulary Committee. British National Formulary 47. 2004. London, British Medical Association and Royal Pharmaceutical Society of Great Britain.

33. Netten A, Dennett J, and Knight J. Unit Costs of Health and Social Care 1998. 1998. Canterbury, Personal Social Services Research Unity, University of Kent.

34. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.

35. Oostenbrink JB, Al MJ, Rutten-van Molken MP. Methods to analyse cost data of patients who withdraw in a clinical trial setting. Pharmacoeconomics 2003;21:1103-12.

36. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc 1996;91:473-89.

37. Little RJA and Rubin DB. Statistical analysis with missing data (2nd ed. ed.). 2002. Hoboken, New Jersey, Wiley-Interscience publication.

38. Ramsey S, Willke R, Briggs A, Brown R, Buxton M, Chawla A, Cook J, Glick H, Liljas B, Pettiti D, Reed S. Best practices for cost-effectiveness analysis alongside clinical trials: an ISPOR RCT-CEA task force report. Value in Health 2005;8.

39. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002;23:377-401.

40. Willan AR, O'Brien BJ. Confidence intervals for cost-effectiveness ratios: an application of Fieller's theorem. Health Econ 1996;5:297-305.

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

42. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ 1994;3:309-19.

43. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. BMJ 2004;329:224-7.

44. Vestbo J. The TORCH (towards a revolution in COPD health) survival study protocol. Eur Respir J 2004;24:206-10.

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Table 1
Missing data observations and implications for complete cases

	SF index		Total Costs	
	Placebo (n=370)	FP (n=372)	Placebo (n=370)	FP (n=372)
Total observations	2,077	2,129	2,077	2,129
Of which complete	1,314	1,482	1,616	1,749
% observations missing	37%	30%	22%	19%
Total cases complete	135	168	242	269
% cases missing	64%	55%	35%	28%

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Table 2
Cost effectiveness analysis based only on complete cases

	Placebo	(95% CI)	FP	(95% CI)	Difference	(95% CI)
Life Years	2.75	(2.68 - 2.81)	2.81	(2.76 - 2.86)	0.06	(-0.02 - 0.14)
QALYs	1.68	(1.56 - 1.79)	1.85	(1.76 - 1.95)	0.18	(0.03 - 0.32)
Cost	£1,341	(£1,084 - £1,597)	£2,494	(£2,271 - £2,717)	£1,153	(£813 - £1,493)
Cost per life year						
Undiscounted					£18,413	(£7,804 - ∞)
Discounted					£20,037	(£8,495 - ∞)
Cost per QALY						
Undiscounted					£6,471	(£3,284 - £35,051)
Discounted					£6,553	(£3,321 - £35,571)

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Table 3
Cost-effectiveness analysis based on full imputation

	Placebo	(95% CI)	FP	(95% CI)	Difference	(95% CI)
Life Years	2.74	(2.68 - 2.80)	2.81	(2.76 - 2.85)	0.06	(-0.02 - 0.14)
QALYs	1.71	(1.64 - 1.77)	1.84	(1.79 - 1.92)	0.14	(0.05 - 0.24)
Cost	£1,526	(£1,276 - £1,823)	£2,500	(£2,335 - £2,749)	£974	(£655 - £1,344)
Cost per life year						
Undiscounted					£15,555	(£6,347 - ∞)
Discounted					£17,065	(£7,847 - £3,896,792)
Cost per QALY						
Undiscounted					£7,199	(£3,556 - £19,540)
Discounted					£7,237	(£3,595 - £18,933)

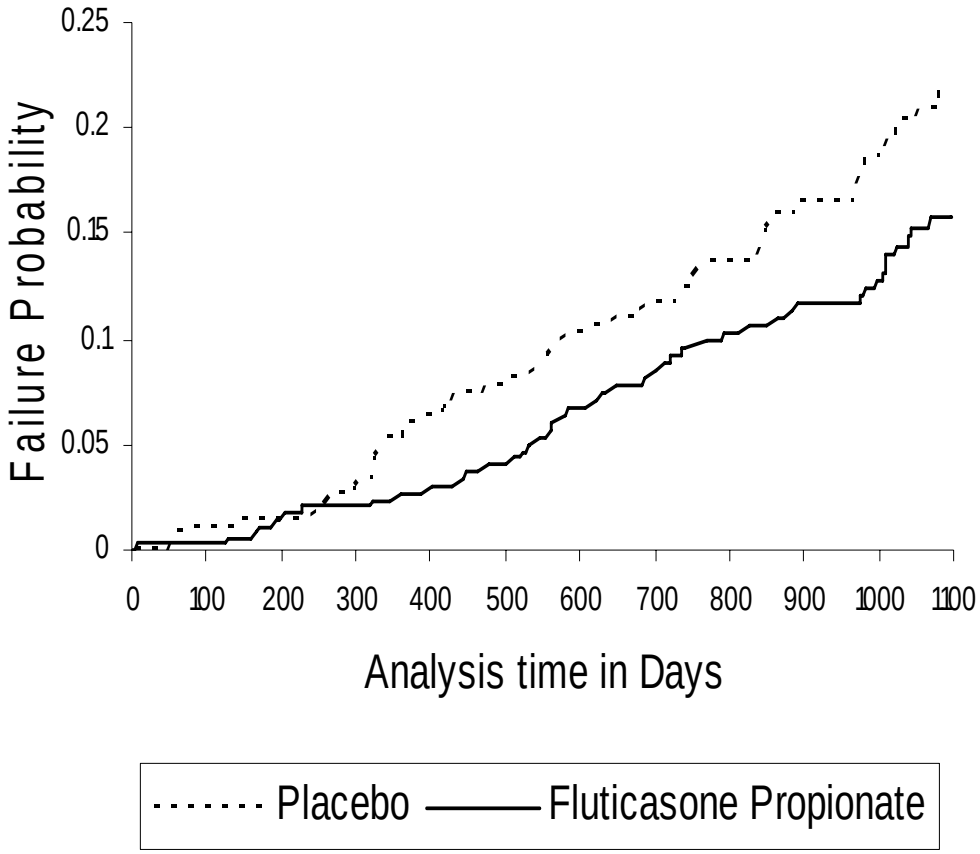

Figure 1
Failure curves for time to death in the Placebo and FP arms
Separation shown is non significant (p=0.11)

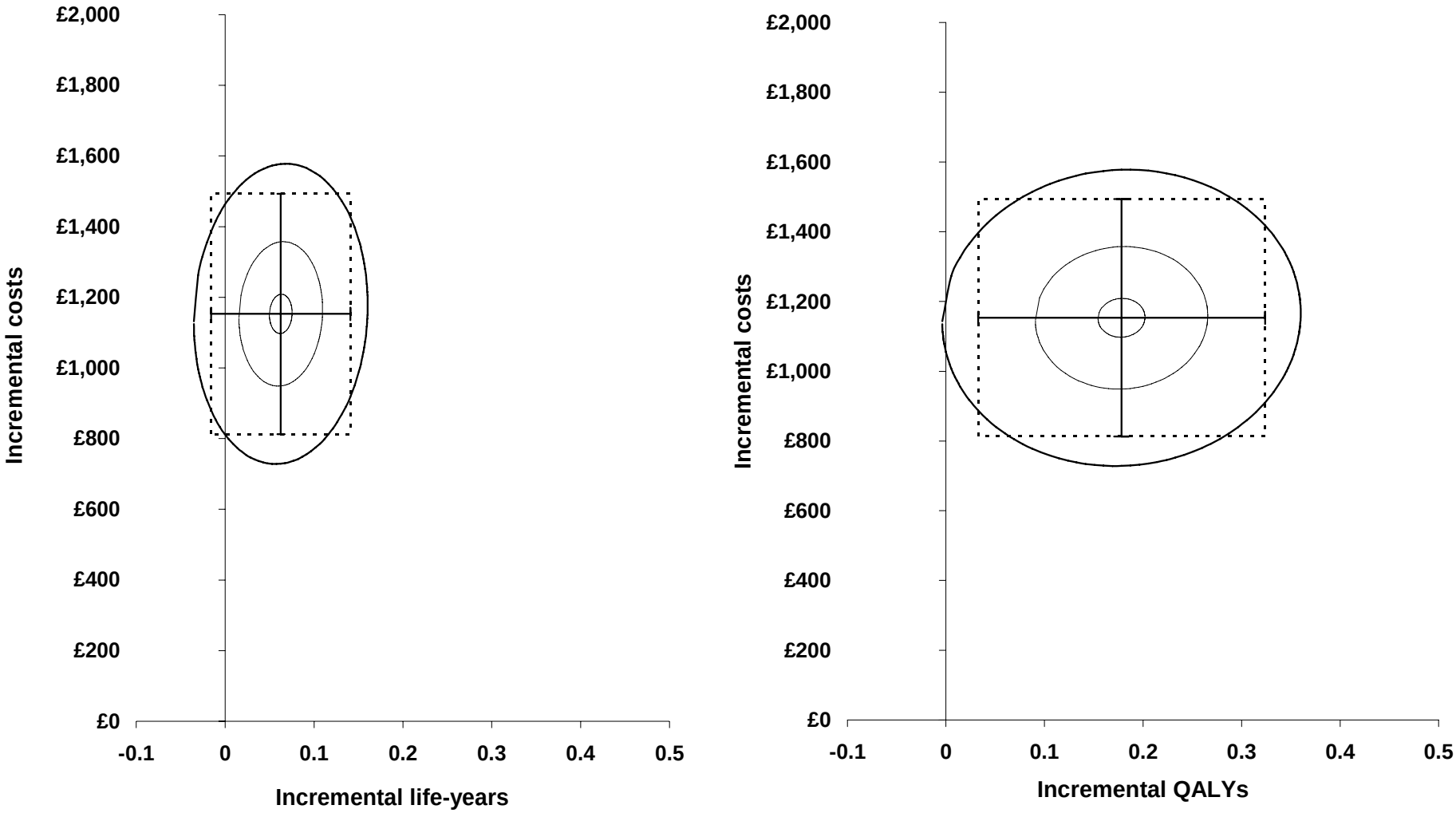

Figure 2
Complete case cost-effectiveness on the cost-effectiveness plane: left panel shows cost per life year; right panel shows cost per QALY
I-Bars show 95% confidence intervals for incremental cost and effect crossing at the point estimates; joint distribution of incremental cost and effect is shown using 5%, 50% and 95% confidence ellipses

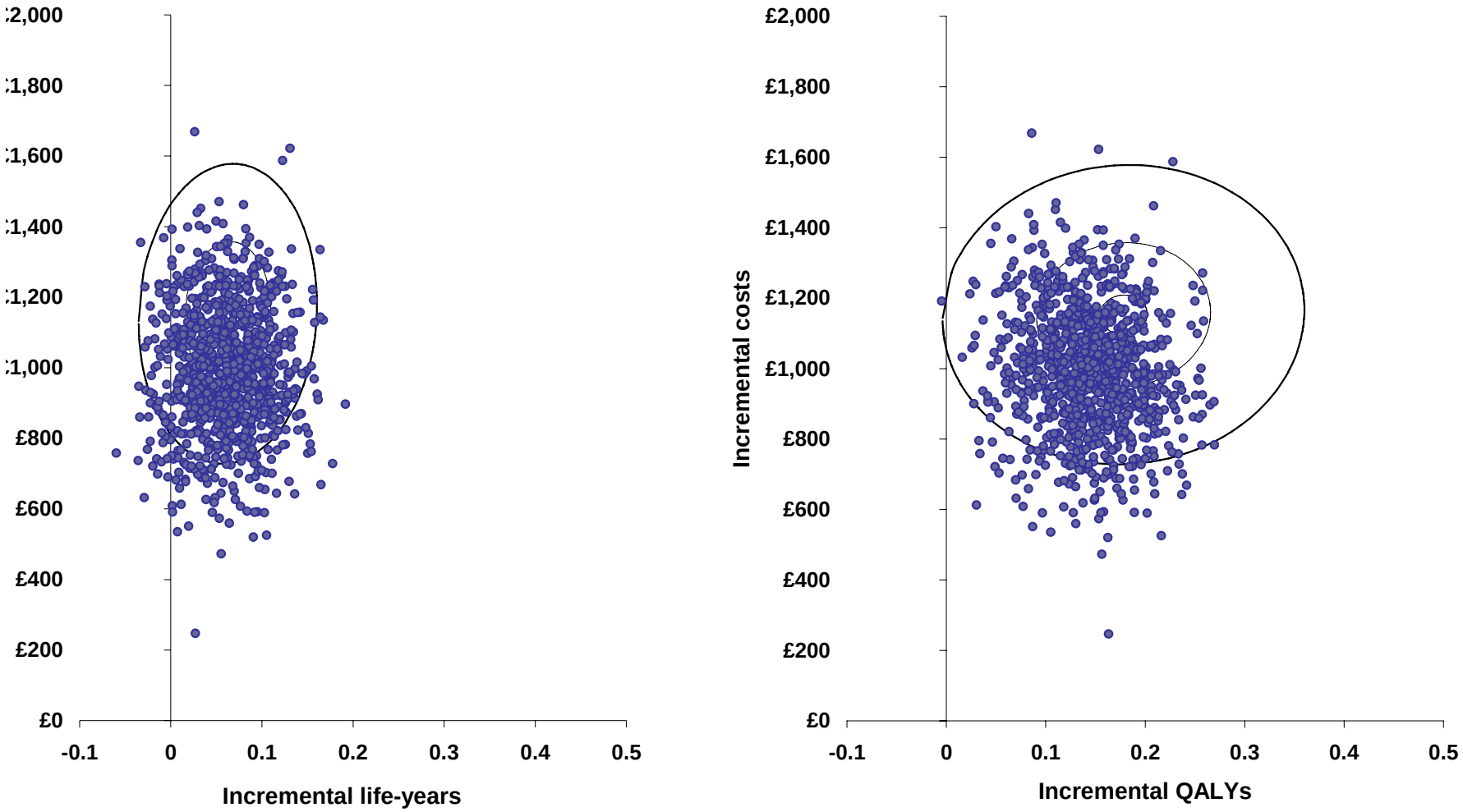

Figure 3
Full imputed cost-effectiveness analysis on the CE plane: left panel shows cost per life-year; right panel shows cost per QALY
Imputed results are shown by the bootstrap joint densities; ellipses based on complete case analysis of Figure 2 overlaid for comparison