Original article

Cost-effectiveness of asthma control: an economic appraisal of the GOAL study

Background: The Gaining Optimal Asthma controL (GOAL) study has shown the superiority of a combination of salmeterol/fluticasone propionate (SFC) compared with fluticasone propionate alone (FP) in terms of improving guideline defined asthma control.
Methods: Clinical and economic data were taken from the GOAL study, supplemented with data on health related quality of life, in order to estimate the cost per quality adjusted life year (QALY) results for each of three strata (previously corticosteroid-free, low- and moderate-dose corticosteroid users). A series of statistical models of trial outcomes was used to construct cost effectiveness estimates across the strata of the multinational GOAL study including adjustment to the UK experience. Uncertainty was handled using the non-parametric bootstrap. Cost-effectiveness was compared with other treatments for chronic conditions.
Result: Salmeterol/fluticasone propionate improved the proportion of patients achieving totally and well-controlled weeks resulting in a similar QALY gain across the three strata of GOAL. Additional costs of treatment were greatest in stratum 1 and least in stratum 3, with some of the costs offset by reduced health care resource use. Cost-effectiveness by stratum was £7600 (95% CI: £4800–10 700) per QALY gained for stratum 3; £11 000 (£8600–14 600) per QALY gained for stratum 2; and £13 700 (£11 000–18 300) per QALY gained for stratum 1.
Conclusion: The GOAL study previously demonstrated the improvement in total control associated with the use of SFC compared with FP alone. This study suggests that this improvement in control is associated with cost-per-QALY figures that compare favourably with other uses of scarce health care resources.

A. H. Briggs[1, 2], J. Bousquet[3], M. V. Wallace[4], W. W. Busse[5], T. J. H. Clark[6], S. E. Pedersen[7], E. D. Bateman[8], on behalf of the GOAL Investigators Group

[1]Public Health & Health Policy, University of Glasgow, Glasgow, UK; [2]Oxford Outcomes Ltd, Oxford, UK; [3]Pneumology, Hôpital Arnaud de Villeneuve, Montpellier, France; [4]Global Health Outcomes, GlaxoSmithKline, Greenford, UK; [5]Allergy and Clinical Immunology, University of Wisconsin Medical School, Madison, WI, USA; [6]Department of Thoracic Medicine, Imperial College, London, UK; [7]Department of Pediatrics, University of Southern Denmark, Kolding Hospital, Kolding, Denmark; [8]The UCT Lung Institute, University of Cape Town, Cape Town, South Africa

Professor Andrew Briggs
Section of Public Health and Health Policy
University of Glasgow
1 Lilybank Gardens
Glasgow G12 8RZ
UK

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For most asthma patients, their asthma is not well controlled and the disease causes a high degree of disruption to their daily lives (1) despite the fact that it is well known that treatment improves health related quality of life (HRQoL) (2). As a consequence, some commentators have argued that the definitions of asthma control that are given in standard guidelines are unrealistic for the majority of asthma patients (3). The Gaining Optimal Asthma controL (GOAL) study (4) was a 1 year, stratified, randomized, controlled trial (protocol no. SAM40027) that examined a strategy of managing patients with uncontrolled asthma by aiming for total control of their symptoms (5). The study showed that the addition of salmeterol to fluticasone propionate in a single inhaler (SFC) leads to greater levels of control at lower doses of inhaled corticosteroids and to an improvement of HRQoL. Despite this clear demonstration of the effectiveness of SFC compared with fluticasone propionate (FP) alone, the combination product represents an additional cost to the health system. It is natural to consider, therefore, whether a strategy of aiming for total control with SFC represents value for money in a health system with competing demands on scarce resources.

The aim of this analysis is to provide an economic assessment of the GOAL study in order to estimate the cost-effectiveness of aiming for total control with SFC *vs* FP alone. In particular, health outcomes are measured in terms of quality adjusted life years (QALYs) in order that the cost per QALY of treating asthma patients can be compared with cost effectiveness ratios in other disease areas.

Methods

The economic analysis was conducted from the perspective of the UK National Health Service and the analysis is designed to meet the

new UK National Institute for Health and Clinical Excellence (NICE) reference case (6). The general principle was to report an analysis based as closely as possible on the clinical trial. The approach taken was to use the whole data set on resource use to maximize use of the data available and therefore the power of the resulting analysis with a UK indicator variable to adjust the analysis for UK specific effects. Due to the lack of direct data on utilities suitable for calculating quality adjusted life-years (QALYs), the analysis makes use of external data providing an algorithm for linking the disease specific scale used in the trial to utility values in order to provide QALY measures of health outcome. The first section below gives a brief description of the trial itself and the data available for the analysis. This is followed by three sections describing the estimation of key components of the cost-effectiveness analysis: the proportion of time spent in different categories of control status; the cost of treatment and of other health service resource use; and the conversion of quality of life outcomes to utilities. The final section describes how these elements are brought together to provide cost per QALY values together with associated confidence intervals to represent uncertainty.

Study design and data

The GOAL study has recently been reported and full details of the trial are published elsewhere (4). Briefly, GOAL was a 52-week, multinational, randomized, double-blind, controlled trial designed to assess the effectiveness of a predefined stepwise programme of increased dosages of FP or SFC in achieving asthma control.

The study comprised two phases. In phase I, patients were in the dose-escalation phase where the dose of FP or SFC would be stepped up if they failed to achieve total control in at least 7 weeks of an 8-week assessment period. Patients entered the second (maintenance) phase, where their dose remained at the level they reached at the end of the first phase. In total, 3416 patients from 44 countries were stratified into three approximately equal groups and randomized between the FP and SFC arms of the trial. The three strata related to patients' use of inhaled corticosteroids for 6-months prior to screening for study entry: stratum 1, no inhaled corticosteroid; stratum 2, 500 μg or less of beclomethasone dipropionate (BDP) or equivalent; or stratum 3, > 500–1000 μg or less of BDP or equivalent. Figure 1 provides an overview of the study design of GOAL showing both the step up phase (phase I) and the maintenance phase (phase II) of treatment together with the difference between the step up phase for strata 1 and 2 and stratum 3.

Categorising control status and estimating proportion of time in each state

For the purposes of this analysis, in each week of the trial patients were classified into four mutually exclusive control categories: 'totally controlled' (TC); 'well controlled' (WC); 'not well controlled' (NWC) but without exacerbation; and 'exacerbation' (X). The TC and WC categories were defined based on treatment guidelines (5). For those not achieving either of the control states in a given week, two categories were distinguished because of the important effect asthma exacerbations have on both resource use and health status – therefore, weeks involving an exacerbation (X) (defined as deterioration in asthma requiring treatment with an oral corticosteroid, or an emergency department visit or hospitalization) were distinguished from those where control was lacking but no exacerbation was experienced (NWC).

The categories of control status identified above were employed as the dependent variable in a multinomial regression model (7–9) in order to estimate the proportion of time patients spent in each

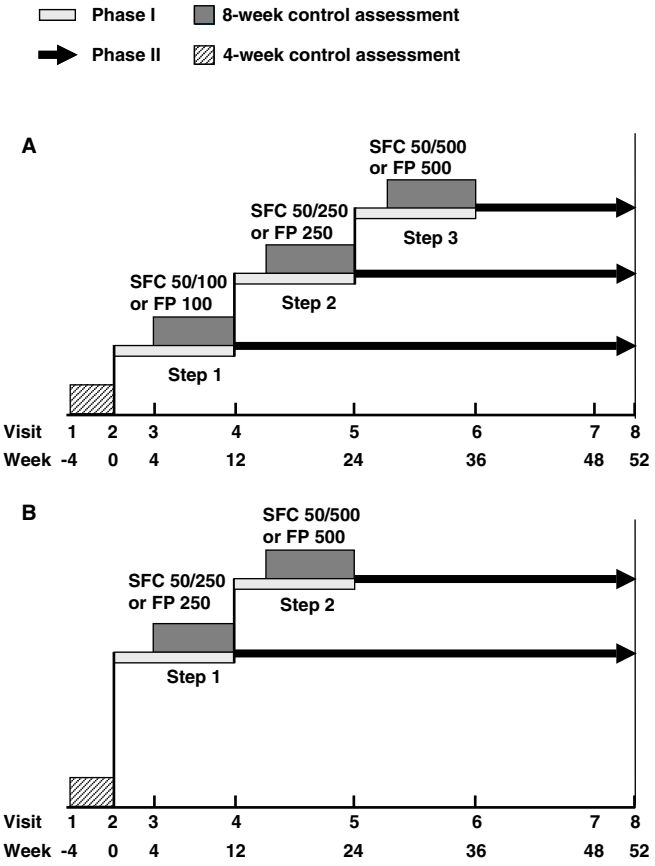

Figure 1. Design of the GOAL study showing the two phases of step-up treatment and maintenance and showing the difference in step-up treatment between strata 1 and 2 (A) and stratum 3 (B). FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate in combination.

category of control while adjusting for the baseline strata and treatment allocation of each patient.

Costs of study treatment and asthma management

For every week of the GOAL study, information on resource use was collected for each patient under three main categories: secondary care visits, primary care visits, and medication. Secondary care information included: visits to emergency departments, length of time (number of days) in ICU, outpatient visits; and inpatient days. Primary care information included: general practitioner home visits during the day and the night, visits to the primary care clinic, and telephone calls to primary care clinic. Information on medications used were distinguished between study drugs (daily cost for each dosage level) and rescue medication use (per occasion cost). Unit costs relating to each of these resources (for the 2003/2004 financial year) were taken from published sources for the UK (10).

For each patient and for each week in the study, the total cost of treatment (study drugs only) and the cost of other health service contacts (all primary/secondary care costs and rescue medication use) was calculated. The approach to estimating costs was to employ standard regression analysis on treatment cost and other cost separately. This approach allowed the analysis to separately estimate costs by stratum (important for treatment cost), facilitates

the linking of costs to the control status of patients (important for other health service costs) and allows adjustment for the UK analysis using the full GOAL data set.

Impact on health related quality of life

If economic analyses are to be useful to decision makers, the outcomes reported must be in a form that is comparable across disease areas. The most popular outcome for this purpose is the quality-adjusted life-year (or QALY) which weights survival by a utility score which reflects the health status of the patient (11). This utility weight is anchored at 1 (representing perfect health) and 0 (representing death). Although the GOAL study did not include a utility measure as part of its design, it did include a disease specific instrument, the Asthma Quality of Life Questionnaire (AQLQ) (12) completed at baseline and at each clinic visit in the study. A mapping algorithm exists to translate AQLQ scores into a utility score suitable for economic appraisal (S. Macran and P. Kind, personal communication). Using this algorithm, the AQLQ scores were translated into utilities which were entered into a regression analysis that allowed the utility scores to be directly associated with control status categories observed in the trial.

Cost-effectiveness and uncertainty

The cost-effectiveness of aiming for total control with SFC is estimated by bringing together the estimates of proportion of time spent in each state, the quality of life in each state, the cost associated with each state and the cost of treatment from each of the equations described above separately for each of the strata in the original study. Uncertainty is handled statistically through uncertainty in the estimated coefficients of each regression model. The non-parametric approach of bootstrapping (13) is employed in order to account for potential correlation between the regression models comprising the analysis and to calculate confidence intervals for cost-effectiveness ratios (14).

Results

Control status

Table 1 shows the proportion of time during the 52-weeks of the trial that patients spent in the four control categories separately by treatment arm and by baseline stratum. The table shows the observed data (first three rows) and predictions from a multinomial model (the second three rows) with allocation group and stratum as explanatory variables (all significant predictors of control status with $P < 0.001$) and it is clear that the model provides a good fit to the observed data. Treatment with SFC clearly has a positive impact on asthma control irrespective of the baseline stratum of the patient.

Table 1. Observed and predicted percentages of time spent in categories of control status by strata and treatment allocation

	FP arm				SFC arm			
	TC	WC	NWC	X	TC	WC	NWC	X
Observed								
Stratum 1	32	33	34	1	40	32	28	0
Stratum 2	22	31	46	1	35	34	30	1
Stratum 3	17	29	52	2	26	33	40	1
Modelled								
Stratum 1	31	32	37	1	42	32	26	0
Stratum 2	24	32	44	1	34	34	32	1
Stratum 3	17	29	52	2	26	32	40	1

FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate in combination; TC, totally controlled; WC, well controlled; NWC, not well controlled (no exacerbation); X, exacerbation.

Resource use costs

Regression models were run separately for study treatment and other health service costs. For costs due to study treatment, allocation to the combination arm was expected to increase costs but that the absolute difference would differ across the strata. Therefore, the regression model for treatment cost included treatment allocation and stratum as explanatory variables (including interaction effects between treatment and strata). The resulting predictions of (weekly) treatment cost are presented in Table 2, which show that SFC results in additional costs compared with FP alone.

The regression for other health service costs is reported in Table 3 and shows that control status was found to be a highly significant predicator of this type of cost ($P < 0.001$). Importantly, the addition of stratum and treatment allocation had no significant effect once control status was accounted for, suggesting that the use of SFC has no effect on other health service resource use beyond the improvement in control status. Furthermore, it was found that including a UK adjustment for the cost of

Table 2. Treatment costs by treatment allocation and by stratum

	FP arm		SFC arm	
	Cost (£)	SE	Cost (£)	SE
Stratum 1	4.98	0.09	8.29	0.09
Stratum 2	5.60	0.09	8.37	0.09
Stratum 3	7.17	0.09	9.21	0.09

FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate in combination.

Table 3. Other health service costs as a function of control status and adjusting for the UK experience

	Regression model		Weekly costs	
	Cost (£)	SE	Cost (£)	SE
TC (constant)	0.02	0.30	0.02	0.30
WC	0.14	0.25	0.16	0.28
NWC	1.09	0.28	1.11	0.28
X	52.35	0.89	32.29	5.62
X * UK	−20.08	5.68		

TC, totally controlled; WC, well controlled; NWC, not well controlled (no exacerbation); X, exacerbation; UK, United Kingdom indicator variable.

exacerbation was highly significant ($P < 0.001$) suggesting that on average UK patients experiencing an exacerbation are treated less resource intensively (a reduced cost of £20) than the average resource use associated with an exacerbation in the trial. The predicted cost of a week in each control status category, with the cost of an exacerbation week adjusted to reflect the UK, are shown alongside the regression results in Table 3 (second column). It is clear from these results that cost decreases with improved control and the most significant healthcare costs are associated with exacerbations.

Health-related quality of life and QALYs

The approach to estimating utilities for the calculation of QALYs mirrors the regression analysis of other cost above. The utility values mapped from the AQLQ scores formed the explanatory variable in a regression with control status as explanatory. The results of this regression model are presented in Table 4 which includes a dummy variable for UK patients (all explanatory variables were significant predictors of quality of life at $P < 0.001$). In contrast to the other health service cost regression, adding in treatment as an explanatory variable resulted in a marginally significant utility gain of 0.01 ($P = 0.044$) even when controlling for control status, suggesting there may be additional benefits of treatment not captured by the simple categorization of control used in this paper. In the analysis presented here, this additional treatment benefit is ignored, making the analysis conservative with respect to the value of the combination product. Similarly, stratum 3 was associated with a small, but significant ($P < 0.001$), reduction in utility of −0.02 which is not accounted for in the analysis presented here.

Table 4. Health related quality of life utilities by control status

	Regression model		Weekly utilities	
	Utility	SE	Utility	SE
TC (constant)	0.902	0.003	0.946	0.011
WC	−0.045	0.002	0.900	0.011
NWC	−0.104	0.003	0.842	0.011
X	−0.216	0.007	0.729	0.013
UK	0.044	0.011		

TC, totally controlled; WC, well controlled; NWC, not well controlled (no exacerbation); X, exacerbation; UK, United Kingdom indicator variable.

Cost-effectiveness

To estimate cost-effectiveness for each of the strata in the GOAL study the four models presented in Tables 1–4 were combined. The mechanics of this approach are illustrated in Table 5 which presents all of the information from the previous tables by control status, stratum and allocation arm. Costs and QALYs are estimated within each stratum and by allocation arm through a process of weighted averaging over control status. The final column of Table 5 summarizes the differences between the arms.

The incremental analysis and cost-per-QALY calculations are reproduced in Table 6 using the information from Table 5, but also presenting confidence intervals for each reported value derived from the bootstrap analysis. The cost-effectiveness results by strata were estimated as £7600 (95% CI: £4800–10 700) per QALY gained for stratum 3; £11 000 (£8600–14 600) per QALY gained for stratum 2; and £13 700 (£11 000–18 300) per QALY

Table 5. Estimating the incremental costs and QALYs by stratum

	FP arm					SFC arm					
	TC	WC	NWC	X	Weighted Average	TC	WC	NWC	X	Weighted average	Difference
Stratum 1											
Status distribution (%)	31	32	37	1		42	32	26	0		
Treatment cost (£)	4.98	4.98	4.98	4.98	4.98	8.29	8.29	8.29	8.29	8.29	3.31
Other health care costs (£)	0.02	0.16	1.11	32.29	0.63	0.02	0.16	1.11	32.29	0.45	−0.18
HRQoL/QALYs	0.946	0.900	0.842	0.729	0.892	0.946	0.900	0.842	0.729	0.903	0.012
Stratum 2											
Status distribution (%)	24	32	44	1		34	34	32	1		
Treatment cost (£)	5.60	5.60	5.60	5.60	5.60	8.37	8.37	8.37	8.37	8.37	2.77
Other health care costs (£)	0.02	0.16	1.11	32.29	0.83	0.02	0.16	1.11	32.29	0.61	−0.22
HRQoL/QALYs	0.946	0.900	0.842	0.729	0.884	0.946	0.900	0.842	0.729	0.896	0.012
Stratum 3											
Status distribution (%)	17	29	52	2		26	32	40	1		
Treatment cost (£)	7.17	7.17	7.17	7.17	7.17	9.21	9.21	9.21	9.21	9.21	2.05
Other health care costs (£)	0.02	0.16	1.11	32.29	1.25	0.02	0.16	1.11	32.29	0.95	−0.31
HRQoL/QALYs	0.946	0.900	0.842	0.729	0.874	0.95	0.90	0.84	0.73	0.886	0.012

FP, fluticasone propionate; SFC, salmeterol/fluticasone propionate in combination; TC, totally controlled; WC, well controlled; NWC, not well controlled (no exacerbation); X, exacerbation.

Table 6. Cost-per-QALY by stratum of GOAL

	Difference		
	Point estimate	Lower 95% limit	Upper 95% limit
Stratum 1			
Total costs (£)	163	147	177
Total QALYs	0.0118	0.0094	0.0143
ICER (£)	13 700	11 000	18 300
Stratum 2			
Total costs (£)	132	114	147
Total QALYs	0.0120	0.0094	0.0145
ICER (£)	11 000	8600	14 600
Stratum 3			
Total costs (£)	90	61	109
Total QALYs	0.0118	0.0093	0.0141
ICER (£)	7600	4800	10 700

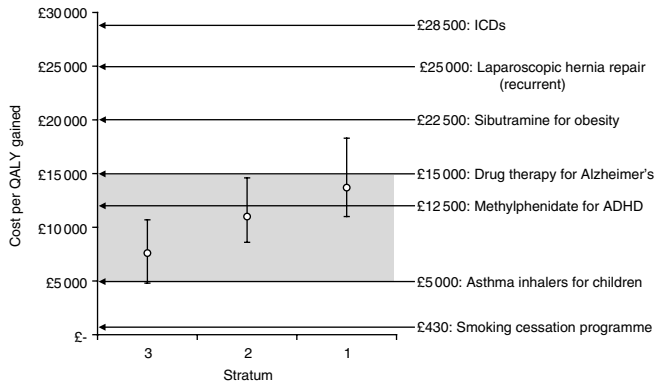

Figure 2. Results for the cost-effectiveness of aiming for total control by stratum including a selection of technologies recently recommended for use in the UK NHS by the National Institute of Health and Clinical Excellence (NICE) (15). The shaded area illustrates the range over which it has been suggested that NICE are unlikely to reject an intervention purely on cost-effectiveness grounds (16). ICD, implantable cardioverter defibrillator; ADHD, attention deficit and hyperactivity disorder.

gained for stratum 1. These results are illustrated in Fig. 2, which also shows the cost-effectiveness of a number of technologies that have been recommended for use in the UK NHS.

Discussion

This paper presents the cost-effectiveness of SFC relative to FP alone for achieving total control of asthma, based on the GOAL study. Since the GOAL study had a stratified design, the cost-effectiveness analysis was presented for each stratum, based on a series of statistical relationships estimated from the data. The results showed cost per QALY values that differ across the different strata of the GOAL study. In order to judge whether these figures represent good value, comparison with other uses of scare health care resources is required.

In the UK, the main public sector body for considering the value for money of treatments to be made available on the NHS is the National Institute of Health and Clinical Excellence (NICE). Although the official position is that there is no single cost-effectiveness threshold below which NICE considers cost-effectiveness to be proven, a threshold can be inferred from previous decisions. For example, Devlin and Parkin assembled a table of reported cost-effectiveness results and the associated guidance decision from NICE based on the information available from NICE's website. By conducting a logistic regression of these decisions they concluded that cost-effectiveness does explain NICE decision making, along with other key factors such as uncertainty and the burden of disease (15). More recently, it has been suggested that

'NICE would be unlikely to reject a technology with a ratio in the range of £5000–£15 000/QALY solely on the grounds of cost-ineffectiveness' (16).

A selection of decisions for which the NICE guidance was positive, taken from the Devlin and Parkin paper (12) are presented alongside the GOAL results in Fig. 2, together with the 'range' over which NICE would be unlikely to reject a technology on cost-effectiveness grounds. Figure 2 is strongly suggestive that aiming for TC with SFC would be considered cost-effective for all strata in GOAL in the context of NICE decision making in the UK.

The approach to estimating cost-effectiveness by stratum highlights a methodological issue when conducting economic analysis alongside a stratified trial. The approach reported here is based on a series of statistical equations for the components of the economic analysis that adjust for treatment allocation and stratum. An alternative approach would have been to present the analysis separately for each stratum. However, such an approach would have involved splitting the data with consequent loss of power. By modelling the effect of the stratum directly, the full power of the data was retained.

Nevertheless, this increased power comes through the extra structural assumptions imposed on the analysis. The aim in this paper was to make those assumptions as transparent as possible to allow the reader to judge their appropriateness. For example, the results from the cost-regression analyses suggest the important predictors of costs differ between treatment costs and other health service resource use. For treatment costs, it is the trial allocation arm and baseline stratum that are the important predictors of cost. By contrast, these variables are not predictive of other health service costs once control status is added to the regression. The results for the HRQoL regression are less definitive. In particular, it was reported in the text that both treatment allocation and stratum 3 were significantly predictive of HRQoL independently of control status. Nevertheless, in the reported cost-effectiveness analysis, these modest additional effects of treat-

ment and stratum 3 were excluded in order to simplify the assumptions of the analysis.

An additional issue is that the GOAL study was a multinational trial, but that the focus of this analysis was the cost-effectiveness in the UK. The approach used was to employ the whole data set on resource use in order to maximize the power of the resulting analysis, but to employ a UK indicator variable to adjust the analysis for UK specific effects. This approach highlighted that, on average, the cost of treating an exacerbation (deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit or hospitalization) in the UK was £20 below the overall cost in the trial.

The use of the non-parametric bootstrap allows confidence intervals to be calculated for the estimates of cost-effectiveness based on combining a series of statistical relationships estimated from the data. These confidence intervals represent uncertainty related to sampling variation and include potential correlation structure between the estimated equations. However, the confidence intervals do not include uncertainty related to the algorithm that links the AQLQ disease specific instrument to the utility scores suitable for calculating QALYs, as this algorithm was based on data external to the trial.

Conclusion

The GOAL study has shown that a strategy of aiming for total control leads to better outcomes for the majority of patients and that these outcomes translate to improvements in quality-adjusted life years. The use of SFC compared with FP alone results in a cost-per-QALY ratio that compares favourably with other uses of scarce health care resources that have recently been recommended by the NICE in the UK.

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