AUDIT, RESEARCH AND GUIDELINE UPDATE

The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry

Stephen O'Neill,[1] Joan Sweeney,[2] Chris C Patterson,[3] Andrew Menzies-Gow,[4] Rob Niven,[5] Adel H Mansur,[6] Christine Bucknall,[7] Rekha Chaudhuri,[8] Neil C Thomson,[8] Chris E Brightling,[9] Ciaran O'Neill,[1] Liam G Heaney,[2] on behalf of the British Thoracic Society Difficult Asthma Network

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2013-204114).

For numbered affiliations see end of article.

Correspondence to
Professor Liam Heaney, Centre for Infection and Immunity, Queen's University of Belfast, Level 8, Belfast City Hospital, Lisburn Road, Belfast, Northern Ireland BT9 7AB, UK; l.heaney@qub.ac.uk

Received 8 July 2013
Revised 28 April 2014
Accepted 22 May 2014

To cite: O'Neill S, Sweeney J, Patterson CC, *et al*. *Thorax* Published Online First: [*please include* Day Month Year] doi:10.1136/thoraxjnl-2013-204114

ABSTRACT

Severe refractory asthma poses a substantial burden in terms of healthcare costs but relatively little is known about the factors which drive these costs. This study uses data from the British Thoracic Society Difficult Asthma Registry (n=596) to estimate direct healthcare treatment costs from an National Health Service perspective and examines factors that explain variations in costs. Annual mean treatment costs among severe refractory asthma patients were £2912 (SD £2212) to £4217 (SD £2449). Significant predictors of costs were FEV_1% predicted, location of care, maintenance oral corticosteroid treatment and body mass index. Treating individuals with severe refractory asthma presents a substantial cost to the health service.

INTRODUCTION

The global prevalence of asthma is estimated to be 300 million[1] and approximately 18% of the UK population have doctor diagnosed asthma.[2] There is a significant economic burden associated with the disease[3] and an association between disease severity and economic burden.[4]

A key issue in prior analyses is the definition of severe asthma. This paper focuses on patients precisely characterised using systematic evaluation protocols as having severe refractory asthma (SRA) and explores the direct annual treatment costs and drivers of cost within this population from the perspective of a publicly funded provider.

METHODS

The data analysed are patient-specific anonymised healthcare data drawn from the British Thoracic Society National Registry for dedicated UK Difficult Asthma Services in 2012. Currently, seven UK Specialist Difficult Asthma Services submit data to the Registry: Belfast City Hospital; Royal Brompton Hospital, London; Glenfield Hospital, Leicester; University Hospital of South Manchester; Birmingham Heartlands Hospital; Gartnavel Hospital, Glasgow; and Stobhill Hospital, Glasgow. After systematic multi-disciplinary assessment, patients were classified using the American Thoracic Society[5] definition for refractory asthma (n=516) and compared with a group with difficult to manage, but non-SRA disease (n=80).

Data from the Registry capture healthcare utilisation including hospital admissions and general practitioner/Accident & Emergency (GP/A&E) unscheduled visits in the 12 months prior to being first seen at the difficult asthma clinics. Published references were used to monetise healthcare utilisation and each aspect of care was multiplied by this cost and aggregated to provide a total healthcare cost for the individual. As costs are estimated for a 12-month time period, no discounting is required.

All asthma-related medications were recorded at the patient's first visit to the Difficult Asthma Service. Unit costs for medication were obtained from the Prescription Cost Analyses for Northern Ireland 2011.

Where data were not captured in the Registry, estimates were made based on expert opinion, using high/low cost scenarios. Scheduled GP visits were estimated at one visit per year in the low cost scenario and in the high cost scenario were matched to unscheduled visits, where it was assumed that each unscheduled GP/A&E visit would be followed up with a scheduled GP visit. Outpatient respiratory reviews were estimated at two visits per year and include the cost of consultant/nurse time and lung function tests. Additional detail on the low/high cost scenario is presented in the online supplementary material.

In addition to asthma treatments, the Registry records any other medication received by the patients. These were costed using a similar methodology and are listed as non-asthma medication. Asthma and non-asthma medication were identified and categorised before analyses. Full references are available in the online supplementary material.

DATA ANALYSIS

After calculating total costs for each patient, a series of regression analyses were used to examine factors that explain variations in treatment costs among SRA patients. Variables used to explain costs (chosen based on available data) were gender, age, clinical centre, best achieved FEV_1, use of maintenance oral corticosteroids (OCS), body mass index (BMI) and smoking status. Analysis was carried out using Stata 10.

RESULTS

Figure 1 displays costs for healthcare utilisation and asthma-related medication for SRA patients (see online supplementary figure S1 for non-SRA costs), a breakdown of costs (see online supplementary table A1), summary of demographic data (see online supplementary table A2), medication costs in the low/high cost scenarios (see online supplementary figures S2A (SRA patients) and S2B (non-SRA patients)) and a breakdown of medication, healthcare utilisation and associated costs (see online supplementary tables A3–A7) together with comparisons by hospital and of patient characteristics.

SRA patients had more unscheduled visits (SRA, median 4 (IQR 2–6) vs non-SRA, median 3 (IQR 0–6)) and hospital admissions (SRA, median 0 (IQR 0–1), 274 of 516 (48%) had no admissions vs non-SRA, median 0 (IQR 0–1), 43 of 80 (54%)), confirming that the admission rate in SRA patients in these specialist centres was relatively low at referral (see online supplementary table A2). The combined average cost of these medical services in the low (high) cost scenario was £1207 (£2077) for SRA patients and £935 (£1764) for non-SRA patients.

The major driver of cost was medication (see online supplementary figure S2). Long acting bronchodilator/corticosteroid combination inhalers represent the greatest share of medication-related costs (£885–£1239 for SRA patients (low/high cost scenario) and £425–£678 for non-SRA patients). Small numbers of patients on oxygen (five SRA) and omalizumab (11 SRA) incurred substantial costs (oxygen, individual patient cost £8908 and omalizumab, costing between £3330 and £26 640 depending on omalizumab dose) and cost differences were also noted between clinical centres (see online supplementary table A7).

Regression analysis (online supplementary tables A8–A11, low cost scenario) revealed that, after adjustment for covariates, patients on maintenance OCS on average cost 43% more than those not on maintenance steroids (95% CI 27% to 59%). Of note also is that non-medication costs (19% greater (95% CI −4% to 42%)) and non-asthma-related medication were also higher (58% greater (95% CI 11% to 104%)) for these patients. Similar results were evident in the high cost scenario (see online supplementary tables A8–11). Patients requiring two or more rescue courses of steroids had 31% higher costs (95% CI 14% to 48%) illustrating the importance of recurrent exacerbations. For each unit increase in percentage of predicted FEV_1, there was an associated 0.34% reduction in asthma-related medication costs (95% CI −0.55% to −0.12%). In the high cost scenario, total costs for severely obese SRA patients (BMI>40 kg/m^2) are 17% higher than those of normal weight patients (95% CI 0.3% to 34%).

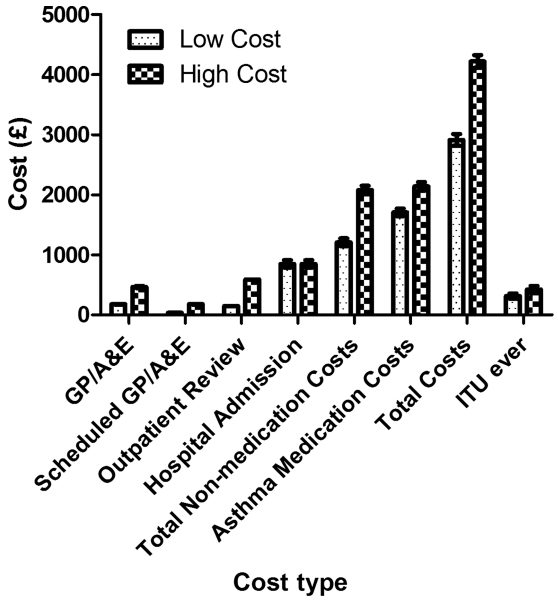

Figure 1 Healthcare and asthma-related medication costs for severe refractory asthma.

DISCUSSION

This study examines the annual healthcare costs in a well-characterised cohort of SRA patients and examines the distribution and drivers of costs in this population. A recent European study demonstrated mean per patient costs in controlled asthma of €509 (£451) and uncontrolled asthma €2281 (£2022), similar to our non-SRA cost. Patients with SRA cost more compared with other conditions (mean costs—type II diabetes £2567; stroke £1301; COPD £819; chronic kidney disease £235 (2% on renal replacement therapy £27 000)) (see online supplementary materials for full discussion and references).

A key finding of the study is that asthma medication is the major driver of total costs, not unscheduled GP/A&E or hospital admissions. This implies that the overall cost of care in this population will significantly decrease if the price of multiple drug therapies used by them falls. This is likely to be most apparent for inhaled combination therapies, specifically with the arrival of generic combination inhalers. Finally, future studies examining the effect of novel therapies or interventions in SRA should consider a 'medication reduction' strategy in their development programme; specifically, if a new therapy could provide a reduction in healthcare utilisation in parallel with a reduction in maintenance asthma medication use, it is more likely to be cost-effective.

We found that subjects on maintenance OCS are 43% more expensive than those not receiving maintenance OCS. In those on maintenance steroids, asthma-related medications were more expensive but notably, their non-medication costs and non-asthma-related medication were significantly higher. Of note, non-asthma medication includes proton pump inhibitor and bisphosphonates, examples of therapies used to manage side effects of OCS induced morbidity. Recurrent exacerbation is also a significant driver of costs; subjects with more than two exacerbations requiring OCS were approximately 31% more expensive than subjects with less than two courses of rescue OCS.

Establishing the costs and cost drivers for SRA will aid policymakers examining the cost-effectiveness of currently available 'add-on' treatments such as omalizumab in this group. Recent National Institute of Health and Care Excellence guidance on omalizumab allows access to subjects receiving recurrent rescue and maintenance OCS (see online supplementary materials for reference). Our data support this analysis, as both subjects requiring recurrent rescue OCS for exacerbation and maintenance OCS appear more expensive based on our results. However, it remains to be seen what additional costs are associated with longer term maintenance OCS in this population.

The association between severe obesity (BMI >40) and asthma cost is interesting—we have previously published data from the Registry that indicate patients with SRA and obesity display particular characteristics and may represent a distinct clinical phenotype. Cluster analyses of severe asthma populations have also identified obesity as an identifiable phenotype in severe asthma (see online supplementary materials for full discussion and references). The association with increased cost may reflect this altered phenotype and poor response to treatment.

Our analysis does have some limitations. Non-National Health Service and indirect costs were excluded, as were

dispensing fees, and so our cost estimates are likely to be conservative. Similarly, as the Registry did not have complete records for all healthcare visits, assumptions around these were required; however, we do not think these threaten the validity of our analyses, as scheduled and unscheduled healthcare visits represent a minor element of total cost.

In conclusion, this paper has estimated treatment costs for SRA patients in the UK to be £2912–£4217 per person per year. These costs are greater than those for patients with poorly controlled 'difficult asthma' referred to the same clinics. The costs are dominated by asthma medication costs and, importantly, these costs outweigh healthcare utilisation costs. Maintenance OCS and frequent exacerbations are important additional drivers of costs in this population.

Author affiliations
[1]JE Cairnes School of Business and Economics, National University of Ireland Galway, Galway, Ireland
[2]Centre for Infection and Immunity, Queen's University of Belfast, Belfast, UK
[3]Centre for Public Health, Queen's University of Belfast, Belfast, UK
[4]Royal Brompton Hospital, London, UK
[5]MAHSC, The University of Manchester & UHSM, Manchester, UK
[6]Severe and Brittle Asthma Unit, Birmingham Heartlands Hospital, Birmingham, UK
[7]Department of Respiratory Medicine, Royal Infirmary, Glasgow, UK
[8]Department of Respiratory Medicine, Division of Immunology, Infection and Inflammation, University of Glasgow and Gartnavel General, Glasgow, UK
[9]Department of Infection, Inflammation and Immunity, Institute for Lung Health, University of Leicester, Leicester, UK

Acknowledgement Many thanks to the data input staff and medical and nursing staff in the UK Difficult Asthma Centres.

Contributors LGH is Co-ordinator of the British Thoracic Society UK Difficult Asthma Registry and with JS and SO'N collated and managed the data for this manuscript. LGH, JS, SO'N, CO'N and CCP were responsible for analysing the data. CEB, AM-G, RMN, AHM, CB, RC and NCT colead the British Thoracic Society Difficult Asthma; all have contributed equally to the writing and review of this manuscript.

Funding Pilot funding for the Registry was provided as unrestricted research grants from Astra Zeneca, GlaxoSmithKline, Novartis and Medimmune. JS is supported by HSC R&D (NI) and GlaxoSmithKline (PhD studentship). CB is supported by a Wellcome Senior Clinical Fellowship.

Competing interests JS is supported by HSC R&D (NI) and GlaxoSmithKline (PhD studentship funding). CEB is supported by a Wellcome Senior Clinical Fellowship and has received consultancy fees and or research funding from GlaxoSmithKline, AZ, MedImmune, Amgen, Novartis, Chiesi, BI and Roche. AM-G has attended advisory boards for Mundi Pharma, Boeringer Ingelheim, Johnson and Johnson, Amgen and Roche. He has received sponsorship to attend international meetings from Novartis and Boeringer Ingelheim. He has received lecture fees from Novartis, GlaxoSmithKline, Roche and NAPP. He has taken part in asthma clinical trials (GSK and Genentech) for which his Institution was remunerated. CB has received travel support from Novartis, GlaxoSmithKline and Boehringer and has received payment for lectures, including service on speakers' bureaus, from Novartis and GlaxoSmithKline. RMN has received payment for lectures from GlaxoSmithKline, Novartis, Chiesi, Boehringer and AstraZeneca; and has received travel expenses from GlaxoSmithKline, Novartis and Boehringer. RMN (or any members of his family) has any shares or any percuniary interest in any pharmaceutical industry and has nothing to gain financially from the publication of this paper. AHM has received travel support from the British Thoracic Society; has consultant arrangements with NAPP and Novartis; has received payment for lectures, including service on speakers' bureaus, from GlaxoSmithKline, Chiesi, Vectura and Novartis; and has received travel expenses from Boehringer and Novartis. RC has received an unrestricted educational grant from Novartis to improve local asthma services, sponsorship to attend international meetings from GlaxoSmithKline, Novartis, Teva and Boeringer Ingelheim and has taken part in Advisory Board meeting (Novartis) and has taken part in asthma clinical trials (Roche, GSK, Astrazeneca, Janssen and Genentech) for which her Institution was remunerated. CCP's spouse holds shares in GlaxoSmithKline. NCT has participated in advisory boards and/or received consultancy fees from Chiesi, GlaxoSmithKline, Respivert and Roche. He has received lecture fees from AstraZeneca, Boston Scientific, Chiesi, Glaxo SmithKline and Novartis; industry-sponsored grant funding to the University of Glasgow from AstraZeneca, Boston Scientific, Genentech, Glaxo SmithKline, Novartis, Pfizer, Respivert and Synairgen for participating in clinical trials. Professor Heaney has received grant funding from Genentech and GlaxoSmithKline, has taken part in Advisory Boards and given lectures at meetings supported by GlaxoSmithKline, Merck Sharpe & Dohme, Nycomed, Novartis and Astra Zeneca. He has received support funding to attend International Respiratory meetings (AstraZeneca, Chiesi, Novartis, Teva and GlaxoSmithKline) and has taken part in asthma clinical trials (GSK and Genentech) for which his Institution was remunerated. None of these activities have any direct relationship to the content of this manuscript.

Ethics approval ORECNI.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Global Initiative for Asthma. Global strategy for asthma management and prevention. 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf (accessed 31 Jul 2013).
2 To T, Stanojevic S, Moores G, *et al*. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012;12:204.
3 Bahadori K, Doyle-Waters MM, Marra C, *et al*. Economic burden of asthma: a systematic review. *BMC pulmonary medicine* 2009;9:24.
4 Cisternas MG, Blanc PD, Yen IH, *et al*. A comprehensive study of the direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003;111:1212–18.
5 American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341–51.

Online Supplement

The Cost of Treating Severe Refractory Asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry

Stephen O'Neill[2], Joan Sweeney[1], Chris C Patterson[3], Andrew Menzies-Gow[4], Rob M Niven[5], Adel H Mansur[6], Christine Bucknall[7], Rekha Chaudhuri[8], Neil C Thomson[8], Chris E Brightling[9] Ciaran O'Neill[2], Liam G Heaney[1] on behalf of the British Thoracic Society Difficult Asthma Network

[1]Centre for Infection and Immunity, Queen's University of Belfast, UK, [2]JE Cairnes School of Business and Economics, National University of Ireland Galway, [3]Centre for Public Health, Queen's University of Belfast, UK, [4]Royal Brompton Hospital, London, UK.[5] MAHSC, The University of Manchester & UHSM, Manchester, UK, [6]Severe and Brittle Asthma Unit, Birmingham Heartlands Hospital.[7]Department of Respiratory Medicine, Royal Infirmary, Glasgow, UK.[8]Department of Respiratory Medicine, Division of Immunology, Infection and Inflammation, University of Glasgow and Gartnavel General , Glasgow, UK, [9]Department of Infection, Inflammation and Immunity, Institute for Lung Health, University of Leicester, UK.

Methods

Costing Scenarios

The high and low cost scenarios were calculated as follows for different aspects of total costs.

Use of health care providers

Two scenarios are considered for visits to health care providers – in the low cost scenario, it is assumed that all of the unscheduled visits are to the GP (£36), that patients make one scheduled visit to the GP per year and one scheduled outpatient visit per year (£147). Published references (1) were used to monetize healthcare utilization by applying a vector of unit costs adjusted for health inflation to activity(2). In the high cost scenario, in addition to the recorded unscheduled hospital admissions (£727), it is assumed that all additional unscheduled visits are to Accident & Emergency(£96), and that each of these is followed by a scheduled visit to the GP. It is also assumed that patients make four scheduled outpatient hospital visits. Outpatient respiratory reviews were estimated to include the cost of lung function tests and consultant and nurse time (3). In respect of the lifetime costs of ITU, the Registry captured data on lifetime use of ITU at entry to the Registry. The per diem ITU costs were based on UK reference costs assumed in the low cost scenario not to involve ventilation (£928) and in the high cost scenario to involve ventilation (£1,248).

Asthma Medication costs

In addition to costs associated with visits to the various care providers, patients incur a number of medication related costs. Unit costs for medications were obtained from the Prescription Cost Analyses (PCA) for Northern Ireland 2011(4). Costs are calculated for the following medications/treatments: (1) Long-Acting Beta-2 Agonists (LABA) and Inhaled Corticosteroids (ICS), (2) Short-Acting Beta Agonists (SABA), (3) Prednisolone (maintenance and rescue courses), (4) Theophyllines, (5) Leukotriene Receptor Antagonists (LTRAs), (6) Oxygen and (7) Nebulised drugs. The dataset also includes information on patients' usage of other medications and these were categorised following consultation with clinicians, as being associated with asthma or relating to non-asthma co-morbidities. Summary statistics for the usage of services and medications for each group is contained in Tables A1 & A2 below.

Long Acting Beta-2 Agonists (LABA) and Inhaled Corticosteroids (ICS)

Almost all patients in the dataset (95%) were receiving regular treatment with LABA either in combination with ICS or as monotherapy. The Registry records whether patients are receiving ICS and whether they receive LABA (Seretide or Symbicort), in addition to the beclometasone dipropionate (BDP) equivalent daily dose received. In most cases, whether the patient is taking Symbicort or Seretide was stated in the data or can be reasonably inferred from the BDP equivalent. However for each medication there are different delivery mechanisms; for Seretide there is the Accuhaler and Evohaler, while for Symbicort there are two models of the Turbohaler, the 200/6 and the 400/12. Limited information was available to identify which delivery mechanism was used in individual cases. Two cost scenarios are considered for both Seretide and Symbicort. For Seretide, in the Low cost scenario patients are assumed to use the Accuhaler while in the High cost they are assumed to use the Evohaler. For Symbicort, in the Low cost scenario patients are assumed to predominantly use the lower cost 400/12 unit, in the high cost scenario they are assumed to use the 200/6 unit for all doses up to 1600 BDP. BDP equivalent dose was not available for 31 SRA and 9 non-SRA patients. In the low cost scenario these patients were assigned the minimum BDP equivalent dose for that patient population in the Registry while in the high cost scenario they were assigned the maximum BDP dose. A number of patients receive inhaled steroids (e.g. fluticasone, ciclesonide, budesonide and beclometasone) separately from LABA treatment in which case costs were calculated using BDP equivalent dose. For Fluticasone, BDP equivalent dose is divided by 2. In the small number of patients, where the branded inhaled steroid was not identified in the data, patients were assumed to receive beclometasone.

Short-Acting Beta Agonists (SABA)

For patients taking SABAs, the average number of uses per day is recorded by the Registry and is costed on the basis of an assumed dose of 200mcg of salbutamol per use unless the SABA is stated (e.g. Airomir).

Prednisolone (maintenance and rescue courses)

Patients receive prednisolone to control inflammation in the airways either as a maintenance steroid or as a rescue steroid in the advent of severe exacerbations. The Registry records the maintenance dose which each patient is on which is used to generate a cost figure for each patient. In case of severe exacerbations, prednisolone is also prescribed as a rescue course, typically 40mg per day for 7 days. The Registry records the number of rescue courses taken by each patient in the previous 12 months.

Theophylline

Theophylline is a bronchodilator which also helps decrease swelling in the lungs. Patients were assumed to receive 300mg of Uniphyllin Continus twice per day, but costs of all branded theophylline are low and similar.

Oxygen

A small number of refractory asthma patients were receiving oxygen (5 subjects). Patients were assumed to rent a concentrator at a fixed cost of £521 per year and to use one cylinder of oxygen DD Light (460L) per day.

Nebuliser use

Although the Registry records whether a nebuliser is used, it does not record the frequency of use. Two scenarios are considered; in the low cost scenario patients are assumed to use their nebuliser on average four times per day for one week every eight weeks. In the high cost scenario patients are assumed to use the nebuliser four times every day.

Anti- IgE

In the low cost scenario patients are assumed to be on a dose of 150mg 4 weekly, and in the high cost scenario 600mg bi-weekly in addition to using two epipens per year in all scenarios.

Excluded costs

Only direct costs from the perspective of the public payer (in this case the NHS) have been included. However, it is important to recognise that asthma patients may face a number of additional costs including travel costs and other costs incurred by patients associated with visits to health care providers and treatment related costs, such as lost earnings due to impaired productivity and/or reduced quality of life due to conditions such as depression which may result from their asthma.

Data Analysis

In Table A2, the Wilcoxon rank sum test (which is equivalent to the Mann-Whitney two-sample statistic) is used to test the null hypothesis that the distribution of the variables are equal for the SRA and Non-SRA groups. These tests are non-parametric and hence do not assume normality. Failure to reject the null hypothesis indicates that the distributions may be the same, while rejecting the null implies that the distributions differ across the two groups. For binary variables (gender and ethnicity [caucasian/non-caucasian]) a Chi-square test was used instead with the null hypothesis that there is no relationship between the variable and the SRA and Non-SRA groups.

After calculating the total costs associated with each patient, a series of semi-logarithmic multiple regressions were carried out to examine the factors that explain variations in treatment costs among SRA patients. The factors considered were dependent on the information available from the Registry and were chosen based on *a priori* expectations of the variables that may influence patients' costs. The chosen factors were gender, age, Clinical Centre, the patients' best FEV_1, whether they receive maintenance steroids, BMI, and smoking status. The dependent variable in each case is natural logarithmically transformed, thus coefficients may be multiplied by 100 and then interpreted as the approximate percentage change in cost resulting from a unit change in the explanatory variable. This provides an approximation which for continuous variables is reasonable given the magnitude of the coefficients. As discussed by Halvorsen and Palmquist(5) and Kennedy(6), for binary variables, we transform the coefficient as follows: $\beta^*=(\exp(\beta)/\exp(0.5*SE(\beta)^2))-1$. Robust standard errors were applied to allow for clustering effects caused by correlation between individuals within clinical centres. The standard errors were calculated by bootstrapping (x 1000) the coefficients or adjusted coefficients as appropriate, which also accounts for any departures from the normality assumptions required for the regression. Error bars on figures 1 and 2 represent standard error of the mean (SEM). To test the joint significance of location (and separately BMI class) we follow the approach suggested in Chapter 21 of Fox (2008) "Applied Regression Analysis and Generalized Linear Models, Second Edition" (see http://www.sagepub.com/upm-data/21122_Chapter_21.pdf). Let be the test statistic calculated for the b^{th} bootstrap sample under the null hypothesis that the bootstrapped estimates for the variables to be tested equal their values from the original sample. This allows us to obtain the sampling distribution of the test statistic. The proportion of times that exceeds the test statistic, *T,* for the original sample gives the p-value for the test. In the current context, T is a Wald test that the chosen coefficients are simultaneously 0.

As can be seen from figure 1, medication costs are a key driver of total asthma costs for SRA patients, accounting for 58% (51%) of total costs in the low (high) cost scenario. Figure 3 displays a breakdown of medication related costs for SRA and non-SRA patients respectively. LABA and inhaled Steroids represent the greatest share of medication related costs with a combined cost of between £885 and £1,239 for SRA patients, while for non-SRA patients they contribute between £425 and £678. Short-acting beta-agonist (SABA) use by SRA patients was an average of 8.8 times per day, and non-SRA patients an average of 4.9 times per day, leading to average costs of £126 and £69 respectively. The average cost of maintenance oral steroids (prednisolone) is comparable to the cost for SABA at an average cost of £140 per year across all patients. Rescue steroid treatments costed a further £84 for SRA patients and £44 for non-SRA. LTRAs also contribute substantially to total costs; £157 for SRA patients and £119 for non-SRA patients. Although only five SRA patients receive oxygen, the costs of doing so are significant - £86 when averaged across all 516 SRA patients, but the individual per patient cost is £8,908.

Approximately 43% of SRA and 21% of non-SRA patients were using nebulised therapy, with costs ranging from £11 to £90 for SRA patients depending on the scenario and from £5 to £41 for non-SRA. Annual costs for theophylline were £27 for SRA patients and £13 for non-SRA patients, with 35% of SRA patients receiving theophylline compared to 26% of non-SRA patients.

The average annual cost of the other asthma medications across all SRA patients was £171 and across non-SRA patients was £33. Patients receiving anti-IgE therapy (n=11) demonstrated a cost of between £6,874 and £29,825 depending on the scenario with Omalizumab alone costing between £3,330 and £26,640 depending on dose.

Table A1: Costs relating to visits to medical service providers by patient type

	Low Cost Scenario:						*High Cost Scenario:*					
	SRA (N=516)			**Non-SRA (N=80)**			***SRA (N=516)***			**Non-SRA (N=80)**		
Cost type:	**Mean**	**Std. Dev**	**Confidence interval**	**Mean**	**Std. Dev**	**Confidence interval**	**Mean**	**Std. Dev**	**Confidence interval**	**Mean**	**Std. Dev**	**Confidence interval**
Cost for unscheduled GP or A&E visits	175	140	(163 , 187)	160	176	(121 , 199)	466	372	(434 , 498)	424	467	(322 , 526)
Cost for scheduled GP or A&E visits	36	0	(36 , 36)	36	0	(36 , 36)	175	140	(163 , 187)	160	176	(121 , 199)
Cost for unscheduled Hospital visits	848	1440	(724 , 972)	592	835	(409 , 775)	848	1440	(724 , 972)	592	835	(409 , 775)
Cost for scheduled Hospital visits	147	0	(147 , 147)	147	0	(147 , 147)	588	0	(588 , 588)	588	0	(588 , 588)
Total Non-Medication Related Costs	1207	1481	(1079 , 1335)	935	884	(741 , 1129)	2,077	1,644	(1935 , 2219)	1,764	1,142	(1514 , 2014)
Total Medication Related Costs	1705	1417	(1583, 1827)	736	705	(582 , 890)	2,139	1,578	(2003, 2275)	1,024	912	(824 , 1224)
Total Cost	2912	2212	(2721, 3103)	1670	1149	(1418 , 1922)	4,217	2,449	(4006, 4428)	2,788	1,449	(2470 , 3106)
Breakdown of Medication related Costs	**Mean**	**Std. Dev.**	**Confidence interval**	**Mean**	**Std. Dev.**	**Confidence interval**	**Mean**	**Std. Dev.**	**Confidence interval**	**Mean**	**Std. Dev.**	**Confidence interval**
LABA and Inhaled Steroids	885	573	(836 , 934)	425	489	(318 , 532)	1239	842	(1166 , 1312)	678	696	(525 , 831)
SABA	126	180	(110 , 142)	69	46	(59 , 79)	126	180	(110 , 142)	69	46	(59 , 79)
Anti-immunoglobulin (anti-IgE) treatment	0	0	(0 , 0)	0	0	(0 , 0)	0	0	(0 , 0)	0	0	(0 , 0)
Prednisolone (Maintenance)	158	259	(136 , 180)	28	148	(-4 , 60)	160	263	(137 , 183)	28	148	(-4 , 60)
Prednisolone (Rescue)	84	79	(77 , 91)	44	45	(34 , 54)	84	79	(77 , 91)	44	45	(34 , 54)
Theophylline	27	58	(22 , 32)	13	23	(8 , 18)	27	58	(22 , 32)	13	23	(8 , 18)
Proton Pump Inhibitor (PPI)	36	50	(32 , 40)	25	40	(16 , 34)	36	50	(32 , 40)	25	40	(16 , 34)
Leukotriene Receptor Antagonists	157	174	(142 , 172)	119	158	(84 , 154)	157	174	(142 , 172)	119	158	(84 , 154)
Oxygen	86	873	(11, 161)	0	0	(0 , 0)	86	873	(11, 161)	0	0	(0 , 0)
Nebuliser uses	11	16	(10 , 12)	5	10	(3 , 7)	90	119	(80 , 100)	41	80	(23 , 59)
Other Asthma Medications	171	767	(105 , 237)	33	116	(8 , 58)	171	767	(105 , 237)	33	116	(8 , 58)
Total Asthma Medication costs	1705	1417	(1583, 1827)	736	705	(582 , 890)	2139	1578	(2003, 2275)	1024	912	(824 , 1224)
Non-Asthma Medications (Excluded)	270	600	(218 , 322)	256	480	(151 , 361)	270	600	(218 , 322)	256	480	(151 , 361)

Note: All costs are averaged across the number of patients in the 2 groups (SRA and Non-SRA) rather than across the number of patients receiving a particular treatment

TableA2.Demographic details of the SRA (n=516) and non-SRA patients (n=80)

	SRA (N=516)				Non-SRA (N=80)				Wilcoxon rank sum test
Variable	**Mean**	**St. Dev**	**Median**	**Inter Quartile Range**	**Mean**	**St. Dev**	**Median**	**Inter Quartile Range**	**p-value**
Age (y)	48.5	13.9	49	(41, 58)	45.7	16.9	56.5	(42.5, 59)	0.133
Female (%)	62%	-	-	-	65%	-	-	-	0.608
Caucasian (%)	91%	-	-	-	95%	-	-	-	0.251
Age at diagnosis of asthma (y)	22	18.8	19	(3, 37)	26.3	21.6	25.5	(5, 45)	0.146
BMI (kg/m^2)	29.7	6.3	28.85	(25.1, 33.1)	30.1	7.1	29.9	(24.5, 34.8)	0.74
Unscheduled GP/A&E (1 year pre-referral)	4.9	3.9	4	(2, 6)	4.4	5	3	(0, 6)	0.05
Hospital admission (1 year pre-referral)	1.2	2	0	(0, 1)	0.8	1.2	0	(0, 1)	0.534
Rescue Oral Steroids (1 year pre-referral)	4.9	4.2	4	(2, 6)	3	2.8	2	(1, 5)	<0.001
FEV_1 % Predicted	67%	27%	68	(48, 85)	86%	24%	87	(76, 101)	<0.001
Inhaled steroid dose (BDP Equivalent mcg)	2,003	1,056	2000	(1600, 2000)	1,188	939	1000	(800, 1600)	<0.001

Table A3: Utilisation of medications and service by patients

	All Patients (N=596)			SRA (N=516)			Non-SRA (N=80)		
	N	Mean	St. Dev	N	Mean	St. Dev	N	Mean	St. Dev
Prednisolone dose in mg (Maintenance)	201	19.3	29.8	196	19.2	30.1	5	20.8	16.8
Prednisolone Courses (Rescue)	552	4.7	4.1	477	4.9	4.2	75	3	2.8
BDP equivalent dose (Inhaled Steroids)	590	1896.8	1076.5	513	2003.2	1056.1	77	1188.3	939.1
SABA uses per day	567	8.3	11.5	492	8.8	12.2	75	4.9	3
Unscheduled visits to GP or A&E	596	4.8	4	516	4.9	3.9	80	4.4	4.9
Scheduled visits to GP or A&E (low)	596	1	0	516	1	0	80	1	0
Scheduled visits to GP or A&E (high)	596	4.8	4	516	4.9	3.9	80	4.4	4.9
Total visits to GP or A&E (low)	596	5.8	4	516	5.9	3.9	80	5.4	4.9
Total visits to GP or A&E (high)	596	9.6	8	516	9.7	7.8	80	8.9	9.7
Unscheduled visits to Hospital	596	1.1	1.9	516	1.2	2	80	0.8	1.2
Scheduled visits to Hospital (low)	596	1	0	516	1	0	80	1	0
Scheduled visits to Hospital (medium)	596	2	0	516	2	0	80	2	0
Scheduled visits to Hospital (high)	596	4	0	516	4	0	80	4	0
Total visits to Hospital (low)	596	2.1	1.9	516	2.2	2	80	1.8	1.2
Total visits to Hospital (medium)	596	3.1	1.9	516	3.2	2	80	2.8	1.2
Total visits to Hospital (high)	596	5.1	1.9	516	5.2	2	80	4.8	1.2

Table A4: % of patients utilising individual medication classes

	All Patients (N=596)		SRA (N=516)		Non-SRA(N=80)	
	Number	%	Number	%	Number	%
Inhaled Steroids	590	99	513	99	77	96
LABA	566	95	496	96	70	88
SABA	567	95	492	95	75	94
Anti-immunoglobulin (anti-IgE)	0	0	0	0	0	0
Prednisolone (Maintenance)	201	34	196	38	5	6
Theophylline	201	34	180	35	21	26
Proton Pump Inhibitor (PPI)	212	36	188	37	24	30
Leukotriene Receptor Antagonists	260	44	229	44	31	39
Oxygen	5	0.84	5	0.97	0	0
Nebuliser Used	241	40	224	43	17	21

Table A5: Medication and healthcare costs (all patients)

	All Patients (N=596)					
	Low Cost Scenario:			*High Cost Scenario:*		
Variable	**Mean**	**Std. Dev.**	**Confidence Interval**	**Mean**	**Std. Dev.**	**Confidence Interval**
LABA and Inhaled Steroids	823	584	(773 , 873)	1164	845	(1091 , 1237)
SABA	118	170	(103 , 133)	118	170	(103 , 133)
Prednisolone (Maintenance)	140	251	(118 , 162)	142	255	(120 , 164)
Prednisolone (Rescue)	79	76	(72 , 86)	79	76	(72 , 86)
Theophylline	25	55	(20 , 30)	25	55	(20 , 30)
Proton Pump Inhibitor (PPI)	34	49	(30 , 38)	34	49	(30 , 38)
Leukotriene Receptor Antagonists	152	173	(137 , 167)	152	173	(137 , 167)
Oxygen	75	813	(5, 145)	75	813	(5, 145)
Nebuliser uses	11	15	(10 , 12)	83	116	(73 , 93)
Other Asthma Medications	152	717	(90 , 214)	152	717	(90 , 214)
Total Asthma Medication costs	1575	1383	(1456, 1694)	1990	1552	(1856, 2124)
Non-Asthma Medications	268	585	(218 , 318)	268	585	(218 , 318)

	All Patients (N=596)					
	Low Cost Scenario:			*High Cost Scenario:*		
Variable	**Mean**	**Std. Dev**	**Confidence Interval**	**Mean**	**Std. Dev**	**Confidence Interval**
Cost for unscheduled GP or A&E visits	173	145	(161 , 185)	460	386	(429 , 490)
Cost for scheduled GP or A&E visits	36	0	(36 , 36)	173	145	(161 , 185)
Cost for unscheduled Hospital visits	814	1377	(703 , 925)	814	1377	(703 , 925)
Cost for scheduled Hospital visits	147	0	(147 , 147)	588	0	(588 , 588)
Total Non-Medication Related Costs	1170	1418	(1056 , 1284)	2,035	1,588	(1908 , 2162)
Total Medication Related Costs	1575	1383	(1456, 1694)	1,990	1,552	(1856, 2124)
Total Cost	2745	2142	(2560, 2930)	4,025	2,389	(3819, 4231)

Note: All costs are averaged across the number of assessed patients in the rather than across the number of patients receiving a particular treatment

Table A6: Comparison of patient characteristics by Specialist Difficult Asthma Services

	Belfast (n=130)	Brompton (n= 105)	Leicester (n=109)	Manchester (n=156)	Birmingham (n= 22)	Gartnavel (n= 32)	Stobhill (n= 42)
Variable	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
Age (y)	46.7	47.6	49.2	50.8	41.6	47.3	45.7
Female	58.50%	64.80%	60.60%	68.60%	50.00%	65.60%	54.80%
Caucasian	100.00%	82.90%	82.60%	98.00%	77.30%	93.50%	95.20%
Age at diagnosis of asthma (y)	23.3	16.4	25.4	23.3	15.1	28.1	25
BMI (kg/m2)	30.1	29.6	29.1	29.7	31.1	28.6	31.4
Underweight	0.80%	1.00%	0.00%	1.30%	0.00%	0.00%	4.80%
(15-18.49kg/m^2)							
Normal weight	23.80%	21.00%	30.30%	23.10%	27.30%	28.10%	11.90%
(18.5-24.99kg/m^2)							
Overweight	30.00%	30.50%	25.70%	32.70%	22.70%	40.60%	28.60%
(25-29.99kg/m^2)							
Obese grade 1	23.80%	36.20%	27.50%	23.10%	22.70%	12.50%	23.80%
(30-34.99kg/m^2)							
Obese grade 2	13.80%	4.80%	12.80%	12.20%	4.50%	3.10%	16.70%
(35-39.99kg/m^2)							
Obese grade 3 (40kg/m^2 plus)	7.70%	6.70%	3.70%	7.70%	22.70%	15.60%	14.30%
Unscheduled GP/A&E (1 year pre-referral)	6.1	3.7	4.9	5.2	3.8	3.9	2.9
Hospital admission (1 year pre-referral)	0.9	1.7	0.9	1	2	0.8	1.1
Rescue Oral Steroids (1 year pre-referral)	5.4	4.8	4.7	3.6	6.1	4.2	5.8
FEV1 % Predicted	90.34	74.54	85.78	80.83	76.43	83.04	85.18
Inhaled steroid dose (BDP Equivalent mcg)	1602.3	1954.9	1852.3	1838.8	2931.4	2325	2152.4

Table A7.Comparison of Costs by Specialist Difficult Asthma Services

Variable	Belfast: (n=130) Mean	Brompton (n= 105) Mean	Leicester (n=109) Mean	Manchester (n=156) Mean	Birmingham (n= 22) Mean	Gartnavel (n=32) Mean	Stobhill (n= 42) Mean
Low Cost Scenario:							
Cost for unscheduled GP or A&E visits	221	135	177	186	145	139	105
Cost for scheduled GP or A&E visits	36	36	36	36	36	36	36
Cost for unscheduled Hospital visits	676	1245	654	715	1421	564	814
Cost for scheduled Hospital visits	147	147	147	147	147	147	147
Total Non-Medication Related Costs	1080	1563	1014	1085	1749	886	1102
Total Medication Related Costs	1274	1773	1416	1673	2243	1832	1518
Total Cost	2354	3336	2429	2757	3992	2717	2619
High Cost Scenario:							
Cost for unscheduled GP or A&E visits	587	359	470	495	384	368.92	279
Cost for scheduled GP or A&E visits	221	135	177	186	145	139	105
Cost for unscheduled Hospital visits	676	1245	654	715	1421	564	814
Cost for scheduled Hospital visits	588	588	588	588	588	588	588
Total Non-Medication Related Costs	2072	2327	1889	1985	2539	1659	1785
Total Medication Related Costs	1600	2261	1813	2050	3001	2397	1914
Total Cost	3672	4588	3701	4034	5540	4056	3699

Regression details and Tables

Table A8 displays results from the multiple regression for the log of total costs for the SRA patients in the low and high cost scenarios. The second and third columns of the table display coefficients and their bootstrapped standard errors. The fourth column presents the effects after transforming coefficients in line with Halvorsen and Palmquist (5) and the fifth and sixth column display the lower and upper bounds of a 95% confidence interval for the effect obtained by bootstrapping the effect. Columns 7 to 11 present similar information for the high cost scenario. Table A9 displays results from the multiple regression for the log of non-medication related costs (such as visits to the GP and A&E) and Table A10 displays results for the log of asthma related medication costs. Finally Table 11 presents results for the log of non-asthma related medication costs. Non-asthma related costs are the same in the low and high scenarios hence only one set of estimates are presented for this category.

Table A8: Regression analysis of logged Total costs for SRA patients

	Ln(Total cost) - low cost scenario					Ln(Total cost) - high cost scenario				
	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper
Female vs. Male	0.084	0.140	8.76%	-3.36%	20.89%	0.078	0.089*	8.08%	-1.55%	17.72%
Age	-0.011	0.276	-1.13%	-3.15%	0.90%	-0.013	0.098*	-1.30%	-2.85%	0.24%
Age^2	0.0001	0.515	0.01%	-0.01%	0.03%	0.0001	0.198	0.01%	-0.01%	0.03%
Brompton vs. Belfast†	0.071	0.460	7.68%	-12.64%	28.00%	0.015	0.842	1.81%	-13.71%	17.32%
Leicester vs. Belfast†	-0.079	0.393	-7.22%	-24.11%	9.67%	-0.073	0.317	-6.82%	-20.22%	6.58%
Manchester vs. Belfast†	-0.059	0.499	-5.39%	-21.57%	10.79%	-0.047	0.503	-4.36%	-17.45%	8.74%
Birmingham vs. Belfast†	0.375	0.003***	46.32%	9.18%	83.45%	0.279	0.012**	32.91%	3.49%	62.32%
Gartnavel vs. Belfast†	0.158	0.122	17.69%	-5.94%	41.33%	0.093	0.275	10.12%	-8.36%	28.61%
Stobhill vs. Belfast†	-0.015	0.898	-0.91%	-23.48%	21.67%	-0.095	0.308	-8.75%	-25.54%	8.05%
Best ever FEV1 % predicted	-0.001	0.286	-0.12%	-0.33%	0.10%	-0.001	0.549	-0.05%	-0.22%	0.12%
Maintenance Steroids Yes *vs* No	0.367	<0.001***	43.12%	27.34%	58.89%	0.262	<0.001***	29.30%	17.73%	40.87%
Underweight vs. Normal weight‡	-0.026	0.914	-2.75%	-55.60%	50.09%	-0.084	0.653	-8.01%	-44.96%	28.95%
Overweight (25-29.99kg/m^2) vs. Normal weight‡	0.077	0.290	7.98%	-7.53%	23.48%	0.088	0.126	9.11%	-3.22%	21.44%
Obese grade 1 (30-34.99kg/m^2) vs. Normal weight‡	0.110	0.149	11.57%	-5.15%	28.28%	0.114	0.062*	12.06%	-1.38%	25.49%
Obese grade 2 (35-39.99kg/m^2) vs. Normal weight‡	0.142	0.092*	15.17%	-3.80%	34.14%	0.135	0.049**	14.40%	-0.97%	29.77%
Obese grade 3 (40kg/m^2 plus) vs. Normal weight‡	0.170	0.059*	18.16%	-2.81%	39.13%	0.162	0.028**	17.39%	0.34%	34.43%
Current smoker *vs* Never smoker	0.093	0.331	9.24%	-11.28%	29.76%	0.111	0.137	11.55%	-4.77%	27.86%
Ex –smoker vs Never smoker	-0.023	0.687	-2.51%	-13.55%	8.53%	-0.023	0.632	-2.36%	-11.34%	6.63%
2+ rescue courses *vs.* < 2 rescue courses	0.269	<0.001***	30.80%	13.55%	48.04%	0.228	<0.001***	25.54%	12.62%	38.45%
Constant	7.740	<0.001***				8.228	<0.001***			

***=significant at 1% level, **= significant at 5% level, *= significant at 10% level. Constant evaluated at the reference category for each categorical variable and at the mean age of 48.5 years and the mean % predicted FEV1 is 81.42%. † Test that Hospital is jointly significant (Low cost scenario p-value = 0.007, High cost scenario p-value = 0.002) ‡ Test that BMI is jointly significant. (Low cost scenario p-value=0.049, High cost scenario p-value = 0.021)

Table A9: Regression analysis of logged Non-medication costs for SRA patients

	Ln(Non-medication cost) - low cost scenario					Ln(Non-medication cost) - high cost scenario				
	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper
Female vs. Male	0.049	0.604	4.74%	-14.58%	24.07%	0.045	0.459	4.49%	-7.87%	16.85%
Age	-0.027	0.137	-2.75%	-6.37%	0.87%	-0.016	0.175	-1.65%	-4.02%	0.73%
Age^2	0.0001	0.286	0.02%	-0.02%	0.06%	0.0001	0.416	0.01%	-0.01%	0.03%
Brompton vs. Belfast†	0.147	0.370	17.02%	-20.64%	54.69%	-0.005	0.961	-0.06%	-20.92%	20.81%
Leicester vs. Belfast†	-0.048	0.748	-3.69%	-31.88%	24.51%	-0.049	0.598	-4.44%	-22.11%	13.23%
Manchester vs. Belfast†	-0.030	0.829	-2.19%	-28.76%	24.38%	-0.019	0.836	-1.51%	-18.79%	15.76%
Birmingham vs. Belfast†	0.145	0.594	19.25%	-46.37%	84.87%	-0.001	0.995	1.29%	-35.89%	38.47%
Gartnavel vs. Belfast†	-0.169	0.424	-13.86%	-49.70%	21.98%	-0.173	0.180	-15.32%	-36.84%	6.20%
Stobhill vs. Belfast†	-0.184	0.401	-15.01%	-52.39%	22.38%	-0.274	0.051*	-23.29%	-44.66%	-1.91%
Best ever FEV1 % predicted	0.002	0.322	0.18%	-0.18%	0.55%	0.001	0.322	0.12%	-0.12%	0.36%
Maintenance Steroids Yes *vs* No	0.189	0.051*	19.02%	-3.85%	41.88%	0.106	0.095*	10.42%	-3.30%	24.15%
Underweight vs. Normal weight‡	0.010	0.981	2.16%	-127.03%	131.35%	0.047	0.859	5.40%	-58.75%	69.54%
Overweight (25-29.99kg/m^2) vs. Normal weight‡	0.278	0.023**	31.73%	-0.15%	63.61%	0.203	0.011**	22.35%	3.18%	41.52%
Obese grade 1 (30-34.99kg/m^2) vs. Normal weight‡	0.135	0.306	14.04%	-15.44%	43.51%	0.130	0.125	13.69%	-5.08%	32.45%
Obese grade 2 (35-39.99kg/m^2) vs. Normal weight‡	0.205	0.187	22.44%	-14.49%	59.37%	0.189	0.053*	20.74%	-2.25%	43.73%
Obese grade 3 (40kg/m^2 plus) vs. Normal weight‡	0.142	0.469	12.52%	-32.70%	57.75%	0.120	0.323	11.54%	-15.90%	38.97%
Current smoker *vs* Never smoker	0.483	0.005***	60.14%	4.43%	115.86%	0.367	0.001***	43.83%	12.90%	74.76%
Ex –smoker vs Never smoker	0.026	0.782	2.15%	-16.76%	21.07%	0.043	0.476	4.15%	-8.07%	16.38%
2+ rescue courses *vs.* < 2 rescue courses	0.421	<0.001***	51.75%	18.70%	84.80%	0.372	<0.001***	45.05%	25.89%	64.20%
Constant	6.614	<0.001***				7.374	<0.001***			

***=significant at 1% level, **= significant at 5% level, *= significant at 10% level. Constant evaluated at the reference category for each categorical variable and at the mean age of 48.5 years and the mean % predicted FEV1 is 81.42%.† Test that Hospital is jointly significant (Low cost scenario p-value < 0.001, High cost scenario p-value = 0.001) ‡ Test that BMI is jointly significant. (Low cost scenario p-value=0.109, High cost scenario p-value = 0.003)

Table A10: Regression analysis of Asthma medication costs for SRA patients

	Ln(Asthma medication cost) - low cost scenario					Ln(Asthma medication cost) - high cost scenario				
	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper	Coefficient	p-value	Effect	95% CI Lower	95% CI Upper
Female vs. Male	0.084	0.126	8.74%	-3.02%	20.51%	0.080	0.138	8.23%	-3.15%	19.61%
Age	0.005	0.578	0.53%	-1.35%	2.41%	-0.004	0.681	-0.39%	-2.23%	1.46%
Age^2	0.0001	0.509	-0.01%	-0.03%	0.01%	0.0001	0.624	0.01%	-0.02%	0.03%
Brompton vs. Belfast†	-0.041	0.656	-3.67%	-20.99%	13.66%	0.032	0.717	3.65%	-14.56%	21.86%
Leicester vs. Belfast†	-0.092	0.297	-8.46%	-24.27%	7.35%	-0.075	0.404	-6.84%	-23.20%	9.52%
Manchester vs. Belfast†	-0.090	0.294	-8.29%	-23.58%	7.01%	-0.059	0.473	-5.50%	-20.80%	9.79%
Birmingham vs. Belfast†	0.398	0.002***	49.98%	11.30%	88.67%	0.445	<0.001***	57.16%	17.98%	96.34%
Gartnavel vs. Belfast†	0.379	<0.001***	46.56%	18.90%	74.22%	0.409	<0.001***	51.05%	21.64%	80.47%
Stobhill vs. Belfast†	0.055	0.596	6.18%	-15.54%	27.91%	0.046	0.684	5.26%	-17.90%	28.41%
Best ever FEV1 % predicted	-0.003	0.002***	-0.34%	-0.55%	-0.12%	-0.002	0.019**	-0.23%	-0.43%	-0.04%
Maintenance Steroids Yes *vs* No	0.450	<0.001***	55.47%	39.72%	71.23%	0.402	<0.001***	48.48%	33.64%	63.31%
Underweight vs. Normal weight‡	-0.016	0.887	-1.81%	-23.50%	19.88%	-0.150	0.159	-14.00%	-32.07%	4.07%
Overweight (25-29.99kg/m^2) vs. Normal weight‡	-0.030	0.659	-3.11%	-16.26%	10.04%	-0.026	0.678	-2.77%	-15.00%	9.45%
Obese grade 1 (30-34.99kg/m^2) vs. Normal weight‡	0.108	0.132	11.27%	-4.33%	26.86%	0.095	0.170	9.96%	-5.00%	24.91%
Obese grade 2 (35-39.99kg/m^2) vs. Normal weight‡	0.100	0.247	10.36%	-8.38%	29.10%	0.082	0.352	8.30%	-10.41%	27.01%
Obese grade 3 (40kg/m^2 plus) vs. Normal weight‡	0.127	0.136	13.12%	-5.80%	32.04%	0.141	0.116	14.44%	-5.69%	34.57%
Current smoker *vs* Never smoker	-0.123	0.130	-12.22%	-26.29%	1.85%	-0.115	0.179	-11.46%	-26.47%	3.56%
Ex –smoker vs Never smoker	-0.021	0.718	-2.21%	-13.57%	9.14%	-0.070	0.230	-6.85%	-17.46%	3.77%
2+ rescue courses *vs.* < 2 rescue courses	0.204	0.008***	22.57%	3.94%	41.19%	0.104	0.127	10.78%	-4.05%	25.60%
Constant	7.028	<0.001***				7.427	<0.001***			

***=significant at 1% level, **= significant at 5% level, *= significant at 10% level. Constant evaluated at the reference category for each categorical variable and at the mean age of 48.5 years and the mean % predicted FEV1 is 81.42%.† Test that Hospital is jointly significant (Low cost scenario p-value < 0.001, High cost scenario p-value < 0.001) ‡ Test that BMI is jointly significant. (Low cost scenario p-value=0.038, High cost scenario p-value = 0.003)

Table A11: Regression analysis of logged Non-asthma medication costs for SRA patients

	Ln(Non-asthma medication cost)				
	Coefficient	**p-value**	**Effect**	**95% CI Lower**	**95% CI Upper**
Female vs. Male	0.048	0.739	4.31%	-25.24%	33.85%
Age	-0.012	0.651	-1.16%	-6.16%	3.85%
Age^2	0.0001	0.184	0.04%	-0.02%	0.09%
Brompton vs. Belfast†	-0.018	0.932	-0.14%	-42.50%	42.22%
Leicester vs. Belfast†	-0.493	0.024**	-37.59%	-65.22%	-9.96%
Manchester vs. Belfast†	-0.254	0.232	-21.02%	-54.07%	12.03%
Birmingham vs. Belfast†	0.318	0.404	46.40%	-68.49%	161.28%
Gartnavel vs. Belfast†	-0.003	0.990	2.38%	-50.79%	55.55%
Stobhill vs. Belfast†	0.576	0.073*	85.34%	-31.64%	202.32%
Best ever FEV1 % predicted	-0.005	0.080*	-0.54%	-1.15%	0.07%
Maintenance Steroids Yes *vs* No	0.467	0.002***	57.53%	10.86%	104.19%
Underweight vs. Normal weight‡	0.663	0.162	104.66%	-90.63%	299.96%
Overweight (25-29.99kg/m^2) vs. Normal weight‡	0.085	0.657	7.74%	-33.37%	48.84%
Obese grade 1 (30-34.99kg/m^2) vs. Normal weight‡	-0.106	0.582	-11.07%	-44.90%	22.76%
Obese grade 2 (35-39.99kg/m^2) vs. Normal weight‡	0.336	0.244	36.63%	-39.52%	112.78%
Obese grade 3 (40kg/m^2 plus) vs. Normal weight‡	0.361	0.239	33.70%	-52.44%	119.83%
Current smoker *vs* Never smoker	-0.040	0.908	-3.86%	-72.18%	64.45%
Ex –smoker vs Never smoker	0.107	0.480	11.18%	-21.83%	44.19%
2+ rescue courses *vs.* < 2 rescue courses	0.082	0.652	5.98%	-33.22%	45.18%
Constant	4.780	<0.001***			

***=significant at 1% level, **= significant at 5% level, *= significant at 10% level. Constant evaluated at the reference category for each categorical variable and at the mean age of 48.5 years and the mean % predicted FEV1 is 81.42%.† Test that Hospital is jointly significant (p-value < 0.001) ‡ Test that BMI is jointly significant. (p-value = 0.028)

Discussion

This study examines the annual healthcare costs in a well characterised cohort of SRA patients and examines the distribution and drivers of costs in this population.

Novel therapeutic strategies and interventional approaches which are targeted at SRA come at a high cost. Therefore, understanding the economic costs, as well as cost drivers, is central to justifying the additional expense of new therapies in this population.

The mean total treatment cost for SRA ranged between £2,912 (SD £2,212) and £4,217 (SD £2,449) depending on the assumptions made in the low and high cost scenarios. Among non-SRA patients, mean total cost ranged from £1,670 (SD= £1,149) to £2,788 (£1,449), but it is important to note that whilst this patient group did not have SRA after careful systematic assessment, they were referred to a Specialist Difficult Asthma service with difficult to manage disease. In a recent cost-of-illness study carried out on 462 patients aged 30-54 years with persistent asthma from 11 European countries (including the UK), total mean costs per patient were estimated at EUR 509 (£451) for patients with controlled asthma and EUR 2,281 (£2,022) for patients with uncontrolled asthma(7). While this examined costs of uncontrolled asthma and not SRA, it is notable that the range of 'difficult to control' mean costs in our study (£1,670 to £2,788) is similar to their figure for uncontrolled asthma in this European-wide study. We add to this information here in demonstrating that SRA is additionally more expensive and exceeds the costs associated with many other chronic conditions (mean costs - Type II Diabetes £2,567; stroke £1,301; COPD £819; chronic kidney disease £235 [2% on Renal Replacement Therapy £27,000](8-10).

One of the key observations of the study is that asthma medication is the major driver of total costs and not unscheduled healthcare attendance or hospital admission as previously thought. This implies that the overall cost of care in this population will significantly decrease if the price of the multiple drug therapies used by this population should reduce. This is likely to be most apparent for inhaled combination therapies, specifically with the arrival of generic combination inhalers. Finally, future studies examining the effect of novel therapies or interventions in SRA should consider a 'medication reduction' strategy in their development programme; specifically if a new therapy could provide a reduction in healthcare utilisation in parallel with a reduction in maintenance asthma medication use, it is more likely that such therapies will be cost effective.

We found that subjects on maintenance OCS are 43% more expensive than those not receiving maintenance OCS. In those on maintenance steroids, asthma related medications were more expensive but notably, their non-medication costs (healthcare utilisation) and non-asthma related medications were also significantly higher. Of note, non-asthma medication includes PPI and bisphosphonate therapy, which are examples of therapies used to manage side effects of OCS induced morbidity. This analysis does not specifically include the cost of steroid induced morbidity in SRA. Previous studies have attempted to cost steroid induced morbidity but not specifically in an asthma population. Manson *et al* (2009) reviewed OCS side effects by examining 63 studies where 21 different types of adverse events were reported and estimated that the annual cost based on a review of all adverse events related to OCS use is £165 to treat the event per patient on OCS in the UK (11). Sarnes et al(12) extended the review of Manson and examined a further 47 studies and identified a correlation with dose of OCS

particularly in relation to fractures, peptic ulcer disease and myocardial infarction, with healthcare costs associated with these events estimated to be $18,358 to $26,472 per patient per year respectively. However, it is important to note that these studies did not focus on side effects of OCS in a SRA patient group. Recurrent exacerbation is also a significant driver of costs, and we noted that subjects with more than 2 exacerbations requiring OCS were approximately 31% more expensive than subjects with less than 2 courses of rescue OCS which support targeting recurrent exacerbations with additional therapies.

Establishing the costs and cost drivers of SRA will aid policymakers in examining the cost-effectiveness of currently available 'add-on' treatments for individuals with severe disease, such as omalizumab. Recent NICE guidance for use of omalizumab allows access to subjects receiving recurrent rescue and maintenance OCS(13). Our data support this analysis, as both subjects requiring recurrent rescue OCS for exacerbation and maintenance OCS are more expensive based on the 1 year costing model in this study. However, it remains to be seen what additional costs are associated with longer term maintenance OCS in this population, as this is likely to be a major additional driver of longer term costs in this population

The association with obesity and asthma cost is novel and interesting – we have previously published data from the Registry to support that patients with SRA display particular characteristics according to BMI suggesting that obesity associated severe asthma may represent a distinct clinical phenotype(14). Cluster analyses of severe asthma populations has also identified obesity as a particular phenotype in severe asthma(15,16). The association with increased cost may reflect this altered phenotype and poor response to treatment, a question that warrants further investigation.

Our analysis does have some limitations. The exclusion of non-NHS and indirect costs provides an incomplete picture of the economic burden of SRA and the factors that drive this. The exclusion of dispensing fees means our estimates of medication costs are likely to be conservative. Similarly, as the Registry did not have complete records for all healthcare visits, assumptions around these regarding costs were required however we do not think these threaten the validity of our analyses, as scheduled and unscheduled healthcare visits represent a relatively minor element of total cost and the cost ranges presented in the high and low cost scenarios are accurate.

In conclusion this paper, using data from the BTS Difficult Asthma Registry, has estimated treatment costs for SRA patients in the UK to be between £2,912 and £4,217 per person per year. These costs are greater than those for patients with poorly controlled "difficult asthma" referred to the same clinics. The costs are dominated by asthma medication costs and importantly, these costs outweigh healthcare utilisation costs. Maintenance OCS and frequent exacerbations are important additional drivers of costs in this population.

Legends to figures-

Figure 2: Healthcare and Asthma Related Medication Costs for Non-Severe Refractory Asthma (Non-SRA)

Figure 3: Medication costs for Severe Refractory Asthma (SRA) and Non-Severe Refractory Asthma

References

(1) O'Neill C, Gamble J, Lindsay JT, et al. The Impact of Nonadherence to Inhaled Long-Acting β2-Adrenoceptor Agonist/Corticosteroid Combination Therapy on Healthcare Costs in Difficult-to-Control Asthma. *Pharm Med* 2011;25(6):379-385.

(2) Eurostat. Eurostat Harmonized Index of Consumer Prices (HICP) - Health index. 2011.

(3) Curtis L. Unit costs of health and social care 2009.Personal Social Services Research Unit, University of Kent, 2009 2010.

(4) HSC Business Services Organisation. HSC Prescription Cost Analysis for Northern Ireland 2011. 2011; Available at: http://www.hscbusiness.hscni.net/services/1806.htm. Accessed July/06, 2012.

(5) Halvorsen R, Palmquist R. The interpretation of dummy variables in semilogarithmic equations. *Am Econ Rev* 1980;70(3):474-475.

(6) Kennedy PE. Estimation with correctly interpreted dummy variables in semilogarithmic equations [The interpretation of dummy variables in semilogarithmic equations]. *Am Econ Rev* 1981;71(4).

(7) Accordini S, Corsico AG, Braggion M, et al. The cost of persistent asthma in Europe: an international population-based study in adults. *Int Arch Allergy Immunol* 2012;160(1):93-101.

(8) Hex N, Bartlett C, Wright D, et al. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabetic Med* 2012;29(7):855-862.

(9) Britton M. The burden of COPD in the UK: results from the Confronting COPD survey. *Respir Med* 2003;97:S71-S79.

(10) Kerr M, Bray B, Medcalf J, et al. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrology Dialysis Transplantation* 2012;27(suppl 3):iii73-iii80.

(11) Manson SC, Brown RE, Cerulli A, et al. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009 7;103(7):975-994.

(12) Sarnes E, Crofford L, Watson M, et al. Incidence and US Costs of Corticosteroid-Associated Adverse Events: A Systematic Literature Review. *Clin Ther* 2011 10;33(10):1413-1432.

(13) National Institute for Health and Care Excellence. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults (review of TA133 and TA201). April, 2013; Available at: http://guidance.nice.org.uk/TA278. Accessed 07/28, 2013.

(14) Gibeon D, Batuwita K, Osmond M, et al. Obesity-Associated Severe Asthma Represents a Distinct Clinical PhenotypeObesity-Associated Severe AsthmaAnalysis of the British Thoracic Society Difficult Asthma Registry Patient Cohort According to BMI. *CHEST Journal* 2013;143(2):406-414.

(15) Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *American journal of respiratory and critical care medicine* 2008;178(3):218-224.

(16) Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *American journal of respiratory and critical care medicine* 2010;181(4):315.

Figure 2. Non-Severe Refractory Asthma costs

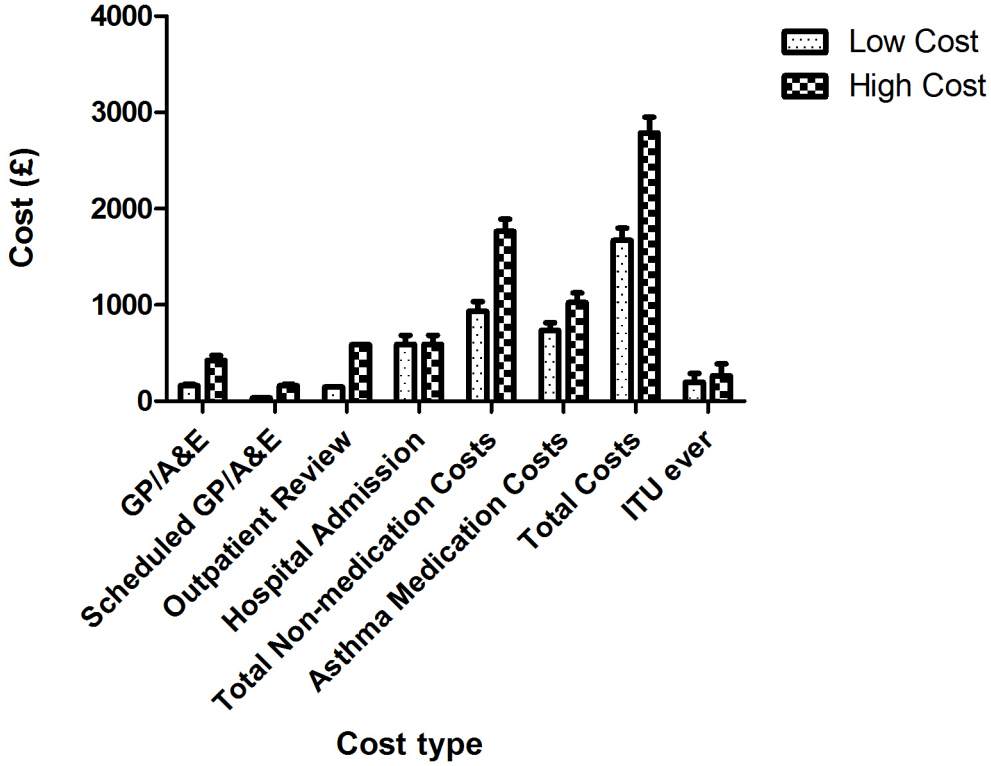

Figure 3a. Severe Refractory Asthma medication costs

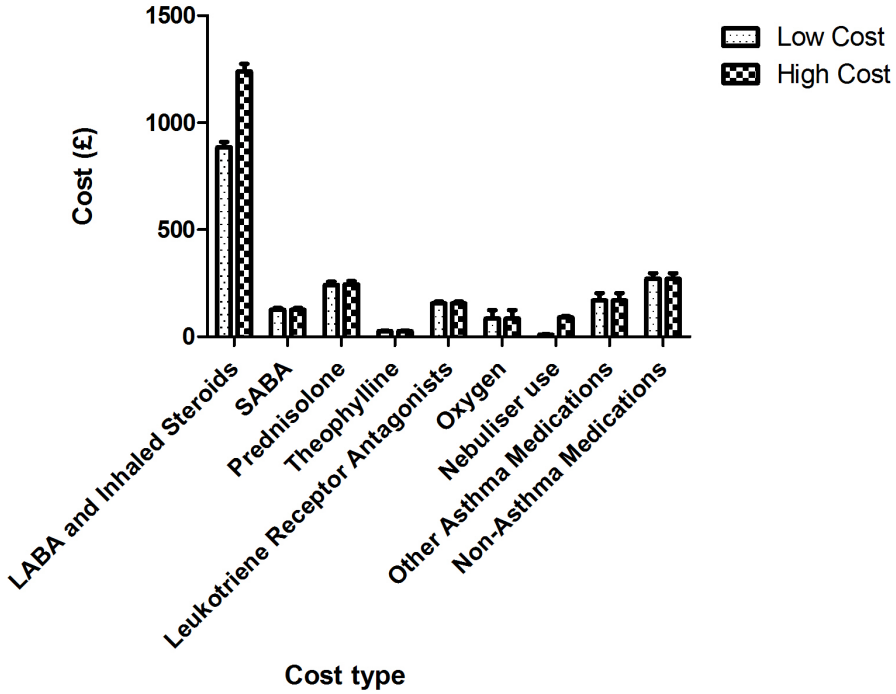

Figure 3b. Non-Severe Refractory Asthma medication costs