

The feasibility of using multiple databases to study rare outcomes: the potential effect of long-acting beta agonists with inhaled corticosteroid therapy on asthma mortality

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ABSTRACT

Purpose Long-acting beta agonists (LABAs) when used without concomitant inhaled corticosteroids (ICS) increase the risk of asthma-related deaths, but the effect on asthma-related death of LABA used in combination with ICS therapy is unknown. To address this question, we explored the feasibility of conducting an observational study using multiple US health care data sources.

Methods Retrospective cohort study to evaluate the likelihood of getting an upper 95% confidence limit ≤ 1.4 for the asthma mortality rate ratio and ≤ 0.40 per 10 000 person-years for the mortality rate difference, assuming no effect of new use of combined LABA + ICS (versus non-LABA maintenance therapy) on asthma mortality. Ten research institutions executed centrally distributed analytic code based on a standard protocol using an extracted (2000–2010) persistent asthma cohort (asthma diagnosis and ≥ 4 asthma medications in 12 months). Pooled results were analyzed by the coordinating center. Asthma deaths were ascertained by linkage with the National Death Index.

Results In a cohort of 994 627 persistent asthma patients (2.4 million person-years; 278 asthma deaths), probabilities of the upper 95% confidence limit for effect estimates being less than targeted values, assuming a null relation, were about 0.05. Modifications in cohort and exposure definitions increased exposed person-time and outcome events, but study size remained insufficient to attain study goals.

Conclusions Even with 10 data sources and a 10-year study period, the rarity of asthma deaths among patients using certain medications made it infeasible to study the association between combined LABA + ICS and asthma mortality with our targeted level of study precision. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—asthma mortality; distributed network; postmarketing evaluation; feasibility; long-acting beta agonist; pharmacoepidemiology

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INTRODUCTION

In February 2010, the United States (US) Food and Drug Administration (FDA) issued a safety announcement requiring changes in how long-acting beta₂-agonist (LABA) medications are used in the treatment of asthma, based on increased risks of severe asthma

exacerbations, including death among patients using LABAs alone without an asthma controller medication. Subsequently, the FDA required a Medication Guide and “boxed” warning of the risks of LABAs and, in 2011, also required the LABA manufacturers to conduct a total of five large postmarketing safety trials, the results of which will be pooled to inform on the safety of LABA plus inhaled corticosteroids (ICS) (LABA + ICS) compared with ICS alone, consistent with current treatment guidelines that no longer recommend LABA as monotherapy.¹ These trials are

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powered for a composite serious asthma endpoint of asthma-related death, endotracheal intubation, or hospitalization given that asthma-related death and intubation are rare.²

Although asthma prevalence has increased over the last two decades, the incidence of asthma death in the USA has been declining by 6% per year, from 2.1 per 10 000 persons with asthma in 2001 to 1.4 per 10 000 persons with asthma in 2009.³ Conducting a clinical trial large enough to assess asthma mortality related to asthma treatments is not feasible.⁴ Indeed, in the first such trial to be completed and published, only one asthma-related intubation and no deaths occurred among 11 679 patients randomized to treatment with fluticasone plus salmeterol or fluticasone alone; 74 total events occurred in 67 patients.² Moreover, no existing database of health care claims or electronic medical records is large enough to provide precise effect estimates comparing maintenance regimens. Meta-analyses of individual studies are useful in aggregating information across studies, but summary estimates of effect from these analyses may not be informative because of heterogeneity of study populations and design differences of the pooled studies, and most studies report zero asthma-related deaths.

This feasibility study was initiated to determine whether an observational study may provide an evaluation of asthma mortality prior to the completion of the FDA-mandated clinical studies, which were powered for composite endpoints that include asthma-related death, intubation, or hospitalization. We assessed the feasibility of conducting a large retrospective cohort study to evaluate the effect of combined use of LABA with inhaled corticosteroid (LABA+ICS) on risk of asthma mortality, relative to non-LABA maintenance therapy in individuals with persistent asthma. This feasibility study was designed to determine whether a sufficiently precise full-scale study could be conducted that would be informative about asthma mortality, an outcome that is too rare to be examined adequately in controlled trials. The plan was to proceed with a full-scale study, focused on risk evaluation, only if the results of the feasibility study indicated that the full-scale study would have enough precision to provide meaningful reassurance about the absence of large increases in risk if there were in fact no increase in asthma-related mortality. If that level of precision were unattainable, then the full-scale study would not be undertaken. The feasibility effort utilized 10 eligible and interested data sources available for a distributed research study—US electronic health care claims or electronic medical records from health

insurers—to assess the expected precision of effect estimates for asthma mortality given the overall study size achieved. The feasibility study population comprised patients with evidence of persistent asthma appropriate for LABA+ICS therapy according to international and domestic asthma treatment guidelines,^{5,6} to create exposure groups with similar background risk for asthma death and minimize confounding. Results describing the outcome of asthma mortality and clinical implications of the study have been published.⁷

METHODS

Study design overview

Our feasibility evaluation involved assembling a retrospective study cohort using a single research protocol implemented using a distributed data approach similar to that of the Mini-Sentinel system.⁸ This involved collaboration among 10 research partners: health insurers or integrated delivery systems with either electronic health care claims or electronic medical record data (Table 1). The majority of these research partners were participating in the Mini-Sentinel system (now the FDA Sentinel System) at the time of the study. A study steering committee, which in part consisted of experts in distributed research networks, provided input on the approach to collaborate with research partners, and the study protocol was not finalized until research partners were added to the collaboration and reviewed the protocol and provided comment. Eligibility criteria were developed for evaluating a list of potential research partners (e.g., identifiable data for linkage, prior experience in a distributed research network, data in suitable format, and length of time consistent with study period). Data partners were screened according to these criteria and, if eligible, invited to provide proposals to the coordinating center. Each research partner was asked to provide a principal investigator, analyst, programmer, and project manager to contribute to the design and implementation of the research locally. Sixteen data partners were contacted regarding their interest in the collaboration, four were ineligible or did not express interest in participating, and 12 were enrolled over a period of approximately 11 months (first contact to final agreement placed). Ten of the data partners were able to complete the first feasibility assessment by providing data that passed quality checks and could be included in the pooled analysis.

A study charter was developed, and a steering committee and technical working group were established to guide the activities of the research collaboration

FEASIBILITY OF USING MULTIPLE DATABASES

Table 1. Research partners participating in ASSESS

Research partner	Time period of data availability*	Estimated size of patient population†
HealthCore	1 January 2001 through 30 June 2011	35 million
OptumInsight (now Optum)	1 January 1993 through 30 September 2011	14 million in 2008
HMO Research Network (HMORN)		
Harvard Pilgrim Health Care	1 January 2000 through 31 December 2010	2.77 million
HealthPartners Research Foundation	1 January 1994 through present	More than 5 million
Henry Ford Health System	1 January 2007 through 31 December 2010	450 000
Kaiser Permanente Hawaii	1 January 1995 (non-Electronic Medical Record), or 1 January 2005 Electronic Medical Record (EMR), through 30 September 2011	538 138
Lovelace Clinic Research Foundation	1 January 1996 through 30 June 2011	600 621
Meyers Primary Care Institute	1 January 1999 through 31 December 2009	436 000
Scott & White Healthcare	1 January 2001 through present	445 000
Southern California Permanente Medical Group	Varies by data source contributing to research data warehouse	7 million

*Recorded as of November 2011.

†The estimated size displayed indicates the number of patients with both medical and pharmacy coverage in the respective research partner database during the time period of data availability.

from protocol development through implementation. Each research partner kept patient-level electronic data on site and generated results using a standard set of code provided by the coordinating center; reported the number of individuals fulfilling the definition of persistent asthma and person-years of follow-up, number of persons and person-years in each exposure category of interest, and number of deaths from asthma during the study period; and contributed aggregated results without patient-identifying or personal health information to the coordinating center via a secure Web portal. To ascertain deaths from asthma, each research partner linked its patients with the US National Death Index (NDI) using a common protocol and program code provided by the coordinating center.

The RTI International Committee for the Protection of Human Subjects determined that the coordinating center activities for the study were exempt [45 CFR 46.101(b)] from institutional review board (IRB) review because of the removal of subject identifiers before data were provided to the coordinating center. Each research partner submitted the study protocol to its local IRB for review, and each received approval or exemption following local review of the protocol. Submission of the protocol to governing IRBs was performed in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice and applicable requirements, including the US Code of Federal Regulations (CFR) 21.312.3(b) for constitution of independent ethics committees.

Source population and general asthma cohort

The source population was derived from the electronic data of insured persons from 10 research partners in

the USA from 1 January 2000 through 31 December 2010. Each research partner had to be able to observe complete data during enrollment, including medical claims and medication exposures (i.e., pharmacy dispensings at the patient level); have access to patient-identifying information needed to link with NDI data; and be able to work with a common data model under a common protocol.

Each research partner prepared a data extract of individuals of all ages likely to have asthma (general asthma cohort) using common criteria: at least one recorded outpatient, inpatient, or emergency department record with a diagnosis of asthma (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 493.x, any position) and at least one recorded pharmacy dispensing of an asthma maintenance medication on or after 1 January 2000. Each research partner transformed this general asthma cohort data extract into a common data model based on version 1.1 of the common data model used in the Mini-Sentinel pilot project (<http://www.mini-sentinel.org/>). Subsequent cohort extraction, data transformation, and analyses were performed locally by each research partner using common programming code written and distributed by the coordinating center, with quality control checks of returned results performed by the coordinating center.

Study population (persistent asthma cohort) and length of observation

Using central programming, a study cohort of individuals with persistent asthma was constructed using a modification of a published algorithm defined by the Healthcare Effectiveness and Data Information Set (HEDIS) criteria⁹: four or more dispensings for any asthma maintenance medication recorded during any

12-month interval of continuous health plan enrollment with complete medical and pharmacy coverage that occurred during the study period (1 January 2001 to 31 December 2010) and at least one outpatient, inpatient, or emergency department record with a diagnosis of asthma (ICD-9-CM code 493.*, any position) between 1 January 2000, and the date of the fourth qualifying medication dispensing. Medications were ICS, LABA, LABA+ICS in fixed-dose combination inhaler, leukotriene receptor antagonists, short-acting beta agonists with or without an anticholinergic, short-acting anticholinergics, xanthines, and mast cell stabilizers. The date of the fourth qualifying medication dispensing in the first 12-month window during the study period that met all criteria became the cohort entry date. Individuals aged less than 4 years at this date were excluded (Figure 1).

Individuals in the persistent asthma cohort were followed from the cohort entry date until the earliest of end of enrollment, date of death, date of dispensing of a prescription for omalizumab, or end of study period (31 December 2010).

Outcome

The outcome of interest was death from asthma. Deaths were ascertained from 1 January 2001 through 31 December 2010, by searching for matching deaths in the NDI in the calendar year of the last recorded claim or health service and during the following calendar year. Each research partner submitted a data file to the NDI for linkage to confirm death and date and cause of death; known decedents were included to obtain cause-of-death information. NDI provided to each research partner results that were evaluated for the best

possible match based on a match-rating computer algorithm adapted by the coordinating center.¹⁰

Exposures

Asthma medication exposure categories of interest were (1) LABA+ICS (of primary interest)—salmeterol/fluticasone propionate in single inhaler (Advair®), formoterol/budesonide in single inhaler (Symbicort®), salmeterol+ICS in separate inhalers dispensed concomitantly, and formoterol+ICS in separate inhalers dispensed concomitantly; (2) ICS monotherapy (all molecules and formulations)—ICS dispensed without concomitant non-ICS controller medication and with no dispensing of any non-ICS controller medication in the 12 months before the ICS; and (3) ICS+non-LABA controller therapy—ICS dispensing(s) plus concomitant dispensing(s) of theophylline, leukotriene receptor antagonist (LTRA), or other non-LABA controller.

The feasibility assessment evaluated a new user design with an active comparator;¹¹ new use was a newly added therapy for persistent asthma according to asthma treatment guidelines.^{5,6} The study definition of index use was the first new use of a medication in any of the aforementioned exposure groups on or after the cohort index date. The index use date could be the same as the cohort entry date if the fourth qualifying medication used to define the persistent asthma cohort was one of the study medications of interest and was the first dispensing of any of the study medications of interest (Figure 1).

A continuous treatment episode concatenated dispensing records as follows: the recorded or imputed days' supply plus 30 days, to bridge gaps between

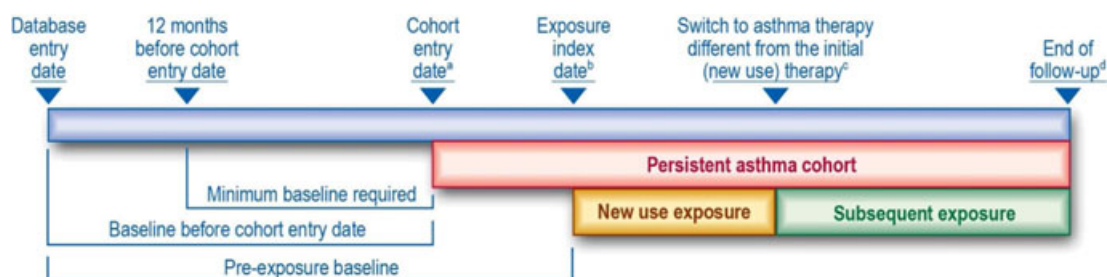


Figure 1. Characterizing person-time of observation. ^aDate of entry into persistent asthma cohort (date of the fourth qualifying medication dispensing in the first 12-month window during the study period that met all cohort entry criteria). ^bStart of "index use," defined as first new use of any of the asthma single or combination therapies of interest: (1) LABA + ICS—salmeterol/fluticasone propionate in single inhaler (Advair®), formoterol/budesonide in single inhaler (Symbicort®), salmeterol + ICS in separate inhalers dispensed concomitantly, and formoterol + ICS in separate inhalers dispensed concomitantly; (2) ICS monotherapy—ICS dispensed without concomitant non-ICS controller medication and with no dispensing for any non-ICS controller medication in the 12 months before the ICS; and (3) ICS + non-LABA controller therapy—ICS dispensing(s) plus concomitant dispensing(s) for theophylline, LTRA, or other non-LABA controller. This date could be the same as the cohort entry date if the fourth qualifying medication was one of the study medications of interest and was the first use of any of the study medications of interest. ^cSubsequent use was new use of any asthma treatment of interest after the index use. ^dDue to study endpoint, end of enrollment in health plan, dispensing of omalizumab, or end of study period (31 December 2010), whichever occurred first. ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist

dispensings of the same medication. Duration of a treatment episode started on the date of the first dispensing that defined the episode and ended on the earliest of the last date of the episode, a switch in treatment, a change to combination therapy, or end of follow-up. Combination therapy for two different medications was defined if the duration periods for the medications overlapped for at least 30 days.

Statistical analysis

Feasibility analyses. Descriptive statistics were tabulated and stratified, where indicated, by age at index date and index exposure. Descriptive statistics for key variables were compared across research partners with eight categories of exposure: Advair, Symbicort, salmeterol+ICS in separate inhalers, formoterol+ICS in separate inhalers, ICS monotherapy, ICS+LTRA, ICS+theophylline, and ICS+other non-LABA controller.

The crude asthma mortality rate for each site was calculated without regard to asthma medication exposures by dividing the total number of asthma deaths by the total person-years of follow-up. Rates, overall and stratified by age and sex, were expressed per 10 000 person-years, with 95% confidence intervals (CIs) estimated using the Poisson distribution in *Episheet*.¹² The overall pooled crude mortality rate was the sum of asthma deaths divided by the sum of person-years across all research partners. The overall standardized asthma mortality rate was standardized to the age distribution of person-years for the index LABA+ICS exposure category across research partners.

At each research partner, the total person-time at risk in each index treatment group was calculated as the number of years from the first dispensing until the first gap (>30 days) in exposure or switch to another treatment, summed over all exposed individuals. We assumed a zero induction time for any exposure effect.¹³ Person-time at risk for each index treatment group was then summed over data sources.

Estimates of the potential precision for the asthma mortality rate ratio (MRR) were calculated using the Study Size Worksheet from *Episheet*¹² using an asthma mortality rate of 1.0 per 10 000 person-years in the unexposed group, the observed lower limit of the 95% CI of the observed overall asthma mortality rate. Separate calculations were made for three index LABA+ICS groups (Advair, LABA+ICS in a single inhaler, and LABA+ICS in separate inhalers) versus

the comparator cohort (the combination of ICS monotherapy and ICS+non-LABA controller). For each comparison, we estimated precision as the probability that the upper 95% confidence limit (CL) of the MRR would be less than 1.4 if the true MRR were 1.0, and the upper 95% CL of the rate difference (RD) would be (1) less than 0.4 and (2) less than 0.8 per 10 000 person-years, if the true RD were 0.

Sensitivity analyses. Given the low precision of effect estimates observed in the feasibility study analyses, we conducted sensitivity analyses to explore the effect of study design modifications on study size and precision. The two largest research partners, A and C, representing 66% of the individuals in the persistent asthma cohort, provided counts for these assessments. Person-years of exposure categories and precision estimates for the MRR and RD were evaluated for each of the following design modifications, which relaxed definitions to increase the number of people or exposures:

- (1) Varied asthma medication dispensings in a 12-month period for the persistent asthma cohort from four to three, or two, and used a sliding time window (any 12-month window during the study period instead of the first) to identify a period with four dispensings that also met all other eligibility criteria.
- (2) Modified the original definition of index new use (definition 1): definition 2—first new use of a study medication on or after cohort entry date with or without use of other study medications before the index date (only one episode of new use per person) and definition 3—all first exposure episodes of any study medication on or after the cohort entry date.
- (3) Increased the allowable gap between the end of one exposure episode and the beginning of the next from 30 to 60 days.
- (4) Explored the effect of increasing the observed exposure group size 50%, 100%, and 200% to simulate the possible effect of adding a large data source and extending the study duration.
- (5) Changed the targeted upper 95% CL of the MRR from 1.4 to 2.0 and the RD from 0.4 and 0.8 to 1.0 per 10 000 person-years.

RESULTS

Primary feasibility results

About 17% of individuals in the general asthma cohort ($n=994\,627$) met the strict criteria for the persistent

asthma cohort, with 2 399 564 person-years of follow-up (Figure 2). The most common reason for exclusion from the persistent asthma cohort was the lack of a fourth qualifying asthma medication dispensing in a 12-month period. Overall, 14.5% of the persistent asthma cohort initiated one of the treatments of interest while enrolled in the health plan and during the study period, reflecting the high number of prevalent users of the medications of interest. The most common treatments of interest were ICS monotherapy, Advair, and ICS+LTRA.

Overall, 18 553 deaths from any cause were identified during the study period; 953 had asthma listed as any cause, underlying or other, on the death record. Of the 953, 278 had asthma as the underlying cause and were considered an asthma death for the analysis, as the goal was to be as accurate as possible in attributing deaths to asthma. The overall crude asthma mortality rate across all research partners was 1.16 (95% CI, 1.03–1.30) per 10 000 person-years (range, 0–2.21).⁷ The pooled overall rate standardized by age and research partner was 1.16 (95% CI, 0.98–1.34) per 10 000 person-years (range, 0–2.33).⁷ Of the asthma deaths, only one occurred during index exposure (any exposure category) and two occurred during subsequent new exposure.

With the observed exposed and unexposed person-years, calculated probabilities that the upper 95% CL for the MRR was <1.4, under the assumption of a null relation, were 0.046 for Advair versus comparator new use exposure, and 0.047 for any LABA+ICS exposure in a single inhaler versus comparator new use exposure (Table 2). Probabilities that the upper 95% CL of the RD were <0.4 were similarly low. For any LABA+ICS exposure compared with non-LABA+ICS or ICS monotherapy, with the given study size and probability fixed at 80%, the MRR upper limit of the 95% CL that could be ruled out was 27 if the true MRR = 1. Similarly, the RD upper limit of the 95% CL that could be ruled out was 3.30 per 10 000 person-years if the true RD = 0.

Results of sensitivity analyses

Decreasing the minimum number of asthma dispensings in the 12-month period necessary for inclusion in the study and using the entire study period to identify the 12-month period (sliding time window) increased the persistent asthma cohort size at research partners A and C by 41% for three dispensings and by 69% for two dispensings (Table 3). Regardless of the size of the gap used to define exposure duration,

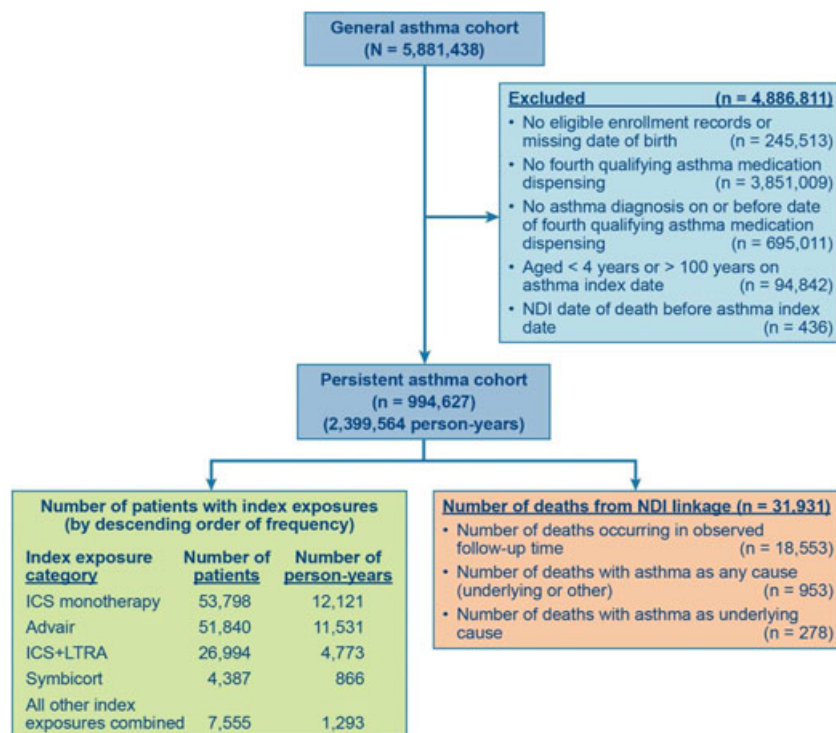


Figure 2. Cohort creation, exposure, and outcome assessment. ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; NDI, National Death Index

Table 2. Estimation of the precision of the mortality rate ratio and rate difference for asthma mortality (with 10 research partners)

Exposed group	Observed person-years exposed group*	Person-years unexposed group†	Ratio unexposed/ exposed person-years	Probability that upper 95% confidence limit of...			For the given study size, there is a 0.8 probability the upper 95% confidence limit of the...	
				MRR < 1.4 if true MRR = 1.0‡	RD < 0.4 (per 10 000 person-years) if true RD = 0‡	RD < 0.8 (per 10 000 person-years) if true RD = 0‡	MRR will be less than or equal to...	RD (per 10 000 person-years) will be less than or equal to...
Advair	11 531	17 231	1.49	0.046	0.052	0.098	29	3.38
Any LABA	12 397	17 231	1.39	0.047	0.053	0.100	27	3.30
+ ICS in single inhaler								
LABA	957	17 231	18.01	0.032	0.033	0.043	11 000	9.31
+ ICS in separate inhalers								

ICS, inhaled corticosteroid; LABA, long-acting beta agonist; MRR, mortality rate ratio; RD, rate difference.

*Total person-years at risk in index new user exposure group.

†Definition of unexposed group: ICS + non-LABA controller or ICS monotherapy (non-LABA controller: leukotriene receptor antagonist, xanthine, or mast cell stabilizer).

‡This calculation assumes that the rate of asthma mortality in the unexposed group is 1.0 per 10 000 person-years.

the Advair-exposed person-years at risk increased by about 57% from new use definition 1 (first new use of a medication in any exposure group on or after the cohort index date) to definition 2 (first episode of new drug use with or without use in any other exposure group) and by an additional 11% from definition 2 to definition 3 (all first exposure episodes of any study medication). Using the 60-day gap increased the Advair-exposed person-years at risk by about 57% for each definition of new use (Table S1).

In the original persistent asthma cohort, research partners A and C contributed 81% of the Advair-exposed person-years at risk and 46% of the person-years of comparator exposure (Table 4). Using the new persistent asthma cohort definition and definition 2 for new use resulted in a 169% increase in the number of Advair-exposed person-years at risk. Even with this substantial increase, there was very little effect on the probability of obtaining an upper 95% CL of the MRR or the RD less than target values, largely because of the rare event rate; the probability remained below 0.1 for all definitions of new use using either exposure duration (Table 5). The lowest value for the upper 95% CL of the MRR associated with 80% probabilities under the null hypothesis that could be achieved was about 7.0.

Table 5 shows the effects of increasing the target upper 95% CL of the MRR and RD on study precision for exposure definition 2 and applying simulated increases in the study size of 50%, 100%, and 200% that might be achieved by adding another large data source to the study and extending the study period beyond 2010. For a 100% increase in study size and using the 60-day gap criterion for calculating exposure duration, the lowest MRR that could be achieved comparing any LABA + ICS in a single inhaler to non-LABA therapy is 4.2, and the lowest RD is 1.2 per 10 000 person-years, still far from the target goals. Figure 3 displays the width of the 95% CI for the MRR for the various study design changes.

DISCUSSION

The feasibility study was a successful collaboration with 10 research partners implementing a standardized analytic approach via distributed programming. This was an efficient way to capture a very large population of individuals with asthma diagnoses and treatments, maintain operational consistency across research sites, and satisfy local data privacy requirements. The persistent asthma cohort of almost 1 million individuals contributed about 2.4 million person-years at risk of follow-up time to the study. The overall asthma death rate in this cohort, 1.2 per 10 000 person-years, was

Table 3. Size of the persistent asthma cohort by different definition criteria, by research partner (sensitivity analyses with two research partners, A and C only)

Definition criterion	Research partner A		Research partner C		Partners A and C	
	<i>N</i>	Increase from primary feasibility analysis (%)	<i>n</i>	Increase from primary feasibility analysis (%)	<i>n</i>	Increase from primary feasibility analysis (%)
Persistent asthma cohort size, primary feasibility analysis	348 367	N/A	311 063	N/A	659 430	N/A
Persistent asthma cohort size, sensitivity feasibility analysis						
Four claims	435 005	25	368 258	18	803 263	22
Three claims	498 744	43	429 691	38	928 435	41
Two claims	590 780	70	525 320	69	1 116 100	69
Number of Advair prescriptions*	2 024 291	N/A	1 497 048	N/A	3 521 339	N/A
Average number of Advair prescriptions per user	9.7		8.7			

N/A, not applicable.

*All Advair prescriptions for all persistent asthma cohort members on or after the cohort entry date (date of third asthma dispensing in a 12-month window that qualified the patient for the persistent asthma cohort), regardless of whether Advair was the patient's first drug exposure after cohort entry.

similar to the published overall rate in the USA, 1.4 per 10 000 persons with asthma in 2009.³ Although the initial study population was quite large, with a new user design to minimize confounding by indication, the initial feasibility precision analyses resulted in a very low probability (less than 0.10) of meeting targeted MRR and RD thresholds for combined LABA+ICS therapy compared with non-LABA medications.

A new user approach with an active comparator was considered the best design for studying two or more different treatment options to minimize potential confounding and to account for the hypothesized short-term effect.¹¹ However, the new user design reduces the size of the exposed cohort.¹⁴ Prescription decisions by physicians are not made at random; thus, new users for whom a new medicine is the first treatment for an indication (on average) may have different characteristics from new users previously prescribed alternative medications; the motive to change treatments may be related to lack of effectiveness or adverse outcomes of previous treatments. Adverse events related to medications often occur early after starting a medication^{15,16}; thus, prevalent users may have lower risks of adverse events than new users,¹⁴ and apart from initial selection, hazards may vary with time after initiation of a drug for biological or behavioral reasons.¹⁵

By restricting the definition of asthma mortality to death with asthma as the underlying cause, we may have underestimated the asthma death rate. Indeed, it has been shown that including asthma as a secondary cause of death may result in an asthma death rate that is twofold to fourfold higher than restricting the definition to asthma as the underlying cause of death,^{17,18} but doing so can increase the number of false

positives. In the current feasibility study, we were interested in an outcome with higher specificity than sensitivity to reduce overall bias in effect estimates due to outcome misclassification. However, in order to closely mimic the outcome definition of asthma death from clinical trials, in which there was limited information in some cases to assess relatedness to asthma, we also captured information on the number of deaths with asthma as any cause (Figure 2) with the intention of performing sensitivity analyses in the full-scale study with different definitions of the outcome. The feasibility results indicated, though, that there would have been little impact on the study precision even if we had used all deaths with asthma as any underlying cause.

As part of the feasibility study, we conducted sensitivity analyses with data from the two largest research partners to estimate whether implementing changes in the protocol could result in adequate study size to proceed with a full study. The sensitivity analyses did not identify any study design changes that resulted in sufficient size of exposure groups to reach the prespecified clinically informative criteria for precision of the MRR or RD. This approach was operationally efficient but is limited by including only a subsample of the entire study cohort. However, it is also worth considering whether the feasibility study should have been conducted only among the two largest research partners, resulting in the same scientific conclusions, but without the benefit of knowing whether the collaboration was scalable for full study implementation.

Study design modifications to increase study precision must be balanced by the possible detrimental effect on the validity and interpretability of the results.

Table 4. Estimation of the precision of the asthma mortality rate ratio and rate difference; comparison of three definitions of new use for revised definition of persistent asthma cohort (sensitivity analyses with research partners A and C combined)

Probability that upper 95% confidence limit of...					For the given study size, there is a 0.8 probability the upper 95% confidence limit of the...		
Definition of exposed group	Person-years exposed group	Person-years unexposed* group	Ratio unexposed to exposed person-years	MRR <1.4 if true MRR = 1.0	RD <0.4 (per 10000 person-years) if true RD=0	MRR will be less than or equal to...	RD (per 10000 person-years) will be less than or equal to...
30-Day gap							
Original persistent asthma cohort, definition 1 [†]							
Advair users	11 531	17 231	1.49	0.046	0.052	29	3.38
Any LABA + ICS in single inhaler	12 387	17 231	1.39	0.047	0.053	27	3.30
Research partners A and C: original persistent asthma cohort, definition 1 [†]							
Advair users	9396	7884	0.84	0.041	0.045	72	4.28
Any LABA + ICS in single inhaler	10 195	7884	0.77	0.041	0.045	67	4.20
New persistent asthma cohort [‡]							
Definition 1 [†]							
Advair users	16 101	14 489	0.90	0.048	0.054	24.7	3.22
Any LABA + ICS in single inhaler	17 491	14 489	0.83	0.048	0.054	23.3	3.15
Definition 2 [§]							
Advair users	25 308	21 993	0.87	0.055	0.064	13.2	2.60
Any LABA + ICS in single inhaler	28 829	21 993	0.76	0.057	0.065	12.3	2.51
Definition 3 [¶]							
Advair users	28 095	24 506	0.87	0.058	0.067	11.6	2.45
Any LABA + ICS in single inhaler	32 780	24 506	0.75	0.059	0.069	10.7	2.37
60-Day gap							
Original persistent asthma cohort, definition 1 [†]							
Advair users	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Any LABA + ICS in single inhaler	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Research partners A and C: original persistent asthma cohort, definition 1 [†]							
Advair users	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Any LABA + ICS in single inhaler	N/A	N/A	N/A	N/A	N/A	N/A	N/A
New persistent asthma cohort [‡]							
Definition 1 [†]							
Advair users	25 291	22 419	0.89	0.056	0.064	13.1	2.57
Any LABA + ICS in single inhaler	27 396	22 419	0.82	0.056	0.065	12.5	2.53
Definition 2 [§]							
Advair users	39 673	33 769	0.85	0.066	0.078	8.0	2.08
Any LABA + ICS in single inhaler	44 889	33 769	0.75	0.068	0.080	7.6	2.02
Definition 3 [¶]							
Advair users	43 899	37 327	0.85	0.069	0.082	7.2	1.98
Any LABA + ICS in single inhaler	50 812	37 327	0.73	0.071	0.085	6.8	1.91

ICS, inhaled corticosteroid; LABA, long-acting beta agonist; MRR, mortality rate ratio; N/A, not applicable as analyses were not performed using the 60-day gap criterion; RD, rate difference.

*Definition of unexposed group: ICS + non-LABA controller or ICS monotherapy (non-LABA controller: leukotriene receptor antagonist, xanthine, or mast cell stabilizer).

†New user definition 1: first new use of a medication in any of the exposure group on or after the persistent asthma cohort entry date.

‡Persistent asthma cohort defined by three asthma medication dispensings in a 12-month period with an asthma diagnosis before or on the date of the third medication dispensing, using the entire study period to ascertain the 12-month window.

§New user definition 2: first episode of new drug use with or without drug use in any other exposure group.

¶New user definition 3: all first exposure episodes of any study medication.

Table 5. Estimation of the precision of the asthma mortality rate ratio and rate difference—sensitivity analyses with data partners A and C combined: revised definition of persistent asthma cohort and definition 2 of new use; exploring the effect of increases in sample size, raising the upper 95% confidence limit for the MRR and RD, and use of a 30-day or 60-day gap between exposure episodes (sensitivity analyses)

For the given study size, there is a 0.8 probability the upper 95% confidence limit of the...								
Probability that upper 95% confidence limit of...				95% confidence limit of...				
Definition of exposed group	Person-years exposed group	Person-years unexposed group [†]	Ratio unexposed to exposed person-years	MRR <2.0 if true MRR = 1.0	RD <1.0 (per 10000 person-years) if true RD = 0	MRR will be less than or equal to...	RD (per 10000 person-years) will be less than or equal to...	
30-Day gap								
New persistent asthma cohort [‡] ; definition 2*								
Advair users	25 308	21 993	0.87	0.114	0.191	13.2	2.60	
Any LABA + ICS in single inhaler	28 829	21 993	0.76	0.118	0.200	12.3	2.51	
Increasing sample size by 50%								
Advair users	37 963	32 989	0.87	0.149	0.264	8.3	2.11	
Any LABA + ICS in single inhaler	43 243	32 989	0.76	0.156	0.277	7.8	2.05	
Increasing sample size by 100%								
Advair users	50 617	43 986	0.87	0.185	0.335	6.2	1.83	
Any LABA + ICS in single inhaler	57 657	43 986	0.76	0.194	0.352	5.9	1.78	
Increasing sample size by 200%								
Advair users	75 925	65 979	0.87	0.255	0.468	4.5	1.50	
Any LABA + ICS in single inhaler	86 486	65 979	0.76	0.268	0.490	4.3	1.45	
60-Day gap								
New persistent asthma cohort [‡] ; definition 2*								
Advair users	39 673	33 769	0.85	0.153	0.271	8.0	2.08	
Any LABA + ICS in single inhaler	44 889	33 769	0.75	0.159	0.284	7.6	2.02	
Increasing sample size by 50%								
Advair users	59 509	50 654	0.85	0.208	0.380	5.4	1.42	
Any LABA + ICS in single inhaler	67 334	50 654	0.75	0.217	0.398	5.2	1.38	
Increasing sample size by 100%								
Advair users	79 346	67 539	0.85	0.262	0.480	4.3	1.20	
Any LABA + ICS in single inhaler	89 779	67 539	0.75	0.275	0.501	4.2	1.17	
Increasing sample size by 200%								
Advair users	119 019	101 308	0.85	0.368	0.648	3.3	0.94	
Any LABA + ICS in single inhaler	134 668	101 308	0.75	0.385	0.672	3.2	0.92	

ICS, inhaled corticosteroid; LABA, long-acting beta agonist; MRR, mortality rate ratio; RD, rate difference.

*New user definition 2: first episode of new drug use with or without drug use in any other exposure group.

^aDefinition of unexposed group: ICS, non-LABA controller or ICS monotherapy (non-LABA controller; leukotriene receptor antagonist, xanthine, or mast cell stabilizer).

^bPersistent asthma cohort defined by three asthma medication dispensings in a 12-month period with an asthma diagnosis before or on the date of the third medication dispensing, using the entire study period to ascertain the 12-month window.

FEASIBILITY OF USING MULTIPLE DATABASES

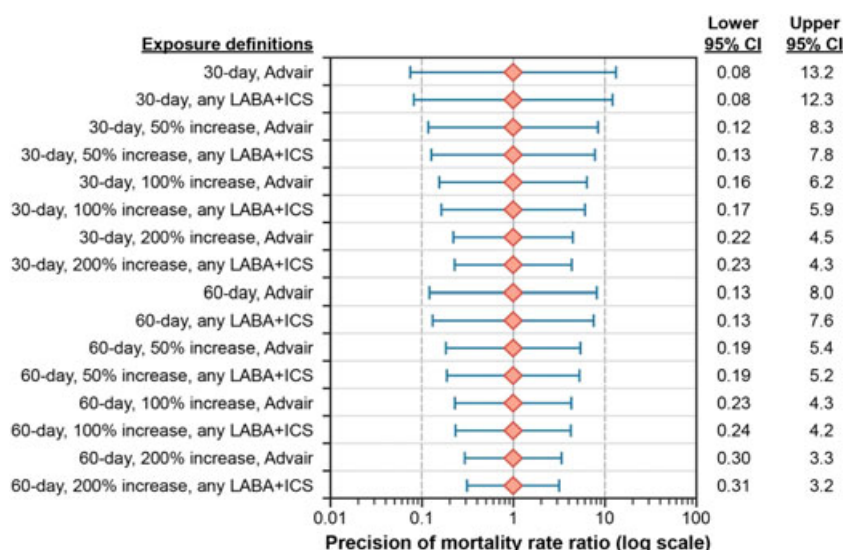


Figure 3. Effect of different study design modifications on the width of the 95%CI for the asthma mortality rate ratio, assuming the true rate ratio is 1.0. ICS, inhaled corticosteroid; LABA, long-acting beta agonist; CI, confidence interval. Note: The figure displays results presented in Table 5

Relaxing criteria for construction of the persistent asthma cohort from the use of four asthma medication dispensings to three in a 12-month period seems to be a reasonable step given the gain in study size, but requiring only two medications would be farther away from the HEDIS definition of persistent asthma.¹⁹ Increasing the allowable gap between exposure episodes could result in misclassification of unexposed time as exposed, potentially leading to a biased estimate of the true relative risk. Relaxing the definition of new use at the index date to allow another asthma controller medication before the index study exposure would be more consistent with the asthma step treatment guidelines for asthma control,⁶ but could increase heterogeneity of disease severity across exposure groups, which could introduce confounding.

The study has limitations inherent to the use of administrative claims data for identification of patients with persistent asthma and for classification of exposures to asthma medications that can be used intermittently over time. Given the low percentage of the general asthma cohort who met the original study criteria for persistent asthma, it is possible that some patients with truly persistent asthma may have been misclassified as not persistent. Further limitations were the assumed concordance between physician assessment of asthmatics (persistent versus intermittent); prescribing practices according to the guidelines; and patient acquisition of medication from pharmacies, inherent in our definition of persistent asthma. In addition, given the nature of employer-based health plans, it is possible for some patients who switched insurers to be included more than once, at different time

periods, reflecting an insurance plan change. We did not have a method to identify and remove such patients, but expect this number to be small.

The results of this feasibility study reinforce the challenges of studying the relation between combined LABA+ICS therapy and asthma mortality. Whether combined LABA+ICS therapy is associated with increased risk of asthma death may remain unknown because of the infeasibility of obtaining precise effect estimates for an expected small relative effect.⁴ It is feasible to study adverse outcomes other than mortality (e.g., serious nonfatal asthma), but risk factors for less severe outcomes appear to differ from the risk factors for asthma mortality.²⁰ To further our understanding of LABA+ICS safety, five ongoing, large randomized clinical trials mandated by the US FDA are comparing LABA+ICS with ICS alone.²¹ Pooled trial results are expected in 2017, but the outcome is a composite of intubation, hospitalization, or asthma-related death; the studies are not powered for asthma death. Of note, the first completed trial of 11 679 patients randomized to fluticasone propionate/salmeterol fixed-dose combination versus fluticasone propionate over 26 weeks reported no difference in risk of serious asthma-related events (HR, 1.03; 95%CI, 0.64–1.66) based on a total of 67 events and no asthma-related deaths.²

In the future, it may be possible to use observational data from the FDA's Sentinel initiative to address the question, when linkage to the NDI is implemented for asthma death information. As of August 2015, the Mini-Sentinel pilot project had compiled data on 193 million individuals with 351 million person-years

of observation time (http://www.mini-sentinel.org/about_us/MSDD_At-a-Glance.aspx). Use of such data was not possible when this feasibility project was initiated, and at the time, our collaborative approach based on the Mini-Sentinel initiative for distributed data analyses under a common data model was not widely used. We demonstrated that this type of collaborative approach is possible for safety studies of rare events, but based on our results, recommend that an initial feasibility assessment be conducted before launching a full-scale investigation.

CONFLICT OF INTEREST

The study was conducted by RTI Health Solutions with financial support from GlaxoSmithKline. Catherine B. Johannes, Lisa McQuay, Kirk Midkiff, Brian Calingaert, and Elizabeth Andrews are employees of RTI Health Solutions and have no other conflict of interest to report. Patricia Tennis was an employee of RTI Health Solutions at the time the study was conducted and has no conflict of interest to report. Jeffrey S. Brown has no conflicts of interest to report. Carlos Camargo, Jr. has provided asthma-related consultation for GlaxoSmithKline, Merck, Novartis, and Teva and has received research grants from Novartis and Teva. Rachel DiSantostefano was an employee of GlaxoSmithKline during the time the study was conducted and is currently a shareholder. Till Stürmer receives investigator-initiated research funding and support as Principal Investigator from the National Institute on Aging (R01 AG023178), as Co-Investigator from the National Institutes of Health (R01 CA174453; R01 HL118255), and as Principal Investigator of a Pilot Project from the Patient Centered Outcomes Research Institute. He also receives salary support as Director of the Comparative Effectiveness Research Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR001111) and as Director of the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Merck) and research support from pharmaceutical companies (Amgen, Merck, AstraZeneca) to the Department of Epidemiology, University of North Carolina at Chapel Hill. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, BASF, and AstraZeneca. Stephan Lanes is an employee of HealthCore, Inc. Kourtney Davis is an employee of GlaxoSmithKline and is currently a shareholder.

KEY POINTS

- The risk of asthma mortality associated with the use of LABA in combination with inhaled corticosteroid therapy is not known and difficult to study because of the rarity of asthma death and expected small relative effect.
- An efficient way to construct a large cohort for a retrospective observational study was to partner with multiple institutions using a distributed research network and common research protocol and analytic programs.
- Despite 2.4 million person-years of observation collected from 10 data sources over a 10-year period, obtaining informative estimates was not feasible.

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OptumInsight (now Optum)	Wendy Carman
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Henry Ford Health Systems	Christine Joseph
HealthPartners Research Foundation	Ann Hanson
Kaiser Permanente Center for Health Research, Hawaii	Cynthia Nakasato
Southern California Permanente Medical Group	Michael Schatz
Lovelace Clinic Foundation Research	Douglas Mapel
Meyers Primary Care Institute	Susan Andrade
Scott and White Healthcare	John Zeber

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PREVIOUS PRESENTATION OF RESULTS

Results from this work have been previously presented in abstract form.

- Tennis P, Davis K, Stürmer T, Brown J, Lanes S. Symposium on Addressing Challenges in Using Multiple Data Sources to Evaluate Medication Risk Factors for Asthma Mortality in Persistent Asthma. *Pharmacoepidemiol Drug Saf* 2011;**20**(Suppl 1):S268.
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- Midkiff K, Johannes C, Tennis P, Calingaert B, McQuay L, Harris D, Andrews EB. Identifying Causes of Death in a Large Cohort of Asthma Patients. *Pharmacoepidemiol Drug Saf* 2013;**22**(Suppl 1):300.

Selected results were included in a companion publication that focused on the clinical outcome of asthma mortality.

- Camargo CA Jr, Davis KJ, Andrews EB, Stempel DA, Schatz M. Pharmacoepidemiological study of long-acting β -agonist/inhaled corticosteroid therapy and asthma mortality: clinical implications. *Clin Drug Investig*. Published online: 31 August 2016. DOI 10.1007/s40261-016-0448-1.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Supplemental Table 1. Number of users and person-years of use in exposure categories using three definitions of new use and a 30-day or 60-day gap between exposure episodes, (sensitivity analysis with research partners A and C combined)

Exposure category	Definition 1 ^a		Definition 2 ^b		Definition 3 ^c	
	Number of patients	Person-years	Number of patients	Person-years	Number of patients	Person-years
30-Day gap						
Advair	73,034	16,101	104,272	25,308	115,685	28,095
Symbicort	6,995	1,390	16,416	3,520	21,893	4,685
Salmeterol+ICS	2,553	396	4,995	783	5,746	888
Formoterol+ICS	1,236	219	3,967	804	5,420	1,079
ICS monotherapy	43,387	8,385	56,637	11,216	61,648	12,257
ICS+LTRA	32,768	5,892	59,045	10,433	67,674	11,837
ICS+theophylline	956	144	1,489	215	1,801	255
ICS+other non-LABA controller	555	68	1,082	130	1,341	158
60-Day gap						
Advair	69,891	25,291	99,597	39,673	110,224	43,899
Symbicort	6,758	2,105	15,594	5,216	20,587	6,913
Salmeterol+ICS	2,561	636	4,838	1,211	5,499	1,362
Formoterol+ICS	1,254	346	3,847	1,264	5,148	1,666

Exposure category	Definition 1 ^a		Definition 2 ^b		Definition 3 ^c	
	Number of patients	Person-years	Number of patients	Person-years	Number of patients	Person-years
ICS monotherapy	42,846	12,518	55,333	16,540	60,087	17,975
ICS+LTRA	34,061	9,562	60,446	16,693	68,711	18,731
ICS+theophylline	965	232	1,433	336	1,683	384
ICS+other non-LABA controller	584	107	1,114	200	1,347	237

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist.

^a New user definition 1: First new use of a medication in any of the exposure group on or after the persistent asthma cohort entry date.

^b New user definition 2: First episode of new drug use *with or without* drug use in any other exposure group.

^c New user definition 3: All first exposure episodes of any study medication.