PROTOCOL FOR THE ASSESSMENT OF FDA REGULATORY POLICIES FOR LONG ACTING BETA$_2$ AGONISTS

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Protocol For The Assessment Of FDA Regulatory Policies For Long Acting Beta$_2$ Agonists

I. INTRODUCTION

Long acting beta$_2$ agonists (LABA) have been shown to be effective at controlling asthma symptoms and reducing exacerbations.[1-3] However, there has been growing safety concerns associated with these agents. The Salmeterol Multicenter Asthma Research Trial (SMART) found patients receiving salmeterol compared to placebo had a greater risk for asthma-related mortality.[4] Risk was greatest among patients receiving LABA monotherapy. In addition to finding an increase in asthma-related deaths among LABA users, a meta-analysis of 19 clinical trials found LABA use was associated with increased severe exacerbations.[5] The risk of these adverse asthma-related outcomes was observed in both adults and children. In light of this new information, FDA communicated the risk associated with LABAs to the public in late 2005.[6-7] FDA also advised health professionals that LABAs should not be prescribed as first line therapy, but added to a regimen that already consisted of an inhaled corticosteroid (ICS). FDA required manufacturers to update their product labeling to reflect the safety information and for manufacturers to also provide FDA with clinical trial data for analyses purposes.

After convening several advisory committee meetings from 2005 to 2010 and examining data from more than 60,000 people enrolled in 110 clinic trials, FDA concluded there was an increased risk of adverse asthma outcomes associated with LABA agents.[8-11] Their analysis showed that the risk of adverse asthma outcomes was greater in the pediatric population compared to adults.[11] In 2010, new FDA regulatory policies were released. These required manufacturers to initiate clinical trials that compared the safety of ICS/LABA combination therapy to ICS monotherapy, to develop risk assessment and mitigation strategies (REMS) for LABAs, and to update their product labeling to reflect the risks associated with LABAs.[9] The following information is now present in LABA manufacturers' product labels:

- The use of LABAs is contraindicated without the use of an asthma controller medication such as inhaled corticosteroid. Single-agent LABAs should only be used in combination with an asthma controller medication and they should not be used alone.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.
- LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.
- Pediatric and adolescent patients who require a LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA to ensure compliance with both medications.

The objective of this Mini-Sentinel workgroup is to assess the impact of the 2010 FDA regulatory action on LABA drug utilization patterns.

II. AIMS

- To assess trends of asthma medication use in an asthma cohort before and after the 2010 FDA regulatory actions on LABAs

- To assess trends of LABA initiation in an asthma cohort before and after the 2010 FDA regulatory actions on LABAs

- To assess combination ICS/LABA product initiation among new users of LABAs before and after the 2010 FDA regulatory actions on LABAs

- To assess the appropriateness of LABA initiation among new users of LABAs before and after the 2010 FDA regulatory actions on LABAs

- To describe the episode of LABA use among new users of LABAs before and after the 2010 FDA regulatory actions on LABAs

- To describe step down therapy after LABA discontinuation before and after the 2010 FDA regulatory actions on LABAs

III. ASSESSMENT PLAN

A. DATA SOURCE

This assessment will use data from as many of the Data Partners as can adhere to protocol and budget requirements. It is expected that all Data Partners will participate in this activity. It should be noted that 3 Data Partners do not have data available for the entire study period.

B. STUDY PERIOD

The study period will be January 1, 2003 to June 30, 2011. Medication use will be measured starting January 1, 2004 to June 30, 2011 to allow for a 12-month baseline period to assess eligibility and to measure cohort characteristics.

C. COHORT IDENTIFICATION

To establish the master asthma cohort, we will identify within the Mini-Sentinel Distributed Database (MSDD), health plan members who meet the following criteria between January 1, 2004 and June 30, 2011: 1) continuous health plan enrollment and pharmacy benefit for at least 365 days prior to any date between January 1, 2004 - June 30, 2011; 2) age 65 years or younger as of January 1, 2004; and 3) at least one office visit, emergency department visit, or hospitalization in the 12 months prior to any date between January 1, 2004 - June 30, 2011 with an ICD-9 code of 493. Health plan members will be excluded if they have a history of chronic obstructive pulmonary disease (COPD) (ICD-9 codes 491, 492, 496); cystic fibrosis (ICD-9 code 277.0x); bronchiectasis (ICD-9 code 494); pulmonary hypertension or embolism (ICD-9 codes 416.0, 415.1); bronchopulmonary dysplasia (ICD-9 code 770.7); or congestive heart failure (ICD-9 code 428).[12-13] The master asthma cohort will be represented by the symbol '**A**'.

Preliminary data attained from the Mini-Sentinel Summary Table request showed as new Data Partners developed their MSDD, the number of health plan members with a diagnosis for asthma almost doubled from approximately 1 million to 2 million between 2004 and 2009.

D. AIM 1 – TO ASSESS TRENDS OF ASTHMA MEDICATION USE IN AN ASTHMA COHORT BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

In this aim, prevalent use of all asthma medications will be measured in the asthma cohort. As a result, we will be able to assess whether use of asthma medications changed during the study period.

1. Cohort Identification

To determine who uses asthma medications, we will use the master asthma cohort '**A**' defined in section III.C. A rolling monthly cohort definition will be used. The inclusion criteria will be assessed in the 365-day period prior to the 1st day of each month [i.e. 1) continuous health plan enrollment and pharmacy benefit; 2) age 65 years or younger; and 3) at least one office visit, emergency department visit, or hospitalization with an ICD-9 code of 493] as will the exclusion criteria. Everyone in the master asthma cohort **'A'** will be represented in at least one of the monthly time periods.

A 12-month baseline period was chosen to assess eligibility because having a 24-month baseline period could drastically reduce the sample size, while an undefined look-back period could introduce information bias. A 12-month baseline period has been used in a number of studies that have assessed asthma medication utilization.[12, 14-16] Most analyses use a criterion for 2 outpatient visits with an ICD-9 code for asthma to confirm a diagnosis of asthma, but a more relaxed definition was desired to capture as many people as possible. This more liberal definition could lead to misclassification if the single identifying ICD-9 code was associated with a visit to rule out asthma versus an actual visit for asthma. The extent of misclassification may be small since results from the Mini-Sentinel Summary Table analysis showed health plan members had an average of 2 outpatient visits per year for asthma.

2. Drugs of Interest

The asthma medications that will be measured in this aim will be grouped by class and are shown in **Table 1**. LABAs will be studied collectively as well as by single and combination status. We will measure prevalent drug use for all classes listed. Prevalent medication use in any given month will be identified by evidence of any day supply of the asthma medications of interest in that month. For simplicity, '**M**' represents a vector of any of the drug classes of interest.

Table 1. Asthma Medications

CLASS	AGENT
LONG-ACTING BETA-AGONISTS$_2$ (LABA)	
Single Agents	Salmeterol
	Formoterol
	Arformoterol
Combination Agents	Budesonide-formoterol
	Fluticasone-salmeterol
	Mometasone-formoterol
LEUKOTRIENE INHIBITORS	Montelukast
	Zafirluskast
	Zileuton
ORAL CORTICOSTEROIDS	Methylpredinsolone tablets

Table 1. Asthma Medications

CLASS	AGENT
	Prednisolone tablets, oral solution, oral syrup
	Prednisone tablets, oral solution, oral syrup
INHALED CORTICOSTEROIDS (ICS)	Beclomethasone
	Budesonide
	Ciclesonide
	Flunisolide
	Fluticasone
	Mometasone inhalation powder
	Triamcinolone
OTHER CONTROLLER MEDICATIONS	Cromolyn
	Nedocromil
	Omalizumab
	Theophylline
SHORT-ACTING BETA-AGONISTS (SABA)	Albuterol
	Levalbuterol
	Pirbuterol
OTHER BRONCHODILATORS	Tiotropium bromide
	Ipratropium bromide
	Albuterol sulfate/ipratropium

Results from the Mini-Sentinel Summary Table analysis show that use of combination LABA products has been increasing over time while use of single agent LABA products has started to decline. It should be noted that the data on medication use from the Summary Table analysis is based on prevalent medication use only and does not account for diagnoses.

3. Outcomes

1) Proportion of members who use any asthma agent (denoted as $\mathbf{O_1}$) = number of members using $\mathbf{M}$/ $\mathbf{A}$.

In this aim, '$\mathbf{M}$' can be substituted for any drug class listed in Table 1.

4. Statistical Analysis

a. Descriptive

Means and standard deviations will be reported for all continuous variables; number and percent will be reported for categorical variables. Basic bivariate analyses will be conducted using T-test and Chi-square test to assess differences in the asthma cohort's '$\mathbf{A}$' characteristics before and after the policy was implemented. We will compare the entire pre-policy period (January 2004 to January 2010) to the post-policy period (February 2010 to June 2011) as well as a shorter pre-policy period (January 2008 to January 2010) to the post-policy period. The characteristics to be examined include age, sex, and co-morbid conditions (e.g. allergic rhinitis, gastroesophageal reflux disease (GERD), and acute respiratory infections). In addition, **'$\mathbf{O_1}$'** will be compared across the pre- and post-policy periods (e.g. January 2004

to January 2010 and January 2008 to January 2010 vs. February 2010 to June 2011). Lastly, subgroups will be studied. We will compare the outcome by sex and by age (0-4, 5-11, 12-17, ≥18 years) before and after the 2010 policy. The outcome will also be presented graphically over time.

b. Regression

To substantiate the descriptive statistics, more rigorous quasi-experimental techniques will be applied to assess the impact of the policy on prevalent LABA use only. A trend graph of the monthly rates will be produced and followed up with the segmented regression to confirm what is seen visually with statistical analysis. Segmented linear regression analysis of interrupted time series design will be implemented to assess the change of level and trend in LABA use (Equation 1).[17-18] The eligible asthma cohort **'A'** will be identified on the 1st day of each month, which constitutes a changing denominator over time (rolling cohort).[19-20] LABA use will be identified from the monthly pools of asthma health plan members. We will produce graphs and segmented regression statistics overall and by sex and age group (<18 vs. ≥18 years).

Since there was an earlier FDA regulatory change introduced in fall 2005, the rate of LABA use during the early part of the study period could have had changes reflecting that policy. We will account for that policy in the model not as the focus of this analysis, but to control for it by creating a level and a trend that would present that period of time. The model will have 3 segments based on the following dates: January 2004-November 2005, December 2005-January 2010, and February 2010-June 2011. The beginning and end of each segment reflects the introduction of FDA regulatory action.

Equation 1

$$Y_t = \beta_0 + \beta_1 T + \beta_2 P_{1_t} + \beta_3 T P_{1_t} + \beta_4 P_{2_t} + \beta_5 T P_{2_t} + \varepsilon_t$$

Y -aggregate outcome at each time; T – month since the start of the study; P_1 – dummy variable representing the black box warning policy in 2005 ; P_2 – dummy variable representing the 2010 regulations; Error terms are autocorrelated.

We will examine whether there is a lagged intervention effect between February 2010 and June 2010 when the regulation was being implemented. If it exists, these time points may be excluded from the segmented regression or modeled within their own segment.

There may be serial autocorrelations of the outcome over time, so we will assess for autocorrelation by studying plots of the residuals against time and conducting statistical tests such as the Durbin-Watson statistic.[17] We will consider first order and second order correlations for outcomes that are close in time to one another and will also assess higher order correlation to account for seasonality. To estimate seasonal autocorrelation we will evaluate autocorrelation models which assess the error terms 12 months apart. Because the study period is several years in length, there are adequate data points to assess and control for seasonality if necessary.

E. AIM 2 - TO ASSESS TRENDS OF LABA INITIATION IN AN ASTHMA COHORT BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

To put the initiation of LABAs into context, we will assess the trends of initiation in the asthma cohort. We can assess whether the rate of health plan members newly initiating a LABA has remained consistent over time or whether the rates of use have been changing.

1. Cohort Identification

To determine who initiates a LABA, the master asthma cohort '**A**' defined in section III.C will be restricted to health plan members "at risk of" starting LABAs. Therefore, current LABA users will be excluded from the risk cohort '$\mathbf{N_R}$'. The eligible cohort will be identified on the 1st day of each month.

2. Drugs of Interest

All LABA agents, single and combination products, are of interest in this aim. See Table 1 for a list of agents. We refer to the date of first prescription of a LABA agent as the index date. Therefore, any health plan member will be classified as an initiator if: 1) a first prescription for LABAs is filled between January 1, 2004 and June 30, 2011; 2) they have continuous health plan enrollment and pharmacy benefit for at least 365 days prior to the index date; 3) there is no prescription of any of the drugs of interest in the 183 days preceding the index date; 4) they are aged 65 years or younger at the index date; and 5) they have at least one office visit, emergency department visit, or hospitalization in the 12 months preceding the index date with an ICD-9 code of 493 and no history of COPD (ICD-9 codes 491, 492, 496); cystic fibrosis (ICD-9 codes 277.0x); bronchiectasis (ICD-9 code 494); pulmonary hypertension or embolism (ICD-9 codes 416.0, 415.1); bronchopulmonary dysplasia (ICD-9 code 770.7); or congestive heart failure (ICD-9 code 428). The new users will be represented by the symbol '$\mathbf{N_L}$'.

Mini-Sentinel uses a 6-month look back period to assess new use, as have others who have studied asthma medication use;[13] however, there are some studies that use a longer washout / look back period (e.g. 12 months).[12, 15]

3. Outcomes

There is one outcome assessing the proportion of asthma health plan members who initiate LABA medications.

1) Proportion of members who initiated any LABA agent (denoted as '$\mathbf{O_2}$') = $\mathbf{N_L/N_R}$.

4. Statistical Analysis

a. Descriptive

As in the previous aim, means and standard deviations will be reported for all continuous variables; number and percent will be reported for categorical variables. Basic bivariate analyses will be conducted using T-test and Chi-square test to assess differences in the asthma cohort's '$\mathbf{N_R}$' characteristics before and after the policy was implemented. We will compare the entire pre-policy period (January 2004 to January 2010) to the post-policy period (February 2010 to June 2011) as well as a shorter pre-policy period (January 2008 to January 2010) to the post-policy period. In addition, O_2 will be compared across the pre- and post-policy periods (e.g. January 2004 to January 2010 and January 2008 to January 2010 vs. February 2010 to June 2011). Lastly, subgroups will be studied. We will compare the outcome by sex and by age (0-4, 5-11, 12-17, ≥18 years) before and after the 2010 policy. The outcome will also be presented graphically over time.

b. Regression

Segmented regression analysis of interrupted time series will be implemented to assess the change of level and trend in LABA initiation. LABA initiators will be identified from the monthly pools of the asthma population at risk 'N_R'. The same statistical analyses used in section III.D.4 will be applied in this aim (e.g. accounting for the earlier FDA regulatory policy, examining lagged policy effects, testing for autocorrelation, and examining the outcome by subgroup).

F. AIM 3 - TO ASSESS THE UPTAKE OF ICS/LABA COMBINATION PRODUCTS AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

One of the label changes associated with the 2010 regulatory action encouraged use of ICS/LABA combination products, especially within the pediatric population, to ensure compliance with both medications. This aim focuses on the cohort of health plan members, pediatric and adult, who initiated LABAs during the study period and assesses whether combination ICS/LABA product use changed.

1. Cohort Identification

New users of LABAs will be identified among individuals in the master asthma cohort if: 1) a first prescription for a LABA is filled between January 1, 2004 and June 30, 2011; 2) continuous health plan enrollment and pharmacy benefit for at least 365 days prior to the index date; 3) no prescription of any of the drug of interest in the 183 days preceding the index date; 4) age 65 years or younger at the index date; and 5) they have at least one office visit, emergency department visit, or hospitalization in the 12 months preceding the index date with an ICD-9 code of 493 and no history of COPD (ICD-9 codes 491, 492, 496); Cystic fibrosis (ICD-9 code 277.0x); bronchiectasis (ICD-9 code 494); pulmonary hypertension or embolism (ICD-9 codes 416.0, 415.1); bronchopulmonary dysplasia (ICD-9 code 770.7); or congestive heart failure (ICD-9 code 428). The new users will be represented by the symbol 'N_L'.

2. Combination Product Use

The subset of new users who were prescribed combination LABA products (i.e. budesonide-formoterol, fluticasone-salmeterol, or mometasone-formoterol) will be identified by the symbol 'N_C'.

3. Outcomes

There is one outcome assessing the proportion of LABA initiators who initiate LABA combination products.

1) Proportion of LABA initiators who initiate combination products (denoted as **'O_3')** = N_C/N_L.

4. Statistical Analysis

a. Descriptive

As in the previous aims, means and standard deviations will be reported for all continuous variables; number and percent will be reported for categorical variables. Basic bivariate analyses will be conducted using T-test and Chi-square test to assess differences in asthma cohort's 'N_L' characteristics before and after the policy was implemented. We will compare the entire pre-policy period (January

2004 to January 2010) to the post-policy period (February 2010 to June 2011) as well as a shorter pre-policy period (January 2008 to January 2010) to the post-policy period. In addition, '$\mathbf{O_3}$' will be compared across the pre- and post-policy periods. Lastly, subgroups will be studied. We will compare the outcome by sex and by age (0-4, 5-11, 12-17, ≥18 years) before and after the 2010 policy. The outcome will also be presented graphically over time.

b. Regression

Segmented regression analysis of interrupted time series will be implemented to assess the change of level and trend in LABA combination product initiation. The eligible cohort '$\mathbf{N_L}$' will be identified on the 1st day of each month. Combination product use will be identified from the monthly pools of LABA initiators. The same statistical processes used in section III.D.4 will be applied in this aim (e.g. accounting for the earlier FDA regulatory policy, examining lagged policy effects, testing for autocorrelation, and examining the outcome by subgroup).

G. AIM 4 – TO ASSESS THE APPROPRIATENESS OF LABA INITIATION AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

One of the label changes associated with the 2010 regulatory action advised use of LABAs only when asthma could not adequately be controlled on other controller medications. Therefore, this aim focuses on the cohort of health plan members who initiated LABAs during the study period and assesses whether the decision to initiate a LABA was appropriate. History of controller medication use and evidence of an exacerbation are markers used to measure appropriateness. Published estimates of appropriate use in adolescents and adults range from 31%-39%.[12, 14-15]

1. Cohort Identification

The cohort definition for new initiators used in section III.E.1 '$\mathbf{N_L}$' will be applied to this aim.

2. Appropriate Use

Appropriate use will be defined by a history of controller medication and evidence of poor control prior to LABA initiation. Health plan members will meet the criteria for prior controller medication use if there is evidence of a controller medication (i.e. ICS or leukotriene inhibitors) within 90 days of the LABA index date. Controller medications use will be defined as any day supply of a controller medication within the 90 days prior to the index date. The number of LABA initiators with the previous controller use will be represented with the symbol '$\mathbf{C}$'. Evidence of poor control will be established if a health plan member has a history of a hospitalization or emergency department visit in the 12-month pre-index period, fills for two or more oral corticosteroids (OCS) with less than a 21-day supply of medication in a 12-month pre-index period; or ≥6 dispensings of short acting beta agonists (SABA) in a 12-month pre-index period. The number of LABA initiators with a history of poor control will be represented with the symbol '$\mathbf{PC}$'.

There is no standard definition for appropriate use. Our definitions differ somewhat from published work in that the time period to assess controller medication use was reduced from a 12-month pre-index window to a 90-day pre-index window.[12, 15] A shorter time period was chosen to be sure the use of the controller medication was still relevant and acute enough to justify LABA use. In this project we

assess SABA use by dispensings not canisters to allow for the differing use of these medications by children. School-aged children often fill 2 inhalers in order to have one at home and one at school. Therefore, if canisters were used to determine poor control, the numbers could be inflated. Our approach also allows us to measure overuse of dosage forms other than canisters (i.e. nebulizers). Most of the published work that uses canisters has been in adult cohorts where these issues are less likely to be present.[12, 15]

3. Outcomes

There are two outcomes assessing the proportion of LABA initiators who initiate LABAs appropriately.

1) Proportion of LABA initiators with previous controller use (denoted as **'O_4')** = **C/N_L**.

2) Proportion of LABA initiators with a history of poor control (denoted as **'O_5')** = **PC/N_L**.

4. Statistical Analysis

a. Descriptive

The descriptive statistics for the initiator cohort will be the same as described in section III.F.4 of Aim 3 because the same cohort is being used for the current aim. '**O_4**' and '**O_5**' will be compared across the pre- and post-policy periods (e.g. January 2004 to January 2010 and January 2008 to January 2010 vs. February 2010 to June 2011). Lastly, subgroups will be studied. We will compare the two outcomes by sex and by age (0-4, 5-11, 12-17, ≥18 years) before and after the 2010 policy. The outcomes will also be presented graphically over time.

b. Regression

Segmented regression analysis of interrupted time series will be implemented to assess the change of level and trend in appropriate use. The eligible cohort will be identified on the 1st of each month. Appropriate use will be identified from the monthly pools of the asthma cohort 'N_L'. The same statistical processes used in section III.D.4 will be applied in this aim (e.g. accounting for the earlier FDA regulatory policy, examining lagged policy effects, testing for autocorrelation, and examining the outcome by subgroup).

H. AIM 5 - TO DESCRIBE THE EPISODE OF LABA USE AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 REGULATORY ACTIONS ON LABAS

Two of the label changes associated with the 2010 regulatory action encouraged concomitant use of a LABA and another asthma controller medication and for the LABA episode to be as short as clinically possible. Therefore, in this aim we will describe the LABA use episode in terms of duration and concomitant controller medication use. From this aim, we can assess if the policy had any impact on the length of LABA therapy and whether recommendations to use a LABA along with a controller medication were followed. LABAs will be studied collectively as well as by single and combination status.

1. Cohort Identification

The cohort of new initiators identified in section III.E.1 'N_L' will be used in this aim. The cohort will be split into two groups, pre-policy cohort (i.e. index LABA prescription is filled between January 1, 2004 and Jan 31, 2010 and post-policy cohort (i.e. index LABA prescription is filled between February 1, 2010 and June 30, 2011).

2. LABA Follow-up Time

We will follow the new users of LABAs from the index date until the earliest occurrence of 183 days of follow-up, discontinuation of use, death, disenrollment from the health plan, or January 31, 2010 if a LABA was initiated in the pre-policy period or June 30, 2011 in the post-policy period. Discontinuation will be defined by a gap in the LABA day supply exceeding 14 days. The discontinuation date (**DD**) will therefore be the date at the start of the gap exceeding 14 days.[19] We will censor day supply at January 31, 2010 in the pre-policy period and June 30, 2011 in the post-policy period. Follow-up is censored at the last date of the pre-period for health plan members who initiated in the pre-period because the regulatory action could have influenced discontinuation behaviors. We chose a maximum follow-up of 183 days to allow more health plan members to have equal follow-up. A longer follow-up time (e.g. 12 months) would limit the number of health plan members who would have the full follow-up period in the post-period to those initiating LABAs between February 2010 and June 2010. The follow-up end date will be given the symbol 'ED_L'.

We will use the information on day supply from the pharmacy dispensing and claims data to allocate daily amounts of the medication until it is exhausted. We define a meaningful gap in therapy as 14 days or more without any LABA medication. The date at which the gap exceeding 14 days begins will be the discontinuation date. We will establish minor gaps as gaps less than 14 days in length. Minor gaps will be summed to create a cumulative gap (**CG**) measure. We will do a sensitivity analysis with additional measures of meaningful gap (e.g. 7, 30 and 45 days).

Health plan members who switch between single and combination LABA agents will be considered as having continued on therapy. Their medication supply will be added to the end of the previous fills days supply. If both single and combination LABA agents have the same index date the day supply will be based on the medication with the longest day supply; if the days supply is the same the combination agent will be used.

3. Controller Medication Follow-up Time

The total day supply of controller medications will be calculated between the LABA index date **(ID)** and the LABA follow-up end date 'ED_L'. The total controller medication day supply during the LABA episode will be given the symbol '**CM**'. If a health plan member switches from controller medications within the same class, the day supply of the new medication will be added to the end of the day supply of the preceding fill. If a health plan member starts a new class of controller medication, follow-up will start from the date when the medication was filled.

4. Outcomes

Three outcomes will be studied in this aim.

1) Total day supply of a LABA episode (denoted as 'O_6') = $(ED_L - ID) - CG$.

2) Proportion of days controller medication overlapped with the LABA episode (denoted as 'O_7') = CM/O_6

3) Proportion of new LABA users with controller medication use during the entire episode (denoted as 'O_8') = # of people where $O_7=1/N_L$.

5. Statistical Analysis

a. Descriptive

The descriptive statistics for the initiator cohort will be just as described in section III.F.4 of Aim 3 because the same cohort is being used for the current aim. In addition, CM, O_6, O_7 and O_8 will be compared across the pre- and post-policy periods (e.g. Jan 2004 to Jan 2010 and Jan 2008 to Jan 2010 vs. February 2010 to June 2011) using log rank test as appropriate. Lastly, subgroups will be studied. We will compare the three outcomes by sex, age (0-4, 5-11, 12-17, ≥18 years), and LABA product (single vs. combination product) before and after the 2010 policy. The outcomes will also be presented graphically over time.

b. Regression

We will use person level Kaplan-Meier survival curves and Cox proportion hazard models to compare the risk of treatment discontinuation in the post- versus pre-policy cohorts of newly treated health plan members.[19, 21] The outcome of this analysis will be O_6. The results will be interpreted as X times the risk of treatment discontinuation relative to the pre-policy cohort (Equation 2). Covariates listed in **Table 2** will be included in the Cox model. These variables will be measured in the pre-index period. Interaction terms consisting of the policy cohort and age, sex, LABA product will be assessed to determine how the policy impact differed by these subgroups.

We will assess if there is an extended number of health plan members who discontinue therapy after 30 days by examining the proportional hazards assumption for those who discontinue at 30 days versus those who discontinue later. Extended Cox model will be used to model two piece-wise hazard ratios comparing two groups if the assumption does not hold.[19, 22] One hazard ratio will be for 30 days or more and the other less than 30 days.

Equation 2

$$\log\left(\mathrm{HR}_i\left[t, \mathrm{P\_coh}, Z\right]\right) = \delta_1(\mathrm{P\_coh} * \mathrm{I}[t \le 30]_i) + \delta_2(\mathrm{P\_coh} * \mathrm{I}[t > 30]_i) + \sum \gamma_i Z_i$$

P_coh– dummy variable representing the cohort (health plan members initialized in post-policy period or pre-policy period); Z – a vector of covariates shown in Table 2; exp(δ1) and exp(δ2) are hazard ratios of interests (one for first 30 days and one for 30-days after). Here i indexes each health plan member and t is day supply.

Table 2. Baseline Covariates		
Confounder	**Categorization**	**Identified by**
Age as of the index date (years)	0-4, 5-11, 12-17, where 18-64	

Table 2. Baseline Covariates		
Confounder	**Categorization**	**Identified by**
	is the reference group	
Sex	Male/Female	
Co-morbidities		
Acute Respiratory Infection	Yes/No	*ICD-9-CM codes: 464, 460, 480, 487, 465, 462, 463, 034, 381, 382, 461, 466, 481-486
GERD[Ŧ]	Yes/No	ICD-9-CM codes: 530.1, 530.81, 530.10, 530.11, 530.12, 530.19
Allergic rhinitis	Yes/No	*ICD-9-CM codes: 477
LABA product	Single/Combination	
Controller medication use in 90 days pre-index	Yes/No	
Poor control in the pre-index period	Yes/No	
Nasal Steroids	Yes/No	NDC
# of unique medications	Quartiles or pre-defined categories	NDC
Season	Jan-Mar; Apr-Jun; Jul-Sep; Oct-Dec	Index Date

*All decimal place suffixes of these ICD-9 codes were included. Ŧ – Gastrointestinal Reflux Disease

We will use person level Poisson regression models to analyze $\mathbf{O_7}$, the portion of days overlap of LABAs and controller medications. The offset option in Poisson regression will allow us to define the denominator (total number of LABA days for each person). The count of days in controller medications will be the numerator. An incident rate ratio comparing the policy cohort to pre-policy cohort will be the parameter of interest (Equation 3).

Equation 3

$$\log(\mathrm{Y_i} = \#\ \text{of controller medication days}) = \beta_0 + \beta_1 P\_coh_i + \sum \gamma_i Z_i + \log(offset_i)$$

P_coh– dummy variable representing the cohort (health plan members initialized in post-policy period or pre-policy period); Z – a vector of covariates shown in Table 2 or other potential confounders or interactions; exp (β1) is the incident rate ratio of interest. Here i indexes each health plan member.

Covariates listed in Table 2 will be included in the Poisson regression model. Interaction terms consisting of the policy cohort and age, sex, LABA product will be assessed to determine how the policy impact differed by these subgroups. We will consider more complicated regression models such as negative binomial regression if overdispersion exists.

Lastly, person level logistic regression models will be used to analyze $\mathbf{O_8}$, the number of health plan members with complete controller and LABA medication overlap during the LABA episode (Equation 4). Covariates listed in Table 2 will be included in the logistic model. Interaction terms consisting of the

policy cohort and age, sex, LABA product will be assessed to determine how the policy impact differed by these subgroups.

Equation 4

$$\text{logit}\,(Pr(O_{7_i}1)) = \beta_0 + \beta_1 P\_coh_i + \sum \gamma_i Z_i$$

P_coh– dummy variable representing the cohort (health plan members initialized in post-policy period or pre-policy period); Z – a vector of covariates shown in Table 2 or other potential confounders or interactions; exp (β1) is the odds ratio of interest. Here i indexes each health plan member.

Health plan members will be included in these analyses multiple times as long as there is a 183-days LABA-free period between the $\mathbf{ED_L}$ and the new index date. We will control for multiple observations per person using generalized estimating equations (GEE) for all the analyses above (i.e. Cox, Poisson, and logistic).

I. AIM 6 – TO DESCRIBE STEP DOWN THERAPY AFTER LABA DISCONTINUATION BEFORE AND AFTER THE 2010 REGULATORY ACTIONS ON LABAS

One of the label changes associated with the 2010 regulatory action encouraged patients to be maintained on asthma controller medications once LABAs had been discontinued. Therefore, in this aim we will assess whether health plan members who discontinued LABA therapy used controller medications within 30 days of discontinuation.

1. Cohort Identification

To determine who discontinues LABAs, the master asthma cohort '**A**' defined in section III.C will be restricted to any health plan member if: 1) their LABA discontinuation date (**DD**) falls between January 1, 2004 and May 31, 2011; 2) they have continuous health plan enrollment and pharmacy benefits for at least 365 days prior to the **DD**; 3) they are aged 65 years or younger at the **DD**; and 4) they have at least one office visit, emergency department visit, or hospitalization in the 12 months preceding the **DD** with an ICD-9 code of 493 and no history of COPD (ICD-9 codes 491, 492, 496); Cystic fibrosis (ICD-9 code 277.0x); bronchiectasis (ICD-9 code 494); pulmonary hypertension or embolism (ICD-9 codes 416.0, 415.1); bronchopulmonary dysplasia (ICD-9 code 770.7); or congestive heart failure (ICD-9 code 428).

Discontinuation will be defined by a gap in LABA days supply exceeding 14 days. The discontinuation date will therefore be the date at the start of the gap exceeding 14 days. We will also do a sensitivity analysis with additional measures of meaningful gap (e.g. 7, 30 and 45 days). The last date a health plan member could be identified as a discontinuer in the pre-policy period will be December 31, 2009 and May 31, 2011 in the post-policy period. The symbol for the number of discontinuers will be '**D**'. The dates for identifying discontinuers in both the pre- and post-policy periods have been shortened to allow for the 30-day follow-up window needed to identify controller use after discontinuation. In addition, we avoid studying follow-up time that may cross over the policy date. Where the gap for defining discontinuation is less than 30 days (e.g. 7 days, 14 days), only members who do not restart LABAs in the 30-day follow-up window will be included in the analyses.

2. Controller Medication Follow-up Time

We will follow discontinuers of LABAs from the **DD** until the earliest occurrence of 14 days of follow-up, death, disenrollment from the health plan, or January 31, 2010 if a LABA was discontinued in the pre-policy period or June 30, 2011 in the post-policy period. The follow-up end date will be given the symbol '$\mathbf{ED_C}$'.

Any health plan member with evidence of a supply of a controller medication (i.e. ICS or leukotriene inhibitors) in the follow-up period ($\mathbf{DD\text{-}ED_C}$) will be considered a health plan member who has stepped down therapy and will be represented by the symbol '**CS**'.

3. Outcomes

There will be one outcome measured in this aim.

1) Proportion of health plan members who discontinued LABAs and used controller medications within 30 days of discontinuation (denoted as $\mathbf{O_9}$**) = CS/D.**

4. Statistical Analysis

a. Descriptive

As with the previous aims, means and standard deviations will be reported for all continuous variables, and number and percent will be reported for categorical variables. Basic bivariate analyses will be conducted using T-test and Chi-square test to assess differences in asthma cohort's (D) characteristics before and after the policy was implemented. We will compare the entire pre-policy period (January 2004 to January 2010) to the post-policy period (February 2010 to June 2011) as well as a shorter pre-policy period (January 2008 to January 2010) to the post-policy period. In addition, $\mathbf{O_9}$ will be compared across the pre- and post-policy periods. Lastly, subgroups will be studied. We will compare the outcome by sex and by age (0-4, 5-11, 12-17, ≥18 years) before and after the 2010 policy. The outcome will also be presented graphically over time.

b. Regression

Person level logistic regression models will be used to analyze $\mathbf{O_9}$, the proportion of health plan members who discontinue LABAs and use controller medications within 30 days of discontinuing therapy (Equation 5). Covariates listed in **Table 3** will be included in the logistic model. They will be measured in the pre-discontinuation period. Interaction terms consisting of the policy cohort and age, sex, LABA product will be assessed to determine how the policy impact differed by these subgroups.

Equation 5

$$\text{logit}\left(Pr(O_{7i}1)\right) = \beta_0 + \beta_1 P\_coh_i + \sum \gamma_i Z_i$$

P_coh– dummy variable representing the cohort (health plan members initialized in post-policy period or pre-policy period); Z – a vector of covariates shown in Table 3 or other potential confounders or interactions; exp (β1) is the odds ratio of interest. Here i indexes each health plan member.

Health plan members will be included in the analysis multiple times as long as there is a 183-days LABA-free period between the **DD** and the new index date. We will control for multiple observations per person using GEE for all of the analyses.

Table 3. Baseline Covariates		
Confounder	**Categorization**	**Identified by**
Age as of the DD (years)	0-4, 5-11, 12-17, where 18-64 is the reference group	
Sex	Male/Female	
Co-morbidities		
Acute respiratory infection	Yes/No	*ICD-9-CM codes: 464, 460, 480, 487, 465, 462, 463, 034, 381, 382, 461, 466, 481-486
GERD	Yes/No	ICD-9 –CM codes: 530.1, 530.81, 530.10, 530.11, 530.12, 530.19
Allergic rhinitis	Yes/No	*ICD-9-CM codes: 477
LABA product	Single/Combination	
Controller medication use 90 days prior to discontinuation	Yes/No	
Poor control in the pre-discontinuation period	Yes/No	
Nasal Steroids	Yes/No	NDC
# of unique medications	Quartiles or pre-defined categories	NDC
Season	Jan-Mar; Apr-Jun; Jul-Sep; Oct-Dec	Index Date

* All decimal place suffixes of these ICD-9 codes were included.

IV. LIMITATIONS

1) In this project, we only consider a selected number of confounders for the person level analyses; therefore, residual confounding may be an issue.
2) Because a US Federal regulation is being evaluated, the entire US population is affected. Therefore, a concurrent comparator population unaffected by the regulations cannot be identified. In addition, the regulations include implications that affect other controller medications so a drug comparison was also not selected.
3) If observations are dropped from the interrupted time series design during the policy transition period between February 2010 and June 2010, the number of post-policy monthly observation periods will decline and, as a result, there may be too few in the analysis.[17] We will explore the ability to add data through September 30, 2011.
4) There may be an under-ascertainment of pediatric health plan members even with the more generous definition of asthma. In the youngest children, a diagnosis for asthma is sometimes not made until the child reaches the age of 2 or 4 years. Some cohort definitions for pediatric populations have included wheezing to overcome this issue.[13]

V. APPENDIX

Table 4 services as a template for the descriptive statistics for the LABA initiator cohort. A similar approach will be applied to each asthma cohort being studied and the corresponding outcomes. Note each outcome will be studied by sex and age group.

Table 4. Template for Descriptive Statistics for the LABA Initiator Cohort

Variable	Year		
	2005-2009	2008-2009	2010-2011
LABA Initiator Cohort (count)			
Male (%)			
Age (%)			
0-4			
5-11			
12-17			
18-45			
45-64			
GERD			
Allergic Rhinitis			
Acute Respiratory Infections			
O_3 - LABA/ICS combination product initiation (%)			
Age			
Sex			
O_4 - LABA initiation after controller medication use in prior 90 Days (%)			
Age			
Sex			
O_5 - LABA initiation with history of uncontrolled asthma in prior 12 months (%)			
Age			
Sex			
O_6 - Duration of LABA episode (days)			
Age			
Sex			
O_7 - Proportion of days of concomitant controller use during the LABA episode			
Age			
Sex			
O_8 - Concomitant controller medication for the entire duration of the LABA episode (%)			
Age			
Sex			

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