A Mini-Sentinel Assessment of FDA Regulatory Policies for Long Acting Beta$_2$ Agonists

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On behalf of the Mini-Sentinel LABA Workgroup

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## Mini-Sentinel LABA Workgroup

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Mini-Sentinel Partner Organizations
Mini-Sentinel Key Feature

- Assessment of the impact of FDA actions on utilization of medical products
Long Acting Beta$_2$ Agonists

- Mechanism of Action and Use
  - LABA are bronchodilators that relax the smooth muscle of the airways of the lungs
  - The onset of action tends to take longer and the duration of action is longer than short-acting beta$_2$ agonists
  - LABA are approved for treating both asthma and COPD
  - LABA may be steroid-spearing

- Safety concerns in asthma began in the 1990s
**LABA Regulation and Safety Timeline**

- **1994**
  - Salmeterol aerosol approval

- **1993**
  - Salmeterol Nationwide Surveillance Study (UK) published

- **1996**
  - Salmeterol diskus approval
  - Reports of serious exacerbations and deaths reported with use of salmeterol
  - SMART Study initiated

- **2000**
  - Salmeterol / fluticasone diskus approval

- **2001**
  - Formoterol fumerate approval

- **2002**
  - Formoterol phase IV trial initiated

- **2004**
  - Additional salmeterol label changes

- **2005**
  - Label changes
  - Information to healthcare professionals released
  - Med Guides requested for LABA containing agents

- **2006**
  - Salmeterol / fluticasone HFA approval
  - Formoterol / budesonide approval
  - SMART Study results published
  - Public Health Advisory on new labeling

- **2007**
  - FDA reviews risk and decides removal of salmeterol not warranted

- **2008**
  - FDA review stressed need for more pediatric data

- **2009**
  - Label changes
  - Safety information released to consumers and healthcare professionals
  - Formoterol / mometasone approval

- **2010**
Overarching Goals of the Project

- To assess the impact of the FDA 2010 regulatory action on LABA drug utilization patterns
  - Population based prevalent use of asthma medications
  - Population based initiation of LABA products
  - Characteristics of LABA initiation and course of therapy
    - Uptake of use of combination LABA products
    - Appropriateness of LABA initiation
    - Length of therapy
    - Concomitant controller medication use
  - Characteristics of LABA discontinuation
    - Use of controller medications after discontinuation
Timeline

- Kick-off meeting: Nov 11
- Final proposal report: Mar 12
- 1st workplan sent: July 12
- Analysis complete: Feb 13
- Draft final report: Apr 13
Quasi-Experimental Designs for Policy Analysis

- Pooled analyses

- Vs.

- Difference-in-difference

- Interrupted time series

- Extended Cox regression
Interrupted Time Series (ITS)

- One of the most rigorous quasi-experimental designs
- Multiple policies can be modeled over time
- ITS shows the immediate effect of a policy as well as trends over time
- The rolling cohort design allows individuals to enter and exit the study base
1 Workgroup creates and submits work plan (a computer program)
2 Data partners retrieve the work plan
3 Data partners review and run work plan against their local data
4 Data partners review results
5 Data partners return results via secure network
6 Results are aggregated and returned
Making Distributed Analyses Efficient

- Use of multiple definitions
  - Number of outpatient visits for asthma
  - Position of diagnosis codes for hospitalizations
  - Discontinuation

- Identifying subgroups a priori

- Programming model alternatives for model diagnostics
  - Poisson and negative binomial

- Pooling individual site data
  - Additive process for ITS
  - Meta-analysis methods for other regression methods
Cohort Creation – Pooled Results

Total population in Mini-sentinel
~90,000,000

Applying eligibility criteria
(age, medical history, etc)

Pooled number of patients with
asthma
1,545,077

LABA – Long-acting beta₂ agonists
ICS – Inhaled corticosteroids
LM – Leukotriene modifiers
OCM – Other controller medications
OCS – Oral corticosteroids
SABA – Short-acting beta₂ agonists

LABA
Pre: 35,095
Post: 6,387

LM
Pre: 275,287
Post: 113,137

Other Bronchodilators
Pre: 69,543
Post: 22,837

OCS
Pre: 340,600
Post: 139,974

ICS-LABA
Pre: 232,439
Post: 98,559

ICS
Pre: 589,176
Post: 274,160

OCM
Pre: 20,432
Post: 3,589

SABA
Pre: 678,770
Post: 307,936

No Medication
Pre: 339,517
Post: 206,675
Summary of Overarching Goals to Date

- Changes in asthma medication use were not unique to LABA during the pre and post policy periods
  - Confirms the difficulty of selecting a control group

- Changes in LABA use started prior to the 2010 regulations
Re-Use of the LABA Framework

- To assess the impact new technology on utilization of medical products
- To assess changes in delivery systems on utilization of medical products
- To assess differences in state regulations on utilization of medical products
  - Allows for the possibility to include a comparison group in the ITS
Proposal Details Can be Found Here

PROTOCOL FOR THE ASSESSMENT OF FDA REGULATORY POLICIES FOR LONG ACTING BETA₂ AGONISTS

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Thank You