Online Supplement
Inhaler Formulary Change in COPD and the Association with Exacerbations, Health Care Utilization, and Costs

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Defining COPD Exacerbations

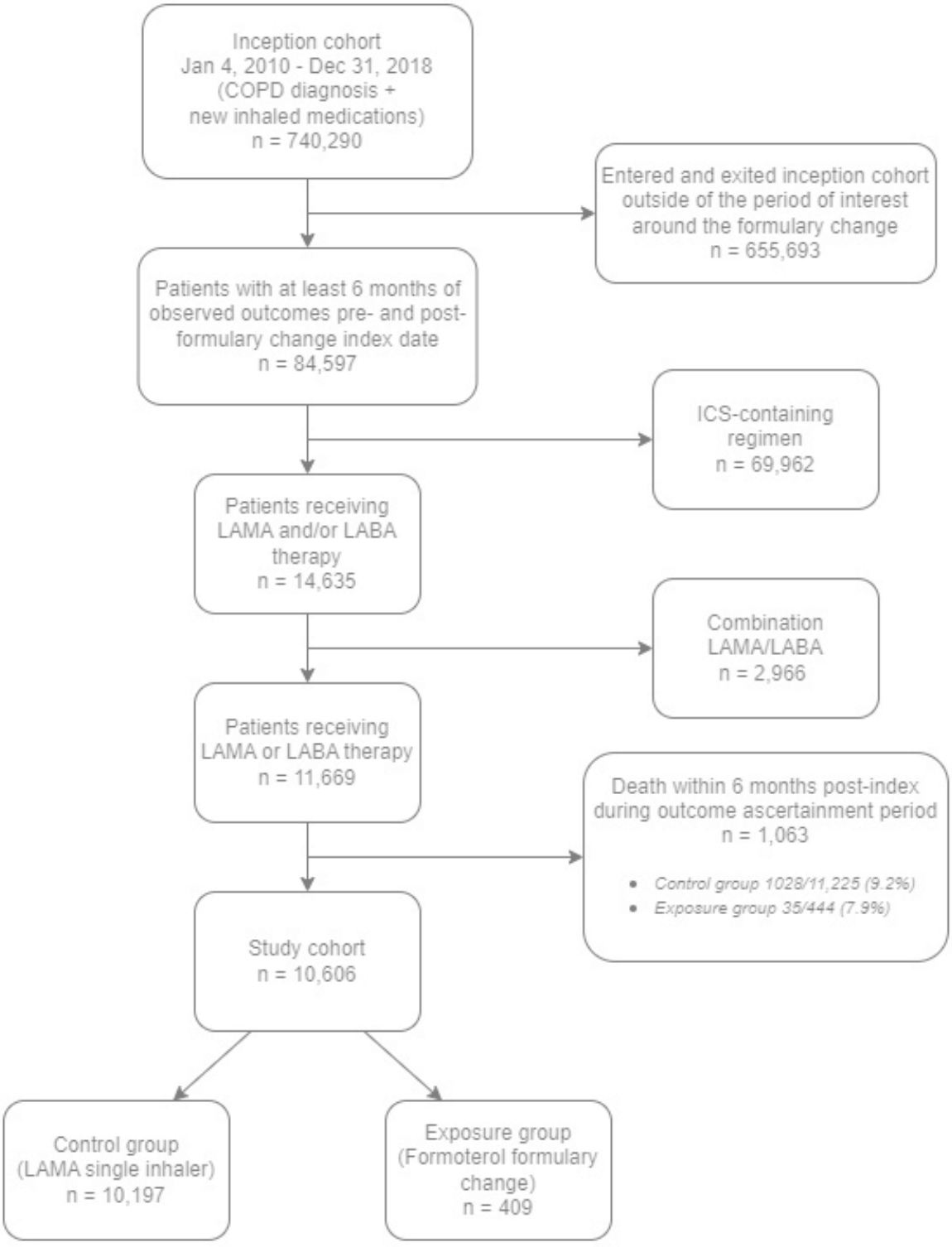
- Inpatient COPD exacerbations: Based on established methods used by others (1, 2), we defined inpatient COPD exacerbations as a hospitalization based on diagnosis codes:
    1. Principal diagnosis of COPD (see appendix Table 1 for list of codes), *OR*
    2. Principal diagnosis of respiratory failure with a secondary diagnosis of COPD (see appendix Table 1 for list of codes)
- Outpatient COPD exacerbation: Based on established methods used by others (3–5) we defined outpatient COPD exacerbations as an encounter with a diagnosis of COPD (see appendix Table 1 for list of codes) *AND* a prescription for steroids or antibiotics within +/- 3 days of the encounter. We used a stricter +/- 3 day cutoff as opposed to 5-7 days typically used in other studies to increase specificity of our primary outcome. For antibiotics to be eligible for consideration for a COPD exacerbation, they must not have been prescribed for an encounter associated with urinary tract infection, skin and soft tissue infection, acute sinusitis or pneumonia.

Supplement Table 1: COPD Diagnosis Codes

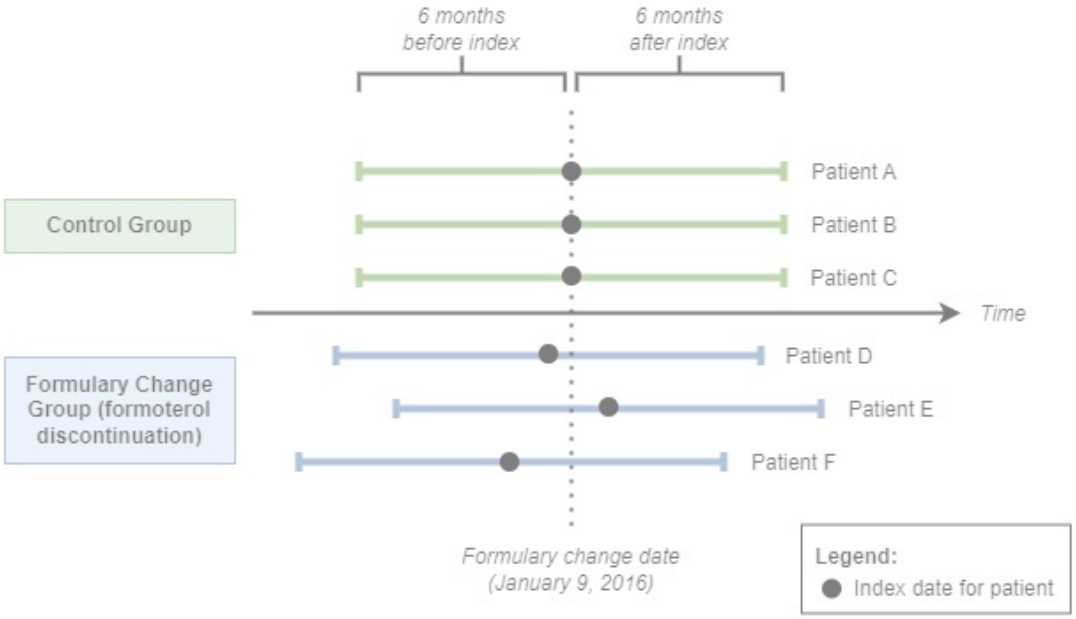
COPD Diagnosis Codes			
ICD9 Code	**Description**	**ICD10 Code**	**Description**
491	SIMPLE CHR BRONCHITIS	J41.0	Simple chronic bronchitis
491.1	MUCOPURUL CHR BRONCHITIS	J41.1	Mucopurulent chronic bronchitis
491.2	OBSTRUCT CHR BRONCHITIS	J41.8	Mixed simple and mucopurulent chronic bronchitis
491.2	OBST CHR BRONC W/O EXAC	J42.	Unspecified chronic bronchitis
491.21	OBS CHR BRONC W(AC) EXAC	J43.0	Unilateral pulmonary emphysema [MacLeod's syndrome]
491.22	OBS CHR BRONC W AC BRONC	J43.1	Panlobular emphysema
491.8	CHRONIC BRONCHITIS NEC	J43.2	Centrilobular emphysema
491.9	CHRONIC BRONCHITIS NOS	J43.8	Other emphysema
492	EMPHYSEMATOUS BLEB	J43.9	Emphysema, unspecified
492.8	EMPHYSEMA NEC	J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
496	CHR AIRWAY OBSTRUCT NEC	J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
		J44.9	Chronic obstructive pulmonary disease, unspecified
Respiratory Failure Diagnosis Codes			
ICD9 Code	**Description**	**ICD10 Code**	**Description**
518.8	LUNG DISEASE NEC	J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
518.81	ACUTE RESPIRATORY FAILURE	J96.01	Acute respiratory failure with hypoxia
518.82	OTHER PULM INSUFF, NEC	J96.02	Acute respiratory failure with hypercapnia
518.83	CHRONIC RESPIRATORY FAILURE	J96.10	Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
518.84	ACUTE & CHRONIC RESP FAILURE	J96.11	Chronic respiratory failure with hypoxia
518.89	OTHER DISEASE OF LUNG, NEC	J96.12	Chronic respiratory failure with hypercapnia
		J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
		J96.21	Acute and chronic respiratory failure with hypoxia

		J96.22	Acute and chronic respiratory failure with hypercapnia
		J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
		J96.91	Respiratory failure, unspecified with hypoxia
		J96.92	Respiratory failure, unspecified with hypercapnia

Supplement Figure 1: Cohort Selection



Supplement Figure 2: Development of Index Date



Parallel Trends Assumption Testing

The parallel trends assumption is important to the validity of the difference-in-differences (DiD) study design. The assumption states that in the absence of the intervention (i.e. the formoterol formulary change in this study), the difference in outcomes between the exposure and control groups would remain constant over time (6). To test the assumption, for each outcome (COPD exacerbations, total encounters and total encounter-related costs), we modeled the relationship between the outcome (monthly) and a time-exposure interaction term using a linear regression model in the 6-month pre-formulary change period. The time-exposure interaction term was constructed by multiplying the time variable (in months) by a dummy variable for our exposure group (patients experiencing a formulary change). We report coefficients, 95% confidence intervals and p-values in Supplement Table 2. A non-statistically significant coefficient for the interaction term suggests that the trend in outcome for the exposure group remain parallel to that of the control group. We did not identify any statistically significant relationships, which suggests that the parallel trends assumption holds.

Supplement Table 2: Parallel Trends Assumption Test Results

Outcome	Coefficient for time-exposure interaction (95%CI)	p-value
COPD Exacerbations (count)	-0.0002 (-0.005, 0.005)	0.92
Total Encounters (count)	0.008 (-0.02, 0.04)	0.61
Total Costs (2016 US$)	-12.89 (-140.16, 114.37)	0.84

Supplement Table 3: Sensitivity Analysis Evaluating Outcomes in Veterans after Formulary Change Relative to Veterans Without Formulary Change Using an Alternative Exposure Group Definition (excluding patients discontinuing inhalers after the formulary change)

Outcome	Difference-in-differences estimates*			
	Unadjusted, per person per 6 months		Adjusted, per person per 6 months**	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
COPD Exacerbations (count)	-0.02 (-0.11, 0.07)	0.65	-0.04 (-0.11, 0.03)	0.27
Total Encounters (count)	0.06 (-0.91, 1.02)	0.90	0.11 (-1.00, 1.21)	0.85
Total Costs (2016 US$)	669 (-900, 2238)	0.40	904 (-566, 2374)	0.23

* Difference-in-differences estimates are reported as average marginal effects, which can be interpreted as the difference in the 6-month number of encounters or 6-month costs in dollars pre- and post-formulary change for the exposure group, compared to that same pre/post difference in the control group

** Adjusted for age, gender, race, ethnicity, body mass index, Charlson comorbidity index, smoking status, marital status, drive distance, and VA priority group.

Supplement Table 4: Sensitivity Analysis Evaluating Outcomes in Veterans after Formulary Change Relative to Veterans Without Formulary Change Excluding Patients with Comorbid Asthma

Outcome	Difference-in-differences estimates*			
	Unadjusted, per person per 6 months		Adjusted, per person per 6 months**	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
COPD Exacerbations (count)	-0.03 (-0.14, 0.08)	0.61	-0.03 (-0.10, 0.04)	0.43
Total Encounters (count)	-0.13 (-0.90, 0.64)	0.73	-0.15 (-0.98, 0.68)	0.72
Total Costs (2016 US$)	797 (-617, 2211)	0.27	875 (-298, 2048)	0.14

* Difference-in-differences estimates are reported as average marginal effects, which can be interpreted as the difference in the 6-month number of encounters or 6-month costs in dollars pre- and post-formulary change for the exposure group, compared to that same pre/post difference in the control group

** Adjusted for age, gender, race, ethnicity, body mass index, Charlson comorbidity index, smoking status, marital status, drive distance, and VA priority group.

Supplement Table 5: Sensitivity Analysis Evaluating Outcomes in Veterans after Formulary Change Relative to Veterans Without Formulary Change Using an Alternative Exposure Group Definition (including patients switched to LABA/ICS after the formulary change)

Outcome	Difference-in-differences estimates*			
	Unadjusted, per person per 6 months		Adjusted, per person per 6 months**	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
COPD Exacerbations (count)	-0.001 (-0.10, 0.09)	0.98	-0.02 (-0.10, 0.07)	0.66
Total Encounters (count)	0.08 (-0.61, 0.76)	0.82	0.19 (-0.52, 0.90)	0.60
Total Costs (2016 US$)	566 (-878, 2010)	0.44	935 (-562, 2432)	0.22

* Difference-in-differences estimates are reported as average marginal effects, which can be interpreted as the difference in the 6-month number of encounters or 6-month costs in dollars pre- and post-formulary change for the exposure group, compared to that same pre/post difference in the control group
** Adjusted for age, gender, race, ethnicity, body mass index, Charlson comorbidity index, smoking status, marital status, drive distance, and VA priority group.

Supplement Table 6: Sensitivity Analysis Evaluating Outcomes in Veterans after Formulary Change Relative to Veterans Without Formulary Change Including ICS and Combination Inhalers

Outcome	Difference-in-differences estimates*			
	Unadjusted, per person per 6 months		Adjusted, per person per 6 months**	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
COPD Exacerbations (count)	-0.04 (-0.10, 0.03)	0.29	-0.05 (-0.11, 0.02)	0.20
Total Encounters (count)	-0.20 (-0.69, 0.28)	0.40	-0.11 (-0.59, 0.38)	0.66
Total Costs (2016 US$)	-196 (-1147, 756)	0.69	-260 (-1149, 628)	0.57

* Difference-in-differences estimates are reported as average marginal effects, which can be interpreted as the difference in the 6-month number of encounters or 6-month costs in dollars pre- and post-formulary change for the exposure group, compared to that same pre/post difference in the control group
** Adjusted for age, gender, race, ethnicity, body mass index, Charlson comorbidity index, smoking status, marital status, drive distance, and VA priority group.

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