MINI-SENTINEL METHODS

TESTING ROUTINE QUERYING TOOLS WITH KNOWN POSITIVE EXPOSURE-OUTCOME ASSOCIATIONS: RISK OF ANGIOEDEMA ASSOCIATED WITH NEW ANGIOTENSIN CONVERTING ENZYME INHIBITORS

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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 multifaceted 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.

Testing Routine Querying Tools with Known Positive Exposure-Outcome Associations: Risk of Angioedema Associated with New Angiotensin Converting Enzyme Inhibitors

This statistical methods project uses exposure/outcome pairs with known positive associations to test new Mini-Sentinel routine querying tools, specifically the Cohort Identification and Descriptive Analysis (CIDA) tool in combination with the new Propensity Score Matching (PSM) tool. CIDA combines modular programs 3, 6, and 9 into a single program package and creates output that can be used for more complex analytic adjustment in combination with particular Mini-Sentinel statistical analysis tools. Click here for more information about the CIDA and PSM tools.

The first known positives test case used the CIDA and PSM tools to assess angiotensin converting enzyme (ACE) inhibitors versus beta-blockers and risk of angioedema. The CIDA tool was used to identify new users of these medications. Information generated by the CIDA tool was used by the PSM tool to match cohort members based on propensity score. Propensity scores were calculated using a list of user-defined covariates. One run of the program was required. The time window was January 1st, 2008 to September 30th, 2013.

History of Modifications

Version	Date	Modification	By
V2	1/22/2016	• Updated calculations for the conditional matched analysis	Mini-Sentinel Applied Surveillance Core

Overview

Request Description	The Protocol Core and FDA has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) and Propensity Score Matching (PSM) tools to investigate exposure to angiotensin-converting-enzyme (ACE) inhibitors and beta blockers and angioedema events in the Mini-Sentinel Distributed Database (MSDD). To be included in the cohort, members must have had no evidence of a prescription for any ACE inhibitor, beta-blocker, angiotensin receptor blocker (ARB), or aliskiren in the 183 days prior to incident drug use. This package was distributed to seven Data Partners on September 23rd, 2014 and an additional ten data partners on September 30th, 2014. This report includes results from 13 Data Partners that successfully executed the package. The query period for this request was January 1st, 2008-September 30th, 2013. Please see Appendix A for a list of generic names used to define ACE inhibitors and beta blockers in this request. Please see Appendix B for a list of codes used to define the outcomes in this request. Please see Appendix C for a list of inclusion and exclusion criteria.
Request ID	to09y05_dev_mpd_wp07_b01, to09y05_dev_mpd_wp07_b02
Requester	Protocol Core Work Group / FDA
Specifications	Program parameter inputs and scenarios
Glossary	List of Terms found in this Report and their Definitions
Monitoring Period	Monitoring Period for this request
Table 1	Table displaying Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Unmatched)
Table 2	Table displaying Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Matched Predefined PS, Caliper = .025)
Table 3	Table displaying Sequential Estimates for Angioedema Events by Analysis Type, and Drug Pair
Appendix A	Table of Generic Names used to Define Exposures in this Request
Appendix B	Table of Diagnosis Codes used to Define Outcomes in this Request
Appendix C	Table of Generic Names used to Define Pre-Existing Inclusions/Excluions in this Request
Appendix D	Table of Codes used to Define Covariate Codes in this Request
Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Specifications for to09y05_dev_mpd_wp07_b01 and to09y05_dev_mpd_wp07_b02

Purpose: To assess the ability of Mini-Sentinel prospective surveillance tools to reproduce the known association between ACE inhibitors and angioedema, compared to beta blockers

Enrollment Gap	45 days
Age Range	18-125
Query Period	01/01/2008 -09/30/2013
Coverage Requirement	Medical and Drug Coverage
Propensity Score Matching Ratio	1:1
Propensity Score Matching Caliper	0.025
Enrollment Requirement	183 days

		Exposure of Interest ACE Inhibitors	**Comparator of Interest** Beta Blockers
Drug/Exposure:	Incident w/ respect to:	Beta Blockers, Aliskiren, ARBs	ACE Inhibitors, Aliskiren, ARBs
	Washout (days)	183 days	183 days
	Cohort Definition	01	01
	Episode Gap	14 days	14 days
	Exposure Extension Period	14 days	14 days
	Minimum Episode Duration	0 days	0 days
	Minimum Days Supplied	0 days	0 days
	Episode Truncation by Incident Exposure	Yes	Yes
Inclusion/Exclusion:	Criterion	Prescription for Aliskiren or any ARB	Prescription for Aliskiren or any ARB
	Include or Exclude	Exclude	Exclude
	Lookback Start	-183 days	-183 days
	Lookback End	-1 days	-1 days
Event/Outcome:	Event/ Outcome	Angioedema	Angioedema
	Care Setting/PDX	IP, ED, AV	IP, ED, AV
	Incident w/ respect to:	Angioedema	Angioedema
	Washout (days)	183 days	183 days
	Blackout Period	0 days	0 days

National Drug Codes (NDCs) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"

ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight

HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight

CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

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Glossary of Terms for Analyses Using Cohort Idendification and Descriptive Analyis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or missing (U)

Cohort Definition (drug/exposure)- Indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive dispensings bridged by the episode gap.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.23

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode

Event Deduplication - specifies how events are counted by the MP algorithm: (0): 0: Counts all occurrences of and HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (3) 3: de-duplicates occurrences of the same HOI group on the same day (eg. de-duplicates at the group level)

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time"

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing)

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered

Query Period - period in which the modular program looks for exposures and outcomes of interest

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code

Users - number of members with exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest.Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous enrollment before exposure" field.

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of the relationship between confounder and exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and 0.05.

Matching Ratio - patients in exposed and comparators are nearest neighbor matched by a 1:1 or 1:100 (up to 100) matching ratio.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of the relationship between confounder and the outcome. This is most suitable for disease risk scores.

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed (during requester-defined lookback).

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate differences, the number needed to treat/harm, the attributable risk, and the population attributable risk.

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Monitoring Period Key

Monitoring Period #	Number of Data Partners	Available Timeframes
1	13	January 1, 2008- September 30, 2013

Monitoring Period Key

Monitoring Period #	Number of Data Partners	Available Timeframes
1	13	January 1, 2008- September 30, 2013

Table 1. Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Unmatched)

	Primary Analysis				Covariate Balance	
Characteristic	**ACE Inhibitors**		**Beta Blockers**			
	N	**%**	**N**	**%**	**Absolute Difference**	**Standardized Difference**
Patients	2,211,215	100%	1,673,682	100%	0.0	-
Events while on therapy	5,158	0.2%	1,292	0.1%	0.1	0.0
Mean (std dev) Person-time at risk (days)	186.9	266.6	149.2	235.1	37.7	0.2
Patient Characteristics						
Gender (F)	997,962	45.10%	946,344	56.50%	-11.4	-0.2
Mean age in years (std dev)	54.6	12.7	53.7	15.6	0.9	0.1
Recorded History of:						
Allergic reactions	207,344	9.4%	190,387	11.4%	-2.0	-0.1
Diabetes	471,661	21.3%	173,083	10.3%	11.0	0.3
Heart failure	41,060	1.9%	74,897	4.5%	-2.6	-0.1
Ischemic heart diseases	109,948	5.0%	224,681	13.4%	-8.4	-0.3
Prescription NSAID use	318,298	14.4%	250,697	15.0%	-0.6	0.0
Health Service Utilization Intensity:	**Mean**	**Std Dev**	**Mean**	**Std Dev**		
Number of generics	3.4	3.5	4.1	4.0	-0.7	-0.2
Number of filled prescriptions	7.5	9.6	8.9	10.8	-1.4	-0.1
Number of inpatient hospital encounters (IP)	0.1	0.4	0.2	0.6	-0.1	-0.3
Number of non-acute institutional encounters (IS)	0.0	0.6	0.1	0.9	-0.1	-0.1
Number of emergency room encounters (ED)	0.2	0.7	0.4	1.0	-0.2	-0.2
Number of ambulatory encounters (AV)	4.8	6.3	6.9	8.4	-2.1	-0.3
Number of other ambulatory encounters (OA)	1.1	2.6	1.5	3.6	-0.4	-0.1

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Table 2. Cohort of New Initiators of ACE Inhibitors and Beta Blockers (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
Characteristic	**ACE Inhibitors**		**Beta Blockers**			
	N	**%**	**N**	**%**	**Absolute Difference**	**Standardized Difference**
Patients	1,309,104	59.2%	1,309,104	78.2%	0.0	-0.4
Events while on therapy	3,311	0.3%	988	0.1%	0.2	0.0
Mean (std dev) Person-time at risk (days)	183.8	263.7	151.8	238.9	31.9	0.1
Patient Characteristics						
Gender (F)	723,955	55.3%	689,617	52.7%	2.6	0.1
Mean age in years (std dev)	54.1	13.1	54.4	14.9	-0.3	0.0
Recorded History of:						
Allergic reactions	137,920	10.5%	134,933	10.3%	0.2	0.0
Diabetes	150,036	11.5%	150,551	11.5%	0.0	0.0
Heart failure	35,302	2.7%	38,966	3.0%	-0.3	0.0
Ischemic heart diseases	102,200	7.8%	106,786	8.2%	-0.4	0.0
Prescription NSAID use	191,798	14.7%	189,612	14.5%	0.2	0.0
Health Service Utilization Intensity:	**Mean**	**Std Dev**	**Mean**	**Std Dev**		
Number of generics	3.7	3.7%	3.6	3.6%	0.0	0.0
Number of filled prescriptions	8.1	10.2%	8.0	9.9%	0.1	0.0
Number of inpatient hospital encounters (IP)	0.1	0.5%	0.1	0.5%	0.0	0.0
Number of non-acute institutional encounters (IS)	0.1	0.7%	0.1	0.7%	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8%	0.3	0.8%	0.0	0.0
Number of ambulatory encounters (AV)	5.6	7.3%	5.6	6.6%	0.0	0.0
Number of other ambulatory encounters (OA)	1.2	2.9%	1.3	3.0%	0.0	0.0

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Table 3: Sequential Estimates for Angioedema Events by Analysis Type, and Drug Pair

Exposure Definition	Monitoring Period	Number of New Users	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1000 Person Years	Risk per 1000 New Users	Difference per 1000 Person Years	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
ACE Inhibitors	1	2,211,215	1,131,526	0.51	5,158	4.558	2.33	2.67	1.56	2.55 (2.40, 2.71)	<.0001
Beta Blockers		1,673,682	683,614	0.41	1,292	1.890	0.77				
1:1 Matched Analysis; Caliper=0.025											
ACE Inhibitors	1	1,309,104	248,697	0.19	1,819	7.314	1.39	4.98	0.95	3.14 (2.86, 3.44)	<.0001
Beta Blockers		1,309,104	248,697	0.19	580	2.332	0.44				

Appendix A. Generic Names used to Define Exposures in this Request

Generic Name
AMLODIPINE BESYLATE/BENAZEPRIL
BENAZEPRIL HCL
BENAZEPRIL/HYDROCHLOROTHIAZIDE
CAPTOPRIL
CAPTOPRIL/HYDROCHLOROTHIAZIDE
ENALAPRIL MALEATE
ENALAPRIL MALEATE/FELODIPINE
ENALAPRIL/HYDROCHLOROTHIAZIDE
ENALAPRILAT DIHYDRATE
FOSINOPRIL SODIUM
FOSINOPRIL/HYDROCHLOROTHIAZIDE
LISINOPRIL
LISINOPRIL/DIETARY SUP.CMB10
LISINOPRIL/HYDROCHLOROTHIAZIDE
MOEXIPRIL HCL
MOEXIPRIL/HYDROCHLOROTHIAZIDE
PERINDOPRIL ERBUMINE
QUINAPRIL HCL
QUINAPRIL/HYDROCHLOROTHIAZIDE
RAMIPRIL
TRANDOLAPRIL
TRANDOLAPRIL/VERAPAMIL HCL
ACEBUTOLOL HCL
ATENOLOL
ATENOLOL/CHLORTHALIDONE
BISOPROLOL FUMARATE
BISOPROLOL FUMARATE/HCTZ
BRIMONIDINE TARTRATE/TIMOLOL
CARVEDILOL
CARVEDILOL PHOSPHATE
DORZOLAMIDE HCL/TIMOLOL MALEAT
DORZOLAMIDE/TIMOLOL/PF
LABETALOL HCL
METOPROLOL SUCCINATE
METOPROLOL SUCCINATE/HCTZ
METOPROLOL TARTRATE
METOPROLOL/DIETARY SUPPL.CMB10
METOPROLOL/HYDROCHLOROTHIAZIDE
NEBIVOLOL HCL

Appendix A. Generic Names used to Define Exposures in this Request

Generic Name
PINDOLOL
PROPRANOLOL HCL
PROPRANOLOL/HYDROCHLOROTHIAZID
TIMOLOL
TIMOLOL MALEATE/PF
TIMOLOL/HYDROCHLOROTHIAZIDE

Appendix B. Codes used to Define Events in this Request

Code	Description	CodeType
Angioedema		
995.1	Angioedema	ICD-9-CM Diagnosis Code

Appendix C. Codes used to Define Pre-Existing Inclusion/Exclusion Codes in this Request

Generic Name	CodeType	Include vs. Exclude
ALISKIREN HEMIFUMARATE	NDC Code	Exclude
ALISKIREN/AMLODIPIN/HCTHIAZIDE	NDC Code	Exclude
ALISKIREN/AMLODIPINE BESYLATE	NDC Code	Exclude
ALISKIREN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude
ALISKIREN/VALSARTAN	NDC Code	Exclude
ALISKIREN/VALSARTAN	NDC Code	Exclude
AMLODIPINE BES/OLMESARTAN MED	NDC Code	Exclude
AMLODIPINE/VALSARTAN	NDC Code	Exclude
AMLODIPINE/VALSARTAN/HCTHIAZID	NDC Code	Exclude
CANDESARTAN CILEXETIL	NDC Code	Exclude
CANDESARTAN/HYDROCHLOROTHIAZID	NDC Code	Exclude
EPROSARTAN MESYLATE	NDC Code	Exclude
EPROSARTAN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude
IRBESARTAN	NDC Code	Exclude
IRBESARTAN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude
LOSARTAN POTASSIUM	NDC Code	Exclude
LOSARTAN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude
OLMESARTAN MEDOXOMIL	NDC Code	Exclude
OLMESARTAN/AMLODIPIN/HCTHIAZID	NDC Code	Exclude
OLMESARTAN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude
TELMISARTAN	NDC Code	Exclude
TELMISARTAN/AMLODIPINE	NDC Code	Exclude
TELMISARTAN/HYDROCHLOROTHIAZID	NDC Code	Exclude
VALSARTAN	NDC Code	Exclude
VALSARTAN/HYDROCHLOROTHIAZIDE	NDC Code	Exclude

Appendix D. Codes used to Define Covariate Codes in this Request

Code	Description	CodeType
ALLERGIC REACTIONS		
477	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
477*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
5186	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
5583	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
691	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
691*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
692	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
692*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
692**	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
693	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
693*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
708*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
9950	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
99527	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
9953	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
9956	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
9956*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
9957	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V071	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V1381	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V14	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V14*	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V150	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
V727	ALLERGIC REACTION	ICD-9-CM Diagnosis Code
DIABETES		
250	DIABETES	ICD-9-CM Diagnosis Code
250*	DIABETES	ICD-9-CM Diagnosis Code
250**	DIABETES	ICD-9-CM Diagnosis Code
HEART FAILURE		
40201	HEART FAILURE	ICD-9-CM Diagnosis Code
40211	HEART FAILURE	ICD-9-CM Diagnosis Code
40291	HEART FAILURE	ICD-9-CM Diagnosis Code
40401	HEART FAILURE	ICD-9-CM Diagnosis Code
40403	HEART FAILURE	ICD-9-CM Diagnosis Code
40411	HEART FAILURE	ICD-9-CM Diagnosis Code
40413	HEART FAILURE	ICD-9-CM Diagnosis Code
40491	HEART FAILURE	ICD-9-CM Diagnosis Code
40493	HEART FAILURE	ICD-9-CM Diagnosis Code
428	HEART FAILURE	ICD-9-CM Diagnosis Code
428*	HEART FAILURE	ICD-9-CM Diagnosis Code
428**	HEART FAILURE	ICD-9-CM Diagnosis Code

Appendix D. Codes used to Define Covariate Codes in this Request

Code	Description	CodeType
ISCHEMIC HEART DISEASE		
410	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
410*	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
410**	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
411	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4110	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4111	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4118	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41181	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41189	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
412	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
413	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4130	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4131	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4139	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
414	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4140	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41400	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41401	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41402	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41403	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41404	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41405	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41406	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41407	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4141	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41410	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41411	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41412	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
41419	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4142	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4143	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4144	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4148	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
4149	ISCHEMIC HEART DISEASE	ICD-9-CM Diagnosis Code
NSAIDS		
	NSAIDS	NDC Code