MINI-SENTINEL PROSPECTIVE SURVEILLANCE PLAN

PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING OF MIRABEGRON

Version 3.0

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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.

History of Modifications

Version	Date	Modification	By
V2.0	06/05/2014	• Edited §3A and Table 1 to clarify that new and non-naïve users will be determined based on overactive bladder (OAB) drugs available by prescription • Edited Table 2 to clarify that Oxytrol for Women® is an over-the-counter product • Clarified, within Table 2, that syrup, transdermal gel, and transdermal patch formulations of oxybutynin will be used when determining new and non-naïve OAB drug users • Edited §3B to clarify that other OAB drugs were considered as comparator exposures and provided a rationale for why they were not selected • Clarified, within §5, that predefined covariates will be determined at baseline • Updated Tables 3 and 4 with "wild card" designations for selected diagnostic codes	Mirabegron Workgroup
V3.0	09/19/2016	• The workgroup prepared Addendum 1, which summarizes the FDA's decision to discontinue the mirabegron surveillance activity in Sentinel.	Mirabegron Workgroup

Mini-Sentinel Prospective Surveillance Plan
Prospective Routine Observational Monitoring of Mirabegron

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I. FOOD AND DRUG ADMINISTRATION REQUEST

A. BACKGROUND

Mirabegron is a non-selective β_3 adrenergic receptor agonist approved by the US Food and Drug Administration (FDA) in June 2012 to treat symptoms of overactive bladder (OAB). Pre-approval clinical trials showed that mirabegron 50 mg (the maximum recommended dose for adults without renal or hepatic impairment[1]) produced an average increase in heart rate (HR) of 4 beats per minute (BPM) in Phase 1 studies and 1 BPM in Phase 3 studies[2]. Further, mean increases in systolic blood pressure (SBP) were approximately 4 millimeters of mercury (mmHg) in Phase 1 studies and 1 mmHg in Phase 3 studies. These elevations in HR and SBP increased with increasing mirabegron dose.

In population-based epidemiologic studies, levels of HR and BP have been positively and monotonically associated with the risk of stroke and coronary heart disease (CHD) across usual ranges of HR and BP[3]. Randomized trials have shown that pharmacologically-reducing diastolic blood pressure by 5-6 mmHg for a few years results in a 42% relative reduction in stroke risk and a 14% relative reduction in CHD risk[4]. A 5 mmHg reduction in SBP results in a 14% overall reduction in mortality due to stroke and a 9% reduction in mortality due to CHD[5]. Further, short-term use of several drugs that increase HR and BP—including phenylpropanolamine, amphetamines, cocaine, and sibutramine—has been associated with an increased risk of acute myocardial infarction (AMI) and/or stroke[6,7,8]. Therefore, there is interest in a prospective surveillance assessment to identify potential early signals of AMI and stroke with use of mirabegron.

B. OBJECTIVE

The objective of this assessment is to conduct prospective sequential surveillance, within the Mini-Sentinel Distributed Database (MSDD), to examine potential risks of AMI (primary health outcome of interest [HOI]) and stroke (secondary HOI) attributable to mirabegron. These HOIs will be examined separately.

II. SELECTION OF ANALYTIC TOOL

A. OVERVIEW

Surveillance will be conducted using *Mini-Sentinel Prospective Routine Observational Monitoring Program Tool: Cohort Matching*[9] (hereafter referred to as PROMPT Module 2)—a pre-existing assessment tool using a propensity score-matched cohort design.

B. PROMPT MODULE 2

PROMPT Module 2 can potentially detect a confounder-adjusted relative risk of HOI development, should a risk be present throughout most of the period of observation. The module will be used to generate propensity scores, produce tables of baseline characteristics before and after matching, and conduct propensity score-matched analyses. Given the low expected frequencies of HOIs, adjustment for potential confounders through propensity score matching is expected to be more feasible than through stratification or multivariable outcome regression adjustment.

III. COHORT IDENTIFICATION

A. INCLUSION AND EXCLUSION CRITERIA

This assessment will utilize data—beginning with the later of July 2012 or the first month in which a mirabegron dispensing appears in the MSDD—from the four largest Mini-Sentinel Data Partners. All persons included for surveillance will have been exposed to either mirabegron or the active comparator. **Table 1** summarizes the cohorts of interest to be examined using PROMPT Module 2.

Table 1. Cohort entry specifications for cohorts of interest and active comparator groups

Analysis Priority	Analysis Name	Cohort of Interest: Exposure = Mirabegron*	Active Comparator Cohort: Exposure = Oxybutynin*
Primary	New user analysis	Persons *without* any OAB prescription drug exposure during a 183-day baseline period that newly-initiate mirabegron	Persons *without* any OAB prescription drug exposure during a 183-day baseline period that newly-initiate oxybutynin
Secondary	Non-naïve user analysis	Persons with at least one exposure to a non-mirabegron OAB prescription drug during a 183-day baseline period that newly-initiate mirabegron	Persons with at least one exposure to a non-oxybutynin OAB prescription drug during a 183-day baseline period that newly-initiate oxybutynin
* Oral tablet dosage forms only			

Primary analyses will focus on new users. Cohort entry will begin upon a person's first prescription dispensing for either mirabegron or the comparator that is preceded by a ≥183-day baseline period with medical and pharmacy benefits (gaps in enrollment <45 days ignored) and devoid of any OAB prescription drug (simply referred to OAB drug hereafter) exposure.

Secondary analyses will focus on non-naïve users. Cohort entry will begin upon a person's first prescription for either mirabegron or the comparator that is preceded by a ≥183-day baseline period with medical and pharmacy benefits and a requirement for at least one prior dispensing of an OAB drug (other than the cohort-defining drug; defined by chemical entity, without regard to immediate- vs. extended-release status) during the 183 day baseline. There is no requirement for this prior OAB drug treatment to be active therapy upon the time of the individual's cohort entry. Therefore, these analyses are a study of non-naïve users of OAB drugs and not specifically persons recently progressing from one OAB drug to another (i.e., switchers, although such persons will be included).

With respect to the primary and secondary analyses, the exclusion criteria will be as follows:

1. Persons under the age of 20 years, as of the date they would have otherwise entered the cohort, will be excluded.
2. Persons newly-initiating mirabegron or the comparator on the same day as another OAB drug will be excluded.

3. Persons with an AMI or stroke in the *30 days prior to cohort entry* will be excluded from the study of that respective outcome. The rationale for these exclusions is two-fold. First, we wish to reduce the risk that the identified HOI is subsequent care rather than a new-onset event. Second, even if the HOI is indeed a distinct event from that occurring previously, the occurrence of the prior event in such close proximity to cohort entry would be a strong risk factor for HOI occurrence during follow-up.

B. EXPOSURE AND COMPARATOR IDENTIFICATION

Mirabegron is the exposure of interest. Oxybutynin is the comparator exposure. Each drug will be defined by prescription dispensings for the products listed in **Table 2**.

Table 2. Mirabegron and oxybutynin products approved in the United States for treatment of OAB in adults

Product	Route / Dosage Form	Inclusion in Surveillance
Exposure of interest		
mirabegron extended-release (ER), as branded Myrbetriq®	oral / tablet	Yes
Comparator of interest		
oxybutynin chloride, including branded Ditropan®	oral / tablet	Yes
oxybutynin chloride, including branded Ditropan®	oral / syrup	No*
oxybutynin chloride ER, including branded Ditropan XL®	oral / tablet	Yes
oxybutynin, as branded Gelnique®	transdermal / gel	No*
oxybutynin, as branded Oxytrol® and Oxytrol for Women®*	transdermal / patch	No*
* Yet, will be considered when determining if an individual is a new user—except for Oxytrol for Women, an over-the-counter product unlikely to be captured in the Mini-Sentinel Distributed Database		

To limit the potential for between-person confounding, an active comparator exposure was selected over an unexposed comparator. Oxybutynin was selected as the active comparator since it is the most commonly-used OAB therapy and is thought to be devoid of BP and HR effects[10]. Other OAB drugs—such as darifenacin, fesoterodine, solifenacin, tolterodine and trospium—have BP and/or other cardiovascular effects, and therefore may not be suitable comparators. To limit the potential for bias in time trends, oxybutynin exposures will be drawn from a concurrent population.

Mirabegron-exposed persons will to be matched to oxybutynin-exposed persons by propensity score at a 1:1 ratio. We considered using a larger fixed matching ratio, but decided against it since: a) that would either lead to fewer mirabegron users being matched or require more relaxed matching criteria; and b) the inclusion of more oxybutynin-exposed persons would allow for a greater opportunity to prematurely censor mirabegron-exposed person time. Operationally, the matching process will follow procedures outlined in the *Mini-Sentinel Prospective Routine Observational Monitoring Program Tool: Cohort Matching Technical Users' Guide*9. In short, nearest neighbor matching on propensity score will be conducted using a caliper distance of 0.025 units on the propensity score scale[11]. Table Creator output will be generated to assess covariate balance, including absolute differences, standardized differences, and Mahalanobis distances.

C. FOLLOW-UP AND CENSORING

Follow-up time will begin with the cohort entry-defining mirabegron or oxybutynin dispensing and will continue based on the days supply of prescriptions for these agents. Follow-up will stop (i.e., person-time will be censored) upon the earliest of the following occurrences:

1) outcome of interest for the respective analysis (e.g., AMI in the AMI analysis, as stroke occurrence would not be a censoring event in the AMI analysis)
2) a gap of 7 days or greater between two consecutive prescriptions for the cohort-defining agent, in which the last day of follow-up included will be [(days supply of the most recent prescription for that agent) + 7 days]
3) lack of a subsequent prescription for the cohort-defining agent, in which the last day of follow-up included will be [(days supply of the most recent prescription for that agent) + 7 days]
4) a prescription for an OAB drug other than the cohort-defining agent, in which the last day of follow-up included would be the day preceding the prescription for the new agent; immediate- and extended-release products will be considered interchangeable when assessing this criterion.
5) end of database time
6) health plan disenrollment

The rationale for the 7-day grace period described above is the desire to continue to follow patients with imperfect adherence. Further, this will allow for the capture of outcomes occurring shortly after discontinuation of therapy, as such events still may be drug-related.

If a subsequent prescription for the cohort-defining drug occurs during the previous prescription's days supply period or the following 7 days, exposure will be said to continue. Stockpiling of drug supply from early refills will be assumed according to the rules implemented by the Data Core[12].

The earliest censoring event occurring with a person of the matched pair will serve as the censoring date for both persons in the pair. Since the proposed 1:1 propensity score-matched analysis stratifies on the matched pair, once one member of the pair is censored, there are no patients remaining in the risk set for the other pair member.

IV. OUTCOMES OF INTEREST

This assessment will have two outcomes of interest—AMI and stroke—each of which will be examined separately.

A. DEFINITION OF ACUTE MYOCARDIAL INFARCTION

AMI will be defined as follows: International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) inpatient diagnosis of 410.X0 or 410.X1 in the principal position on an inpatient record.

Based on a medical record review of N = 143 charts arising from MSDD-identified events, the above definition would be expected to have a positive predictive value (PPV) of 86% overall, with a range of 76% to 94%[13]. We excluded ICD-9-CM 410.X2 from our definition because such codes specifically refer to prior rather than acute events and because a prior validation activity suggested that the inclusion of these codes lowers the PPV for AMI[14].

If there are multiple principal discharge diagnoses associated with a single hospital episode (e.g., because of a transfer), a single principal discharge diagnosis of AMI will be sufficient. In a sensitivity analysis, AMI will be defined based on the presence of a principal or non-secondary diagnosis (i.e., where PDX = P or X), rather than a principal diagnosis alone.

B. DEFINITION OF STROKE

Stroke will be defined as presence of an ICD-9-CM code for 430, 431, 433.X1, 434.X1, or 436 in the principal position on an inpatient record.

This algorithm has been defined based on the Women's Health Initiative (WHI). It is expected to have a PPV and sensitivity both >80%, given the exclusion of the suboptimally-performing ICD-9-CM 432.X originally evaluated by WHI.

If there are multiple principal discharge diagnoses associated with a single hospital episode (e.g., because of a transfer), a single principal discharge diagnosis of stroke will be sufficient. In a sensitivity analysis, stroke will be defined based on the presence of a principal or non-secondary diagnosis, rather than a principal diagnosis alone.

V. PREDEFINED COVARIATES

PROMPT Module 2 will control for confounding by generating propensity scores based on the pre-defined baseline covariates listed in **Table 3** (for AMI) and **Table 4** (for stroke). These covariates and their operational definitions were adopted from *Mini-Sentinel Medical Product Assessment: A Protocol for Active Surveillance of Acute Myocardial Infarction in Association with Use of Anti-Diabetic Agents*[15] and *de novo* for this surveillance plan, respectively.

As long as the model converges (and there are sufficient numbers of mirabegron-exposed individuals relative to the number of covariates), the module goes forward. If the model fails to converge, the module will provide only baseline characteristic for the unmatched cohort. At each monitoring period, the propensity score is estimated on all included persons from all prior periods within each Mini-Sentinel Data Partner site; prior propensity score matches are retained however and initiators in each period are only matched to other initiators in that same period.

Table 3. List of cofactors to be included as pre-defined covariates in PROMPT Module 2 examination of AMI (in addition to calendar year and Mini-Sentinel Data Partner)

Cofactor category	Codes / Comments*
Demographics	
Age at cohort entry Sex Residence in nursing home (or stay in other non-hospital institution) during prior year	Residence in nursing home is determined from the Encounter Type, Discharge Status and Admitting_Source values in the MSDD Encounter table (including nursing home, skilled nursing facility, hospice, rehabilitation center, overnight non-hospital dialysis, and other non-hospital institutional stays).
Utilization measures	
# of hospitalizations # of emergency department visits # of outpatient visits # of distinct medications, by generic name	Distinct medications are determined by counting unique 11-digit NDC codes in the MSDD dispensing table. Combination drugs are not broken into their constituents.
Generalized comorbidity measure	
Combined Charlson-Elixhauser comorbidity score	
Comorbid conditions, non-cardiovascular	
Asthma	493.XX
Cancer (excluding non-melanoma skin cancer)	140.XX-209.XX (excluding 173.XX and 209.4X-209.6X)
Chronic kidney disease (excluding end-stage renal disease)	585.1–585.4 HCPCS: G0420, G0421, G8487, G8771
Chronic obstructive pulmonary disease	491.XX, 492.X, 496
Dementia	290.0X–290.4X, 291.2, 292.82, 294.0, 294.1X, 294.8, 331.0–331.2, 331.7–331.9, 797
Depression	296.2X, 296.3X, 300.4, 311
Diabetes mellitus	250.XX, 357.2, 362.0X, or 366.41
End-stage renal disease	458.21, 585.5, 585.6, 996.56, 996.68, 996.73, V42.0, V45.1X, V56.XX ICD9P: 38.95, 39.27, 39.42, 39.43, 39.53, 39.93, 39.94, 39.95, 54.98, 55.6X CPT4: 36145, 36800, 36810, 36815, 36825, 36830-36833, 50323, 50325, 50327-50329, 50340, 50341, 50360, 50365, 50366, 90918-90925, 90935, 90937, 90939-90944, 90945, 90947, 90951-90969, 90970, 90976-90979, 90982-90985, 90989, 90993, 90995, 90996, 90997, 90998, 90999, 93990, 99512 HCPCS: A4653, A4656, A4657, A4670-A4674, A4680, A4706-A4709, A4712, A4714, A4719, A4720-A4726, A4728, A4730, A4736, A4737, A4740, A4750, A4755, A4760, A4765, A4766, A4770, A4771, A4773, A4774, A4802, A4860, A4870, A4890, A4911, A4913, A4918, A4928, A4929, C1881, E1500, E1520, E1530, E1540, E1550, E1560, E1570, E1575, E1580, E1600, E1610, E1615, E1620, E1625, E1634-E1639, E1699, G0257, G0308-G0327, G8727, G9013, G9014, J0635, J0636, S2065, S9335, S9339
Fracture	733.1X, 733.93-733.98, 805.XX–815.XX (excluding 807.5

Cofactor category	Codes / Comments*
	and 807.6), 818.X-825.XX, 827.X, 828.X, V54.13, V54.23 ICD9P: 79.01-79.03, 79.05-79.07, 79.11-79.13, 79.15-79.17, 79.21-79.23, 79.25-79.27, 79.31-79.33, 79.35-79.37, 79.61-79.63, 79.65-79.67, 81.65, 81.66
HIV/AIDS	042, 043, 044, 795.71, V08
Hyperlipidemia or lipid disorder	272.0, 272.1, 272.2, 272.4
Hypertension	401.X–405.XX (excluding 402.01, 402.11, 402.91)
Obesity (or weight gain)	278.0X, 783.1, 793.91, V85.3X, V85.4X
Osteoporosis	733.0X, V17.81, V82.81
Tobacco use	305.1, V15.82
Comorbid conditions, cardiovascular	
Prior AMI (i.e., 31-365 days prior)	410.XX
Other ischemic heart disease	411.XX–414.XX
Other heart disease	402.01, 402.11, 402.91, 420.XX-429.XX, 440.XX
Stroke (narrow)[†]	430, 431, 433.X1, 434.X1, 436
Stroke (broad)[†]	430–434.XX, 436
Peripheral arterial disease	443.9
Coronary revascularization procedures	
Coronary artery bypass graft	ICD9D: 996.03, V45.81 ICD9P: 36.1X, 36.2 CPT4: 33510-33514, 33516-33523, 33525, 33528, 33530, 33533-33536, 33560, 33570, 33572, 33575, 35600 HCPCS: S2205-S2209
Percutaneous coronary intervention	ICD9D: V45.82 ICD9P: 0.66, 36.01-36.09, 37.22, 37.23, 88.5X CPT4: 92973, 92974, 92977, 92980, 92981, 92982, 92984, 92987, 92995, 92996 HCPCS: G0290, G0291
Carotid revascularization procedures	
Carotid endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 00.61, 00.63, 38.11, 38.12 CPT4: 35301, 35390, 35501, 35601, 35901, 0075T, 0076T, 37215, 37216 HCPCS: S2211
Carotid bypass	ICD9P: 39.28
Lower Extremity revascularization	
Lower extremity endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 38.18, 38.19 CPT4: 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35492, 35493, 35495, 37207, 37208, 37220-37235
Lower extremity bypass	ICD9P: 39.25, 39.29 CPT4: 35351, 35355, 35361, 35363, 35371, 35372, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681-35683, 35879
Lower extremity amputation	ICD9P: 84.10-84.17 CPT4: 27295, 27590-27592, 27598, 27880-27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825
Drug[††] markers of comorbid conditions	

Cofactor category	Codes / Comments*
Anti-asthmatic/anti-chronic obstructive pulmonary disease agent use	NDC codes for anticholinergics (inhaled), anti-asthma sympathomimetics, corticosteroids (inhaled), leukotriene agents, mast cell stabilizers, omalizumab, selective phosphodiesterase-4 inhibitors, xanthine derivatives
Anti-dementia agent use	NDC codes for cholinesterase inhibitors, NMDA receptor antagonists
Antidepressant use	NDC codes for monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, tricyclics (excluding doxepin, amitriptyline, clomipramine), tetracyclics, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin-2 receptor antagonists (excluding trazodone), alpha-2 receptor antagonists, and miscellaneous antidepressants; excluding lithium, excluding trimipramine in persons <19 years old
Antidiabetic agent use	NDC codes for alpha-glucosidase inhibitors, amylin analogs, biguanides, dipeptidyl peptidase-4 inhibitors, glucagonlike peptide-1 receptor agonists, insulins, meglitinides, sodium-glucose co-transporter 2 inhibitors, sulfonylureas, thiazolidinediones
Antiretroviral agent for HIV use	NDC codes for CCR5 antagonists, fusion inhibitors, integrase inhibitors, NARTIs, NNRTIs, NRTIs, protease inhibitors
Antihyperlipidemic use	NDC codes for bile acid sequestrants, ezetimibe, fibrates, icosapent, lomitapide, mipomersen, statins, niacin
Anti-obesity agent use	NDC codes for anorexiant combination products (e.g., phentermine/topiramate), lipase inhibitors (orlistat), serotonin 2C receptor agonist (lorcaserin), sympathomimetic anorexiants (benzphetamine, diethylpropion, phendimetrazine, phentermine), sibutramine
Smoking cessation agent use	NDC codes for nicotine replacement, varenicline, branded only: Zyban, Buproban
Anti-osteoporosis agent use	NDC codes for bisphosphonates, calcitonin, denosumab, SERMs, teriparatide
Antihypertensive agent use	NDC codes for renin angiotensin aldosterone system antagonists, alpha blockers, beta blockers (oral), alpha-beta blockers, calcium channel blockers, direct vasodilators, reserpine derivatives, central alpha-2 receptor antagonists, postganglionic blockers, loop diuretics, potassium-sparing diuretics, thiazide diuretics

ICD9D = ICD-9-CM diagnosis codes; ICD9P = ICD-9 procedure codes; CPT4 = Current Procedural Terminology codes; HCPCS = Healthcare Common Procedure Coding System codes; AIDS = acquired immunodeficiency syndrome; CCR5 = cellular chemokine receptor; HIV = human immunodeficiency virus; NARTI = nucleotide analog reverse transcriptase inhibitor; NMDA = N-methyl-D-aspartate; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; SERM = selective estrogen receptor modulator

* Use only codes associated with visits (inpatient or outpatient). All diagnoses and procedures are sought for the baseline period prior to cohort entry.

† The narrowly defined stroke includes the principal discharge diagnoses. The more broadly defined stroke includes diagnoses associated with an inpatient or outpatient encounter.

Cofactor category	Codes / Comments*
†† Excluding those with intravenous or miscellaneous routes of administration	

Table 4. List of cofactors to be included as pre-defined covariates in PROMPT Module 2 examination of stroke (in addition to age, sex, calendar year, and Mini-Sentinel Data Partner)

Cofactor category	Codes / Comments*
Demographics	
Age at cohort entry Sex Residence in nursing home (or stay in other non-hospital institution) during prior year	Residence in nursing home is determined from the Encounter Type, Discharge Status and Admitting_Source values in the MSDD Encounter table (including nursing home, skilled nursing facility, hospice, rehabilitation center, overnight non-hospital dialysis, and other non-hospital institutional stays).
Utilization measures	
# of hospitalizations # of emergency department visits # of outpatient visits # of distinct medications, by generic name	Distinct medications are determined by counting unique 11-digit NDC codes in the MSDD dispensing table. Combination drugs are not broken into their constituents.
Generalized comorbidity measure	
Combined Charlson-Elixhauser comorbidity score	
Comorbid conditions	
Alcohol use disorder	Any-position, any-claim ICD-9 code of 291.XX, 303.XX, 305.0X, 357.5, 425.5, 535.3X, 571.0, 571.1, 571.2, 571.3, 977.3, 980.0, E947.3, V11.3
Atrial fibrillation / atrial flutter / sick sinus	427.3X, 427.81
Chronic kidney disease (excluding end-stage renal disease)	585.1–585.4 HCPCS: G0420, G0421, G8487, G8771
Depression	296.2X, 296.3X, 300.4, 311
Diabetes mellitus	250.XX, 357.2, 362.0X, or 366.41
HIV/AIDS	042, 043, 044, 795.71, V08
Hyperlipidemia or lipid disorder	272.0, 272.1, 272.2, 272.4
Hypertension	401.X–405.XX (excluding 402.01, 402.11, 402.91)
Ischemic heart disease	410.XX–414.XX
Migraine	346.XX
Obesity (or weight gain)	278.0X, 783.1, 793.91, V85.3X, V85.4X
Other heart disease	402.01, 402.11, 402.91, 420.XX-429.XX (excluding 427.3X and 427.81), 440.XX
Peripheral arterial disease	443.9
Pulmonary circulation disease	415.XX–417.X
Rheumatic heart disease, chronic	393–398.XX
Sickle cell disease	282.6X
Stroke (narrow)†	430, 431, 433.X1, 434.X1, 436
Stroke (broad)†	430–434.XX, 436
Tobacco use	305.1, V15.82
Transient cerebral ischemia	435.X
Drug†† markers of comorbid conditions	

Cofactor category	Codes / Comments*
Antidepressant use	NDC codes for monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, tricyclics (excluding doxepin, amitriptyline, clomipramine), tetracyclics, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin-2 receptor antagonists (excluding trazodone), alpha-2 receptor antagonists, and miscellaneous antidepressants; excluding lithium, excluding trimipramine in persons <19 years old
Antidiabetic agent use	NDC codes for alpha-glucosidase inhibitors, amylin analogs, biguanides, dipeptidyl peptidase-4 inhibitors, glucagonlike peptide-1 receptor agonists, insulins, meglitinides, sodium-glucose co-transporter 2 inhibitors, sulfonylureas, thiazolidinediones
Antiarrhythmic agent use	NDC codes for amiodarone, disopyramide, dofetilide, dronaderone, flecainide, mexiletine, moricizine, procainamide, propafenone, quinidine, sotalol, tocainide
Antiretroviral agent for HIV use	NDC codes for CCR5 antagonists, fusion inhibitors, integrase inhibitors, NARTIs, NNRTIs, NRTIs, protease inhibitors
Antihyperlipidemic use	NDC codes for bile acid sequestrants, ezetimibe, fibrates, icosapent, lomitapide, mipomersen, statins, niacin
Anti-obesity agent use	NDC codes for anorexiant combination products (e.g., phentermine/topiramate), lipase inhibitors (orlistat), serotonin 2C receptor agonist (lorcaserin), sympathomimetic anorexiants (benzphetamine, diethylpropion, phendimetrazine, phentermine), sibutramine
Anti-migraine agent use	NDC codes for ergotamine derivatives, analgesic vasoconstrictors, sympathomimetics (isometheptene), triptans, diclofenac (selected formulations)
Smoking cessation agent use	NDC codes for nicotine replacement, varenicline, branded only: Zyban, Buproban
Antihypertensive agent use	NDC codes for renin angiotensin aldosterone system antagonists, alpha blockers, beta blockers (oral), alpha-beta blockers, calcium channel blockers, direct vasodilators, reserpine derivatives, central alpha-2 receptor antagonists, postganglionic blockers, loop diuretics, potassium-sparing diuretics, thiazide diuretics
Anti-alcohol drug use	NDC codes for acamprosate, disulfiram, naltrexone
Drugs that may modify stroke risk	
Aspirin use (by prescription)	NDC codes for products with aspirin as a lone agent
Anticoagulant use	NDC codes for coumarin and indandione anticoagulants (e.g., warfarin), direct and indirect factor Xa inhibitors (apixaban, fondaparinux, rivaroxaban), direct thrombin inhibitors (dabigatran, desirudin), low molecular weight heparins (e.g., dalteparin, enoxaparin)
Antiplatelet agent use	NDC codes for platelet aggregation inhibitors (clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine, anagrelide)

Cofactor category	Codes / Comments*
Contraceptive hormone / postmenopausal hormone replacement use	NDC codes for estrogens and progestins, including monophasic, biphasic, triphasic, 4-phasic, and progestin-only contraceptive hormones

HCPCS = Healthcare Common Procedure Coding System codes; AIDS = acquired immunodeficiency syndrome; CCR5 = cellular chemokine receptor; HIV = human immunodeficiency virus; NARTI = nucleotide analog reverse transcriptase inhibitor; NMDA = N-methyl-D-aspartate; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor

* Use only codes associated with visits (inpatient or outpatient). All diagnoses and procedures are sought for the baseline period prior to cohort entry.

† The narrowly defined stroke includes the principal discharge diagnoses. The more broadly defined stroke includes diagnoses associated with an inpatient or outpatient encounter.

†† Excluding those with intravenous or miscellaneous routes of administration

VI. ANALYSIS

A. RISK ESTIMATE / ADJUSTMENT FOR CONFOUNDERS

We will calculate propensity score-matched hazard ratios. The analysis will be conducted using aggregated data across Mini-Sentinel Data Partners in a stratified Cox regression model. Further detail on this approach can be found in the PROMPT User's Guide.

B. SEQUENTIAL ANALYSIS

PROMPT Module 2 will be run as soon as possible and not await accumulation of a critical mass of mirabegron use. Data looks will be asynchronous in that each Mini-Sentinel Data Partner will run the module at the time of their data refresh, as permitted by Mini-Sentinel workload. Each Mini-Sentinel Data Partner is not necessarily on the same schedule for refreshing.

Group sequential analysis will test the null hypothesis that the hazard of the outcome among mirabegron users is equal to the hazard among oxybutynin users. For each outcome, the surveillance team will suspend the sequential analysis at the earliest occurring of the following: a) the null hypothesis is rejected (i.e., an alert is generated); b) the maximum sample size is reached, where the sample size is defined as the number of HOIs observed; c) a pre-specified sample size (less than the maximum) is reached, such that it is mathematically impossible that the null hypothesis can be rejected; or d) surveillance has been in place for 24 months from the initial PROMPT Module 2 analysis. The surveillance team may revise the last criterion to something shorter or longer than 24 months, based on other information accrued in the Mini-Sentinel system and/or other data sources.

The module will use an alpha spending function that corresponds to a flat stopping boundary with respect to the log likelihood ratio.

The module-specific maximum sample size—that is, the number of outcomes needed to be observed in exposure of interest and comparator groups in order to rule-out risks *as large as* or *larger than* the minimum detectable effect size for a given power level—is presented in **Table 5**. This calculation is approximate and slightly conservative, as it is based on continuous (not group) sequential analysis, but exact sample size calculations are not possible since we do not know the group sizes *a priori*.

Depending on the distribution of observed outcomes between the exposure of interest and comparator groups for a given analysis, the prospective surveillance may reach the conclusion that the null hypothesis cannot be rejected prior to reaching the maximum sample size.

Table 5. Sample size calculations, by health outcome of interest

Input	AMI	Stroke
Type 1 error*	0.05	0.05
Statistical power*	0.90	0.90
Minimum detectable relative risk of interest	2.0	2.0
Stopping boundary shape, with respect to log likelihood ratio	flat	flat
Maximum sample size requirement**	112	112
Minimum number of outcomes needed to signal	7	7
Frequency of testing	upon each data refresh	
Estimated incidence among referent-exposed persons	2.1/1,000 p-y†	5.2/1,000 p-y‡

* actual alpha will be slightly less than 0.05 due to the discrete nature of the data, whereas actual power may be greater than overall power, since we are using a group sequential design while power was calculated for a continuous design with the same maximum sample size.

† age- and sex-adjusted incidence of AMI in a diverse, adult community-based population[16]

‡ age-adjusted incidence of stroke and atherothrombotic brain infarction, as calculated from 1999-2004 in Framingham[17]

VII. TRANSPARENCY AND A PLAN FOR FOLLOW-UP OF ALERTS

Any alert arising from the proposed work will be evaluated and followed-up based on the recommendations described within the Mini-Sentinel Methods Report entitled *Framework for Assessment of Signal Refinement Positive Results*.

VIII. REFERENCES

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IX. ADDENDUM 1

Based on calculated sample size and power needed, and the low uptake of mirabegron in the US, the FDA team decided on April 22, 2016 to discontinue the mirabegron surveillance activity in Sentinel. Assuming that the current uptake pattern for mirabegron continues to hold, FDA would need to wait several years to reasonably assess risk. For example, even allowing for a background rate for AMI to be twice as large as listed in the protocol (see Table 5), it would take about 6.4 years to accumulate the required number of person-years needed to detect a hazard ratio of 1.5 with 90% statistical power, albeit fewer years to observe a hazard ratio greater than 1.5. FDA will remain vigilant as to any report of potential exacerbation in risk using other resources. FDA will revisit Sentinel at a later date should there be a revised concern.