MINI-SENTINEL ASSESSMENT PROTOCOL
METABOLIC EFFECTS OF SECOND GENERATION ANTIPSYCHOTICS IN YOUTH

Version 2

Prepared by: Tobias Gerhard, PhD, MSc,[1] Marsha Raebel, PharmD,[2] Marsha Reichman, PhD,[3] Ali Mohamadi, MD,[3] Simone Pinheiro, ScD, MSc, [3] Susan Andrade, ScD,[4] William Bobo, MD, MPH,[5] Chadi Calarge, MD,[6] Christoph Correll, MD,[1] Stephen Crystal, PhD,[1] Jess Fiedorowicz, MD, PhD,[6] Kristin Goddard, MPH, [2] Robert Penfold, PhD,[7] Susan Shetterly, MS,[2] Darren Toh, ScD,[8] Zhiying You, MD, PhD,[9] Ann McMahon, MD, MS[10]

Author Affiliations: 1. Rutgers University Institute for Health, New Brunswick, NJ; 2. Kaiser Permanente Colorado, Denver, CO; 3. Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 4. Meyers Primary Care Institute, a joint endeavor of Fallon Community Health Plan, Reliant Medical Group, and University of Massachusetts Medical School, Worcester, MA; 5. Vanderbilt University School of Medicine, Nashville, TN; 6. University of Iowa, College of Medicine, Iowa City, IA; 7. Group Health Research Institute, Seattle, WA; 8. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; 9. University of Alabama at Birmingham, Birmingham, AL; 10. Office of Pediatric Therapeutics, Office of the Commissioner, US Food and Drug Administration, Silver Spring, MD.

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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
2	10/30/2013	• Inserted workgroup's response to public comments at the end of Section I • Minor corrections and clarifications	Mini-Sentinel Metabolic Effects of Second Generation Antipsychotics in Youth Workgroup

Mini-Sentinel Assessment Protocol
Metabolic Effects of Second Generation Antipsychotics in Youth

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I. BACKGROUND AND PROJECT OVERVIEW

Important questions remain unanswered about differential safety of the use of second generation antipsychotics (SGAs) in younger individuals, particularly regarding adverse metabolic effects including type 2 diabetes and the metabolic syndrome. The overall goal of this project is to determine whether individual second generation AP medications, when used in children and adolescents, are associated with differential risks of developing type 2 diabetes. The overall project contains 3 subprojects.

Subproject 1: Comparative Analysis of Type 2 Diabetes Risk among Young Patients Newly Initiated on Second Generation Antipsychotics in the Mini-Sentinel Partner Sites Subproject 1 aims to replicate (with opportunity for revisions and adjustments) an AHRQ and FDA funded study conducted with Medicaid Analytic Extract (MAX) data by the Rutgers and Vanderbilt CERTs. The MAX study compared the risk of incident type 2 diabetes among new users of individual second generation antipsychotic medications (APMs) using near national MAX data from 2001 to 2005. For subproject 1, the Mini-Sentinel Distributed Database (MSDD) will be employed to define a Mini-Sentinel (MSN) patient cohort of new initiators of SGAs to "replicate" the MAX analyses. Results of Subproject 1 will inform whether or not the model developed using the MAX-derived cohort performs similarly in the MSN-derived cohort. The patient cohort developed in Subproject 1 will be referred to in this document as the Antipsychotics in Youth (APY) cohort.

Subproject 2: A) Exploring the Feasibility of Using BMI and Laboratory Data for Baseline Confounding Adjustment in Selected Mini-Sentinel Partner Sites A few MSN Data Partners (DPs) have patient height and weight data available from the Electronic Health Records (EHR) of their members. These data have been incorporated into the MSDD. Several MSN DPs have also incorporated glycosylated hemoglobin (HbA1c) and blood glucose laboratory data into the MSDD. However, as these data elements -- extracted from information obtained as part of routine clinical care -- are newly-incorporated into the MSDD, the completeness and timing of these clinical measurements within a cohort of youth newly-initiating antipsychotics have not been determined. The specific aims of Subproject 2A: Exploring the Feasibility of Using BMI and Laboratory Data for Baseline Confounding Adjustment in Selected Mini-Sentinel Partner Sites, are therefore to

1. Determine the proportion of the patients in the APY cohort with height and weight data available at baseline (i.e., within a narrowly-defined time window indexed to date of antipsychotic initiation),
2. Determine the proportion of patients in the APY cohort with baseline HbA1c and/or blood glucose (jointly referred to as "GLU" in this document) laboratory results available,
3. Characterize and compare the proportion of patients with/without baseline height, weight, HbA1c, and/or blood glucose laboratory results data, and
4. Characterize the availability of these data elements based on cohort characteristics including timeframe, age, gender, and specific AP exposure.

Subproject 2: B) Integrating BMI and Laboratory Data into Subproject 1 Analyses to Improve Confounding Adjustments. Conditional on feasibility (subproject 1), adequacy of the BMI and Laboratory data (subproject 2A) and continued support from FDA, subproject 2B will integrate laboratory and BMI data into the subproject 1 analyses to improve control of confounding. These analyses will be limited to those Data Partners that can provide access to BMI and/or laboratory results.

Subproject 3: Examining Longitudinal Change in BMI and Laboratory Parameters between Young Patients Newly Initiated on Individual Second Generation Antipsychotics Conditional on adequate data quality (Aim 2a) and continued support from FDA, subproject 3 aims to examine longitudinal changes in BMI and metabolic lab parameters between individuals initiated on alternative second generation APMs in the APY cohort.

This protocol describes the analytic plans for the currently funded subprojects 1 and 2A. It includes edits made in response to public comments. These edits were limited in scope because the planned comparison of findings to those of a previous Medicaid study precluded major changes to the shared analytic approach as budgetary restrictions and time constraints did not allow significant revisions to the protocol of the Medicaid study.

II. SUBPROJECT 1

A. DATA SOURCE

The assessment will include all Data Partners contributing data to the Mini Sentinel Distributed Database (MSDD). The study period will differ between individual Data Partner sites based on each site's data availability and completeness. A table of start and end dates for each Data Partner site is currently in development.

B. STUDY COHORT

New initiators of second generation antipsychotics (study SGAs; see section D) meeting all inclusion and exclusion criteria (Table 1, Table 2, Appendix A). The study uses a 180 day look-back period to define new initiations. A 365 day look-back period is used in sensitivity analysis. Note that the protocol refers only to the 180 look back period unless it specifically addresses the 365 day sensitivity analysis.

1. Inclusion Criteria

- Age 2-24 years on t_0, known date of birth and gender. The upper age limit corresponds to the World Health Organization's definition of youth.
- Enrollment with both medical and prescription drug coverage for 180 days preceding t_0, allowing enrollment lapses of ≤45 days.
- Current use of a study SGA (see section D) on t_0, which includes depot antipsychotics, but excludes non-depot injections (identified by NDC).
- At least 180 consecutive days with no current use of <u>any</u> antipsychotics (see "all antipsychotics" section D), except for non-depot injections, in the period [t_0-180, t_0-1].
    - Medical care encounters (inpatient, ED, physician or other outpatient) in the year preceding t0. Specifically, at least 2 medical care encounters (inpatient, ED, physician or other outpatient) in the year preceding t0 ([t0-365, t0-1]), one of which must be in the 90 days preceding t0 ([t0-90, t0-1]). This assures that cohort members have active contact with the medical care system. It also assures availability of data for calculation of the propensity scores needed to select control medication episodes.
- Not in long-term care institution on t_0 or in the preceding 180 days.

2. Exclusion Criteria

- Serious somatic illness exclusion: No evidence somatic exclusion illness on t_0 or in the 180 days preceding t_0 (Appendix A, M1).
- Endpoint-related exclusion: No evidence of diabetes, on t_0 or in 180 days preceding t_0 (Appendix A, M2)
- Other condition exclusion: Pregnancy, polycystic ovarian syndrome (Appendix A, M3)
- Follow-up exclusion: Have at least 120 days of study follow-up (necessary due to the confirmation window of the computer case definition for type 2 diabetes; see Table 3)
- Initiation of more than one AP on t_0
- Index AP with 0 days supply

Table 1. Somatic exclusion illnesses*

Somatic exclusion illnesses
Sickle cell disease
Cystic fibrosis
Cerebral Palsy
Cancer
HIV
Other serious infections: hepatitis B or C, tuberculosis
Organ transplant
Liver failure
Renal dialysis
Respiratory failure
Childhood diseases potentially lethal or associated with premature death: fatal metabolic diseases, aplastic anemia, congenital immune deficiencies, chromosomal anomalies (Down syndrome, Trisomy 13, Trisomy 18, Autosomal deletion syndrome), serious neuromuscular disease
Hospice care

*See Appendix A, N1 for detailed definitions.

Table 2. Cohort inclusion-exclusion criteria

Cohort inclusion-exclusion criteria	
1	Age 2-24years on t_0, with known date of birth and gender.
2	Enrollment with both medical and prescription drug coverage for 180 days preceding t_0, allowing enrollment lapses of ≤ 45 day.
3	Current use of a study antipsychotic on t_0, which includes depot antipsychotics, but excludes non-depot injections (identified by NDC).
4	At least 180 consecutive days with no current use of any antipsychotics (except for non-depot injections) in the period [t_0-180, t_0-1].
5	Medical care encounters (inpatient, ED, physician or other outpatient) in the year preceding t_0 ([t_0-180, t_0-1]). This assures that cohort members have active contact with the medical care system. It also assures availability of data for calculation of the propensity scores needed to select control medication episodes.
5-a	At least 2 medical care encounters (inpatient, ED, physician or other outpatient in the year preceding t_0 ([t_0-180, t_0-1]).
5-b	At least one of which must be in the 90 days preceding t_0 ([t_0-90, t_0-1]).
6-a.	Not in the hospital on t_0 or in the preceding 29 days **(flag only)**

Cohort inclusion-exclusion criteria	
6-b.	Not in long-term care institution on t_0 or in the preceding 180 days.
	Criteria 1-6 are used to define t_0. Once such a t_0 is identified, criterion 7 is applied to further exclude persons from the cohort.
7-a.	*Serious somatic illness exclusion:* No evidence of somatic exclusion illness on t_0 or in the 180 preceding days (Appendix A1).
7-b	*Diabetes exclusion:* No evidence of diagnosed or treated diabetes on t_0 or in 180 preceding days (Appendix A2). No procedure indicating possible diabetes testing/management in the period [t_0-29, t_0] **(flag only)**. The procedures are glucose test strips, diabetes self management training, islet cell antibody test, insulin pump, glucose monitor, HbA1c, insulin RIA, or metabolic panel.
7-c	*Pregnancy exclusion:* No evidence of diagnosis or procedure indicating possible pregnancy (Appendix A3) on t_0 or in 180 preceding days preceding t_0.
7-d	*Polycystic ovarian syndrome exclusion:* A female > 11 years of age with any diagnosis on t_0 or in 180 preceding days of polycystic ovarian syndrome (Appendix A3)
7-e	*Follow-up exclusion:* Have at least 120 days of study follow-up
7-f	Index claim exclusion: More than one AP on t_0; Index dispensing with 0 days of supply

Table 3. Computer case definition for diabetes according to type of diabetes-related medical care encounter

	Inpatient	*Outpatient*	*Prescription*[b]
Diabetes-Related Medical Care Encounter[a]			
Definition	Inpatient stay with 1) a diagnosis for diabetes (ICD-9-CM: 250, 250.0x, 250.1x, 250.2x, 250.3x, 250.9x)[c]; or 2) an outpatient encounter (including ED) with a primary diagnosis of diabetes during the *hospital stay period*, defined as the day prior to admission through the day following discharge.	Outpatient visit (including ED) with a primary diagnosis of diabetes, excluding those during the hospital stay period.	Filled prescription for any diabetes medication, including insulin, insulin adjuncts (pramlintide), and oral hypoglycemics. There can be no diagnosis, primary or secondary, of polycystic ovarian syndrome in the interval [t_x-120,t_x+120]
Index date, t_x, initial	t_a (admission date) unless ED/outpatient visit with diabetes diagnosis on t_a-1 in which case t_a-1.	Day of visit	Day of prescription fill
Additional Criteria Required to Meet Criteria for Diabetes Case			
Exclusion[d]	Polycystic Ovarian Syndrome		
Confirmation[d] (primary definition)	Diabetes medication prescription, outpatient diagnosis, inpatient diagnosis	Diabetes medication prescription, inpatient diagnosis	1. Outpatient diagnosis, inpatient diagnosis, or 2. Subsequent prescription, and procedure indicating diabetes management[e], and no diagnosis absent/irregular menses (ICD-9-CM: 626.0x,

	Inpatient	*Outpatient*	*Prescription*[b]
			626.4x)
Confirmation[d] (secondary definition)	As above or glycated hemoglobin test (indicating possible diabetes management).		As above
Index date, final	If diabetes-related procedure[f] in the interval [t_x-29, t_x-1] t_x is set to procedure date.		

[a]Does not include deaths as there were none with diabetes coded as an underlying cause of death for cohort members during the study period.
[b]If both a prescription and other encounter on the same day, classified as a prescription encounter.
[c]Does not include ICD-9-CM: 250.4-250.8, which are chronic complications of diabetes and thus unlikely to be present for newly diagnosed cases, particularly in a population of children/youth.
[d]Period for exclusion or confirmation is [t_x-120, t_x+120].
[e]Diabetes management: HbA1c (CPT: 83036,83037 , glucose test strips (CPT: A4253), glucose monitor (CPT: E2101,E2100,E0609,E0607, insulin pump (CPT: Y3204,Y3286,Y3264,Y3284,E0784).
[f]Diabetes-related procedure: HbA1c (glycated hemoglobin), islet cell antibody test, insulin RIA, or metabolic panel.

C. OUTCOME (TYPE 2 DIABETES)

The construction and validation of a computer case definition for diabetes in youth has been previously described by Bobo et al. (BMC Res Methodol. 2012). Note that the Bobo et al. computer case definition has been modified (see Table 3) for the present study to accommodate differences in the coding of inpatient visits between Tennessee Medicaid data and the MSCDM. Table 3 reflects these changes.

Cases are considered type 1 diabetes (and censored) if there was at least one prescription for insulin within 120 days of the index date, with no more than a single prescription for an oral hypoglycemic (PRAMLINTIDE, METFORMIN, PHENFORMIN, CHLORPROPAMIDE, TOLAZAMIDE, TOLBUTAMIDE, ACETOHEXAMIDE, GYLBURIDE, GLIPIZIDE, ACARBOSE, GLIMEPIRIDE, TROGLITAZONE, REPAGLINIDE, MIGLITOL, ROSIGLITAZONE, PIOGLITAZONE, MATEGLINIDE, EXENATIDE, SITAGLIPTIN) in that interval. The single prescription for an oral agent was allowed because, on occasion, these drugs may be prescribed while awaiting the results of confirmatory testing for type 1 diabetes. Otherwise, the case was classified as type 2 diabetes.

A secondary, outcome definition, also shown in Table 3, will be implemented to avoid underascertainment of type 2 diabetes cases that resolve quickly without pharmacological treatment (see section G).

D. EXPOSURE AND FOLLOW-UP

The following second generation antipsychotics (SGAs) were considered study medications (all second generation agents available in the US in 2012 except clozapine): Aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone, asenapine, iloperidone, lurasidone, paliperidone.

The following list of medications constitutes the group of all antipsychotics (APMs), including first generation and second generation agents: aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, thioridazine, ziprasidone, paliperidone, mesoridazine, promazine, trifluoperazine, triflupromazine, chlorprothixene, loxapine, molindone, pimozide, thiothixene, clozapine, asenapine, iloperidone, lurasidone.

- Create calendar of study SGA exposure based on days-supply of the index agent). Because the days supply variable is manually entered by the pharmacist, we perform two quality checks/quantity adjustments. If the days supply exceeds the quantity dispensed, days supply is replaced by quantity dispensed. In addition, the days supply variable is capped at a maximum of 120 days.
- Early refills (stockpiling) were not explicitly considered but were implicitly considered by allowing breaks of up to 14 days. The index study SGA is considered to be discontinued (at the last day of supply) if there is a break in supply of >14 days.

Follow up begins at t_0. The base case end of follow-up (censoring date) is defined as the first of the following dates:

- Study SGA discontinuation (30 days added to reduce potential bias from informative censoring if patients discontinue the SGA because of adverse effects experienced shortly before)
- Addition of 2nd APM/APM switch
- Day prior to 25th birthday
- No medical care encounters (day 365 without at least 2 medical encounters)
- Pregnancy
- Polycystic ovarian syndrome
- Serious somatic illness
- Type 1 diabetes
- 120 days prior to end of data set (data partner specific)
- 120 days prior to date of death
- 120 days prior to loss of eligibility (plan enrollment with both medical and prescription drug coverage)
- Type 2 diabetes

Including the base case, there are a total of 6 alternative definitions for the censoring date.

1. 30 days follow-up added after index SGA discontinuation **(base case)**

Sensitivity Analyses:

2. 30 days follow-up added after index SGA discontinuation or 2nd APM/APM switch
3. 90 days follow-up added after index SGA discontinuation
4. No days added after index AP discontinuation or 2nd APM/APM switch
5. 180 day intent to treat (index exposure carried forward until day 180)
6. 365 day intent to treat (index exposure carried forward until day 365)

E. COVARIATES

Covariates are assessed during the 180 day pre-index period and defined in Tables 4-14. Table 15. shows a crosswalk between select summary variables and the variable definitions from Tables 4-14.

Table 4. Psychiatric diagnoses

Variable	ICD9CM diagnosis
1. Bipolar disorder	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 301.13
2. Mood disorders, major depression	296.2x, 296.3x, 296*, 298.0x
3. Mood disorders, other	296.9x, 300.4x, 301.10, 301.12, 309.0x, 309.1x, 311
4. ADHD, hyperkinetic syndrome	314.0x, 314.2x, 314.8x, 314.9x
5. Other disruptive behavior disorders	309.3, 312.8x, 312.xx (not 312.3), 313.81
6. Impulse control disorders	312.3x
7. Learning disability, other	315.00, 315.1x, 315.2x, 315.9x
8. Sleep disorder, not organic	307.41, 307.42, 307.44, 307.45, 307.46, 307.47, 307.49, 327.02, 347.xx, 780.52, 780.55, 780.56, 780.58, 780.59
9. Anxiety disorder/phobia	300.0x, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3x, 309.81
10. Personality disorders	301.0x, 301.11, 301.20, 301.22, 301.4, 301.50, 301.59, 301.6x, 301.7x, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9x
11. Acute stress, adjustment disorder	308.xx, 309.xx (except 309.0, 309.1, 309.3)
12. Ethanol, diagnosed	291.xx, 303.xx (dependence), 305.0 (abuse), V113
13. Other substance abuse, diagnosed	292.xx, 304.xx, 305.xx(except 305.00, alcohol abuse, and 305.1, tobacco use disorder)
14. Somatoform spectrum disorders	300.1x, 300.5, 300.7, 300.8x, 306.xx, 307.8x, 307.9x
15. Learning disorder/ developmental delay (non-PDD, non-MR)	315.xx, 314.1x
16. Other psychiatric	293.xx, 294.0x, 294.8x, 295.xx-319.xx, not above
17. Psychiatric symptoms	780.1x, 780.71, 799.2x
18. Injury, self-inflicted or undetermined intent	E950.x-E958.x, E959, E980.x-E988.x, E989
19. Schizophrenia, schizophrenia-like psychotic disorders	295.xx, V11.0, 297.xx, 298.3x, 298.4x, 298.8x, 298.9x
20. Tics disorder	333.xx, 307.3x, 781.0x
21. Pervasive developmental disorders	299.xx
22. Mental retardation	317.xx-319.xx, V79.2
23. Organic Psychosis	293.81, 293.82
24. Tourettes	307.20-307.23

* '296' with no 4th digit considered major depression

Table 5a. Obstetric/Gynecologic: Medical care encounters (Must be female to have this covariate set)

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Pregnancy, prior	630-677, 760-763, 779.6, V22, V23, V24, V27, V28, V30-V39	36460, 59000-59899, 76801-76828, 76946	66.62, 66.11, 69.0x, 69.51, 72.xx-75.xx, 87.71, 88.78
Pregnancy, screen	V72.4x	84702, 81025	
Sterilization	V25.2, V26.51	58565, 58600, 58605, 58611, 58615, 58670, 58671, S2255	66.21, 66.22, 66.29, 66.31, 66.32, 66.39
Contraception management	V25.4x		
Menstruation, absence	626.0x		
Menstruation, infrequent	626.1x		
Menstruation, irregular	626.4x		
Menstruation, heavy/frequent	626.2x		
Menstruation, other disorder	626.8x, 626.9x		
Cervical cancer screening	V72.32, V76.2	88141-88143, 88147, 88148, 88150, 88152-88155, 88164-88167, 88174, 88175	
Cervical dysplasia	622.1x		
Ovarian cysts	620.0, 620.2		
Other	760-779		

Table 5b. Obstetric/Gynecologic : Medications (Must be female to have this covariate set)

Obstetric/Gynecologic : Medications	
Oral contraceptives	Estradiol Norethindrone Norgestrel
Other contraception	Etonogestrel Levonorgestrel Ethinyl estradiol vaginal ring Ortho Evra
Medroxyprogesterone	Medroxyprogesterone acetate

Table 6a. Metabolic and related: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Obesity, not morbid	259.9x, 278.0x, 278.00, V77.8, V85.30-V85.34, V85.53, V85.54		
Obesity, morbid	278.01, V85.35-V85.39 V85.4		
Abnormal weight gain	783.1x		
Acanthosis nigricans	701.2x		
Weight management program	V65.3 (dietary surveillance and counseling)	medical nutritional therapy (97802, 97803)	
Insulin resistance/metabolic syndrome	Hyperinsulinemia (251.1x), metabolic syndrome (277.7x)	Insulin RIA (83525)	
Metabolic panel		metabolic panel (80048)	
Diabetes screen	Diagnosis: polyuria (788.42), polydipsia (783.5x), V77.1	glycosylated hemoglobin (83036), blood glucose (82947), glucose tolerance (82951, 82952)	
Hyperlipidemia	272.0x, 272.1x, 272.2x, 272.3x, 272.4x, 272.7x		
Hyperlipidemia screen		82465, 83718, 83721, 84478	
Hypothyroidism	243, 244.xx		
Hypothyroid screen	V77.0	84436, 84443	
Hyperthyroidism	242.xx		
Other endocrine	240.xx, 241.xx, 245.xx, 246.xx, 255.xx (adrenal disorders), 253.xx (pituitary disorders), 259.0x (delayed puberty), 259.1x (precocious puberty)		

Table 6b. Metabolic and related: Medications

Metabolic and related: Medications	
Lipid-lowering drugs	lovastatin| pravastatin simvastatin fluvastatin atorvastatin rosuvastatin cerivastatin clofibrate gemfibrozil fenofibrate cholestyramine colestipol colesevelam ezetimibe probucol niacin aluminum nicotinate sitosterols
Hypothyroid treatment	thyroid levothyroxine liothyronine
Antithyroid agents	propylthiouracil(PTU) methimazole sodium iodide
Anorexiants	phentermine sibutramine orlistat

Table 7a. Cardiovascular: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Hypertension	401.xx-403.xx, 404.xx, 405.xx, V81.1		
Other cardiovascular disease	Congenital heart anomalies: 745.xx-747.xx (except 747.6x, 747.81); Acute MI: 410.xx; Ischemic heart disease: 411.xx-414.xx, 429.7x; Cardiac valve disease: 394.x, 396.x, 424.0; Bicuspid aortic valve: 746.4; Other cardiac valve disease: 395.x, 397.x, 424.1, 424.2, 424.3; Conduction disorder: 426.xx; Arrhythmia: 427.xx; Cardiomyopathy: 425.x; Coronary artery anomaly: 746.85; Heart failure: 428.xx; TIA: Occlusion	Note: prior cardiovascular hospitalization is exclusion criteria, thus, won't have valve repair procedures, etc	

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
	of cerebral arteries (430, 431, 432.x, 433.xx, 434.xx, and 436), TIA (435.x); Other cerebrovascular disease: 437.x, 438.xx; Peripheral vascular disease: 440.2x, 440.3, 443.xx, 444.2x, 444.8x, 445.0x,785.4x; Renal insufficiency: 582.xx-588.xx; Other cardiovascular diseases (in absence of any of the above): 390.xx-459.xx (not including codes for above conditions) – except 455.x (hemorrhoids), 453.x (VTE), 451.xx (phlebitis)	as these are inpatient	
Symptoms, possibly cardiovascular	Cardiovascular symptoms (in absence of any of the above): 780.2x, 785.0x-785.3x, 785.50, 785.51,785.9x, 786.5x;		

Table7b. Cardiovascular: Medications

Cardiovascular: Medications	
Thiazide diuretic	hydrochlorothiazide chlorothiazide chorthalidone bendroflumethiazide polythiazide hydroflumethiazide quinethazone benzthiazide metylchlothiazide metolazone indapamide trichlormethiazide cyclothiazide
ACE inhibitor/ARBs	benazepril captopril enalapril enalaprilat fosinopril lisinopril moexipril perindopril quinapril ramipril trandolapril losartan valsartan irbesartan telmisartan candesartan

Cardiovascular: Medications	
	eprosartan olmesartan
Anti-hypertensives, other	acebutol atenolol betaxolol bisoprolol carteolol carvedilol esmolol labetalol metoprolol nadolol oxprenolol penbutolol pindolol propranolol sotalol timolol **Dihydropyridines** (nifedipine nicardipine felodipine isradipine nisoldipine amlodipine lacidipine nimodipine) bepridil mibefradil verapamil diltiazem **Potassium-sparing** (amiloride triamterene spironolactone eplerenone) acetazolamide dichlorphenamide mercaptomerin mannitol ethoxzolamide mersalyl merethoxylline

Other cardiovascular	warfarin heparin **LMW heparin** (dalteparin enoxaparin) **Factor Xa inhibitor** (fondaparinux idraparinux razaxaban) hirudin lepirudin argatroban ximelagatran thrombin bishydroxycoumarin phenindione phenprocoumon acenocoumarol anisindion diphenadione danaparoid sodium ardeparin tinzaparin **Class IA drugs** (quinidine procainamide disopyramide) **Class IB drugs** (mexiletine tocainide) **Class IC** (flecainide propafenone moricizine) **Class III drugs** (miodarone bretilium ibutilide dofetilide sotalol azimilide) digoxin

Cardiovascular: Medications	
	amrinone milrinone enoximone vesnarinone pimobendan, levosimendan dopamine dobutamine ibopamine xamoterol metaraminol digotoxin digitalis gitalin lanatoside deslanoside midodrine inamrinone furosemide bumetanide torsemide ethacrynic nitroglycerin isosorbide pentaerythroid erythritol amyl nitrate dipyridamole cilostazol **PLT inhibitors** (abciximab clopidogrel eptifibatide tirofiban ticlopidine)

Table 8a. Respiratory/Allergy: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Anaphylaxis	995.0X		
Allergic reaction	995.2x, 995.3X		
Asthma	493.xx		
Wheezing	786.07		
Asphyxia	799.0x		
Sleep apnea	327.20, 327.21, 780.51, 780.53, 780.57	94660	
Shortness of breath	786.05		
Smoking, diagnosed	305.1X , 649.0x (tobacco use disorder complicating pregnancy), 989.84 (toxic effect of other substances, incl. tobacco)	99406, 99407	

Table 8b. Respiratory/Allergy: Medications

Antihistamines, non-sedating	Desloratadine fexofenadine loratadine
Antihistamines, other	Carbinoxamine centrizine chlorpheniramine clemastine cyproheptadine dexchlorpheniramine diphenhydramine hydroxyzine levocentrizine meclizine
Corticosteroids	methylprednisolone prednisolone prednisone
Asthma medications, other	metaproterenol levalbuterol

Respiratory/Allergy: Medications	
	bitolterol pirbuterol terbutaline salmeterol formoterol aminophylline dyphylline oxtriphylline theophylline beclomethasone budesonide flunisolide fluticasone triamcinolone betamethasone mometasone ipratroprium tiotropium montelukast zafirlukast zileuton cromolyn nedocromil epinephrine omalizumab
Smoking cessation	varenicline nicotine

Table 9a. Gastrointestinal disease: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Abdominal pain	789.0x		
Gastroesophageal reflux	530.1x, 530.8x		
Other upper GI disease	578.x, 530.xx-537.xx (except 530.1x, 530.8x)	43200, 43202, 43216, 43217, 43220, 43227, 43234, 43239, 43241, 43246, 43247, 43250, 43251, 43255	45.11-45.14, 45.16

Table 9b. Gastrointestinal disease: Medications

Gastrointestinal disease: Medications	
Histamine 2 receptor antagonists	Cimetidine famotidine nizatidine ranitidine
Proton-pump inhibitors	Esomeprazole lansoprazole omeprazole pantoprazole rabeprazole
Other prescription dyspepsia	Misoprostol Sucralfate
Antacids	Alka-seltzer aluminum hydroxide bicarbonate+citrate aluminum hydroxide+magnesium hydroxide magaldrate calcium carbonate_magnesium hydroxide
Anti *H pylori*	Helidac (bismuth subsalicylate+metronidazole+tetracycline) Prevpac (lansoprazole_amoxicillin+clarithromycin) Pylera (biskalcitrate+metronidazole+tetracycline)
Phenothiazine antiemetics	Promethazine meclizine prochlorperazine
Ulcerative colitis treatment	Balsalazide mesalamine olsalazine sulfasalazine

Table 10. Neurologic/musculoskeletal: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Seizure disorder	345x, 780.3x (not 780.31)		
Migraine	346.xx		
Neuropathic pain	053.1x, 053.9, 350.1, 352.1, 729.2, 350.8, 350.9, 337.2x, 338.0, 357.0, 357.1, 357.3-357.7, 357.8x, 357.9, 354.x, 355.0-355.6, 355.7x, 355.8, 355.9, 352.1, 353.0-353.4, 353.8, 353.9, 356.2, 356.8, 956.9, 336.9, 350.2, 356.0, 723.1, 723.4, 724.1, 724.4, 729.2, 782.0, 957.9, 353.6		
Back pain	724.1x - 724.5x		
Osteoarthritis	715.xx		
Other musculoskeletal symptoms	719.4x, 719.5x, 723.1, 723.4, 781.99		
Other rheumatologic disease	524.60, 710.x, 712.xx, 714.xx, 716.xx, 719.2x, 719.3x, 720.xx-722.xx, 723.x (except 723.1, 723.4, 723.5), 724.0x, 724.6, 725, 726.xx-729.xx		
Injury, other	E800-E999, 800.xx-999.xx	See fracture/dislocation codes below	79.0x, 79.1x, 79.2x, 79.3x, 78.1x
CPT4 procedure codes: fracture reduction, setting, casting, etc			
23500, 23505, 23515, 23520, 23570, 23615, 23665, 23670, 23675, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565, 24566, 24575, 24576, 24577, 24579, 24582, 24586, 24620, 24635, 24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575, 25600, 25605, 25606, 25607, 25608, 25609, 25622, 25624, 25628, 25630, 25635, 25645, 25650, 25651, 25652, 25680, 25685, 26600. 26605, 26607, 26608, 26615, 26645, 26650. 26665, 26720, 26725, 26727, 26735, 26740, 26742, 6746, 26755, 26756, 26765, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27254, 27500, 27501, 27502, 27503, 27506, 27507, 27508, 27509, 27510, 27511, 27513, 27514, 27520, 27524, 27530, 27532, 27535, 27536, 27538, 27540, 27750, 27752, 27756, 27758, 27759, 27760, 27762, 27766, 27780, 27784, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 27824, 27825, 27826, 27827, 27828, 28400, 28405, 28406, 28415, 28420, 28430, 28435, 28436, 28445, 28450, 28455, 28456, 28465, 28470, 28475, 28476, 28485, 28490, 28495, 28496, 28505, 28510, 28515, 28525, 28530, 28531, 29000–29799, 29846, 29850, 29851, 29855, 29856, 29892,			
CPT4 procedure codes: dislocation			
23525, 23530, 23532, 23540, 23545, 23550, 23552, 23650, 23655, 23660, 23665, 23700, 24600, 24605, 24615, 25660, 25670, 25671, 25675, 25676, 25690, 25695, 26641, 26670, 26675, 26676, 26685, 26686, 26700, 26705, 26706, 26715, 26770, 26775, 26776, 26785, 27250, 27252, 27253, 27256, 27257, 27258, 27259, 27265, 27266, 27550, 27552, 27556, 27557, 27558, 27560, 27562, 27566, 27830, 27831, 27832, 27840, 27842, 27846, 27848, 28540, 28545, 28546, 28555, 28570, 28575, 28576, 28585, 28600, 28605, 28606, 28615, 28630, 28635, 28636, 28645, 28660, 28665, 28666, 28675			

Table 11. Neurologic/musculoskeletal: Medications

Neurologic/Musculoskeletal Medications	
Migraine treatment/prevention	methysergide dihydroergotamine ergotamine almotriptan eletriptan frovatriptan naratriptan rizatriptan sumatriptan zolmitriptan
NSAID, includes coxibs	aspirin acetylsalicylic aceclofenac choline salicylate comb diclofenac diflunisal etodolac fenoprofen flurbiprofen sodium ibuprofen indomethacin ketoprofen ketorolac meclofenamate sodium mefenamic acid meloxicam nabumetone naproxen oxaprozin phenylbutazone oxyphenbutazone piroxicam salsalate salicylamide sulindac tolmetin sodium tiaprofenic acid celecoxib etoricoxib lumiracoxib parecoxib rofecoxib valdecoxib
Narcotic analgesic	codeine fentanyl

Neurologic/Musculoskeletal Medications	
	hydromorphone levorphanol meperidine methadone morphine oxycodone oxymorphone propoxyphene hydrocodone dihycrocodeine pentazocine
Non-narcotic analgesic	acetaminophen
Cyclobenzaprine	cyclobenzaprine
Other skeletal muscle relaxants	baclofen carisoprodol dentrolene metaxalone methocarbamol orphenadrine tizanidine
Other rheumatologic	abatacept adalimumab anakinra etanercept infliximab auranofin azathioprine thiomalate hydroxychloroquine leflunomide methotrexate

Table 12a. Other somatic: Medical care encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Urinary tract infection	599.0		
Other infections	001.xx-139.xx, 480.xx-487.x, 507.x, 510.x, 513.x,		
Malaise and Fatigue	780.79		
Hypersomnia	780.54, 327.11, 327.12		
Other organic sleep disorder	327.0x, 327.2x, 327.5x,327.1x, 327.30		
Edema	782.3x		
Cholecystitis, cholelithiasis	574.1x-574.9x, 575.0x, 575.1x		
Nephrotic syndrome	581.81, 581.9		

Table 12b. Other somatic: Medications

Other somatic: Medications	
Antibiotics	azithromycin erythromycin clarithromycin dirithromycin troleandomycin capreomycin clofazimine cycloserine dapsone ethambutol ethionamide isoniazid kanamycin para-aminoslicyclic acid pyrazinamide rafabutin rifamate rifampin rifapentine rifater cefadroxil

Other somatic: Medications	
	cefazolin cephalexin cefaclor cefotetan cefoxitin cefprozil cefuroxime cefidinir cefoperazone cefotaxime cefditoren cefixime cefpodoxime ceftazidime cefibuten deftizoxime ceftriaxone penicillin dicloxacillin nafcillin oxacillin amoxicillin ampicillin piperacillin ticarcillin naldixic acid ciprofloxacin lomefloxacin norfloxacin orfloxacin levofloxacin gemifloxacin MESYLATE" moxifloxacin sulfadiazine sulfisoxazole trimethoprim-sulfamethoxazole demeclocycline doxycycline minocycline oxytetracycline tetracycline clindamycin metronidazole nitrofurantoin rifaximine telithromycin

Table 13. Psychiatric Medications

Psychiatric Medications	
A. Mood Stabilizers	
1. Lithium	Lithium
2. Anticonvulsant, primary	Valproic acid Divalproex sodium Lamotrigine Carbamazepine
3. Anticonvulsant, secondary	Acetazolamide Felbamate Gabapentin Lacosamide Levetiracetam Oxcarbazepine Pregabalin Topiramate Zonisamide
B. Antidepressants	
4. SSRI/SNRI/mirtazapine	Citalopram Duloxetine Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Venlafaxine Mirtazapine
5. TCA and heterocyclic compounds	Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline
6. Antidepressants, MAOI	Phenelzine Tranylcypromin Isocarboxazid
7. Antidepressants, trazodone-related	Nefazodone Trazodone
8. Antidepressants, bupropion	Bupropion
C. ADHD Drugs	
9. Psychostimulants	Amphetamine Atomoxetine Dexmethylphenidate Dextroamphetamine

Psychiatric Medications	
	Lisdexamfetamine Ethamphetamine Methylphenidate Pemoline
10. Alpha-agonists, used for ADHD	Clonidine Guanfacine
D. Anxiolytic/Hypnotics	
11. Benzodiazepines**	Alprazolam Bromazepam Chlordiazepoxide Clonazepam Clorazepate Diazepam Estazolam Flurazepam Halazepam Lorazepam Oxazepam Quazepam Temazepam Triazolam
E. Other Psychotropic Drugs	
12. Other GABA agonists	Eszopiclone Zaleplon Zolpidem Zopiclone
13. Other anxiolytic/hypnotic, newer	Ramelteon Buspirone
14. Other anxiolytic/hypnotic, older	Chloral hydrate Ethchlorvynol Meprobamate Amobarbital Butabarbital Mephobarbital Secobarbital
15. Other psychiatric drugs	Modafinil Oxybate Phendimatrazine Benzphetamine

Table 14. Other Covariates

Variable Names in descriptive table (SAS output)	
Users	Total in cohort
indexCPZ	Index daily dose in chlorpromazine equivalents (using Andreasen conversion algorithm)
indexCPZ_high	>75mg chlorpromazine equivalents
indexCPZ_low	≤75mg chlorpromazine equivalents
AgeAtIndex	Age on the index date
age1_2to5	Age group based on age on the index date
age2_6to12	Age group based on age on the index date
age3_13to17	Age group based on age on the index date
age4_18to24	Age group based on age on the index date
index_year1	Index year 1
index_year2	Index year 2
index_year3	Index year 3
index_year4	Index year 4
index_year5	Index year 5
race_b	Race: African American
race_h	Race: Hispanic
race_o	Race: Other
race_w	Race: White
sex_female	Gender: Female
sex_male	Gender: Male
diabete_test29prior	Diabetes testing/management in 30 days prior to the index date
ED1to30daysPrior	ED visit in 30 days prior to the index date
ED31to365daysPrior	ED visit in 31 days to 365 days prior to the index date
IP1to29daysPrior	In hospital on the index date or in the preceding 29 days
IP30to89daysPrior	In hospital in 30 to 89 days prior to the index date
IP90to365daysPrior	In hospital in 90 to 365 days prior to the index date
OP1to7daysPrior	Outpatient visit in the 7 days preceding the index date
OP8to30daysPrior	Outpatient visit in 8 to 30 days prior to the index date
OP31to365daysPrior	Outpatient visit in 31 to 365 days prior to the index date
RX1to7daysPrior	Having at least 1 prescriptions filled in the 7 days preceding the index date
RX8to30daysPrior	Having at least 1 prescriptions filled in 8 to 30 days prior to the index date
RX31to365daysPrior	Having at least 1 prescriptions filled in 31 to 365 days prior to the index date
days_IP1to29daysPrior	Number of inpatient days in the 29 days leading to the index date
days_IP30to89daysPrior	Number of inpatient days in 30 to 89 days prior to the index date
days_IP90to365daysPrior	Number of inpatient days in 90 to 365 days prior to the index

Variable Names in descriptive table (SAS output)	
	date
nFills_RX1to7daysPrior	Number of filled prescriptions in the 7 days preceding the index date
nFills_RX8to30daysPrior	Number of filled prescriptions in 8 to 30 days prior to the index date
nFills_RX31to365daysPrior	Number of filled prescriptions in 31 to 365 days prior to the index date
nVisits_ED1to30daysPrior	Number of ED visits in the 30 days prior to the index date
nVisits_ED31to365daysPrior	Number of ED visits in 31 to 365 days prior to the index date
nVisits_OP1to7daysPrior	Number of outpatient visits in the 7 days prior to the index date
nVisits_OP8to30daysPrior	Number of outpatient visits in 8 to 30 days prior to the index date
nVisits_OP31to365daysPrior	Number of outpatient visits in 31 to 365 days prior to the index date

Table 15. Crosswalk for Select Aggregate Covariates

Comorbidities:	
Psychiatric Comorbidities:	
Schizophrenia and related psychoses	Table 4: Row 19
Bipolar disorder	Table 4: Row 1
Depression and other mood disorders	Table 4: Rows 2+3
ADHD and disruptive behavior disorders	Table 4: Rows 4+5
Sleep disorder, not organic	Table 4: Row 8
Anxiety disorder/phobia	Table 4: Row 9
Personality disorders	Table 4: Row 10
Acute stress, adjustment disorder	Table 4: Row 11
Substance use disorders	Table 4: Rows 12+13
Somatoform spectrum disorders	Table 4: Row 14
Learning disorder/ developmental delay (non-PDD, non-MR)	Table 4: Rows 7+15
PDD, autism, mental retardation	Table 4: Rows 21+22
Organic Psychosis	Table 4: Row 23
Tics	Table 4: Row 20
Other	Table 4: Rows 6+16
Psychiatric Symptoms	Table 4: Row 17
Injury, self-inflicted or undetermined intent	Table 4: Row 18
Somatic Comorbidities:	
OB/GYN and related	Table 5 a (any)
Metabolic	Table 6 a (any)
Hypertension	Table 7 a (row 1)
Other CV	Table 7 a (all except row 1)
Respiratory/Allergy	Table 8 a
GI	Table 9 a

Comorbidities:	
Neurologic/muscoskeletal	Table 10
Medications:	
Psychiatric:	
Mood Stabilizers	Table 13 A
Antidepressants	Table 13 B
ADHD drugs	Table 13 C
Anxiolytics/Hypnotics	Table 13 D
Other psychotropics	Table 13 E
Somatic:	
Contraceptives	Table 5 b (any)
Lipid lowering agents	Table 6 b (row1)
other metabolic (hypothyroid, antithyroid, anorexiants)	Table 6 b (all except row 1)
Antihypertensive (thiazides, ACE/ARB, other antihypertensives)	Table 7 b (Rows 1-3)
Other CV	Table 7 b (Row 4)
Respiratory/Allergy (antihistamines, corticosteroids, other asthma, smoking cessation)	Table 8 b
GI	Table 9 b
Neurologic/muscoskeletal	Table 11
Antibiotics	Table 12 b

F. ANALYTIC APPROACH

Analyses will first be performed at individual Data Partner sites. Site-specific estimates or aggregate data from each site will then be transferred to the Mini-Sentinel Operations Center (MSOC) for further analyses to create MS-wide estimates. The workgroup will work closely with the MSOC to develop distributed SAS programs that will enable the Data Partners to send to the MSOC 1) summary counts for descriptive analyses; and 2) SAS output and log files; and 3) a pre-specified aggregate-level dataset for additional statistical analyses. As described below, none of the analyses will require the Data Partners to transfer individual-level data.

1. Comparison of baseline characteristics

We will compare the baseline characteristics (see section V) of new users of individual APs (referent: risperidone) both at the individual-site level and across Data Partners, by requesting summary counts from each Data Partner (to obtain the site-specific results), and by combining these summary counts (to obtain the MS-wide results). At each site and for all sites combined, we will examine the between-group imbalances using standardized differences, calculated as the difference in means or proportions between two groups divided by the pooled estimate of the standard deviation of the two groups.

2. Calculation of incidence and incidence rate of type 2 diabetes

We will calculate the incidence per 1,000 persons and incidence rate per 1,000 person-years of type 2 diabetes and the 95% confidence intervals (CIs) separately for each SGA. Each Data Partner will send its site-specific summary counts to the MSOC, who will then sum up the number of type 2 diabetes cases and the persons or persons-years from all sites to obtain the MS-wide estimates.

END OF WORKPLAN 1

CHANGES IN WORKPLAN 2 IN RESPONSE TO FINDINGS FROM WORKPLAN 1

At the time of the posting of this protocol on the MS website, workplan 1 results showed significantly lower than expected event counts. Based these results the inferential analyses as originally planned (outlined in the workplan 2 specifications below) are not feasible. Instead, a modified workplan 2 will be implemented to generate descriptive data on antipsychotic utilization in the MSDD (see Addendum 1).

3. Crude analysis comparing the risk of type 2 diabetes of each SGA with risperidone

a. Site-specific estimates

We will work with the MSOC to develop a distributed SAS program that for each site will fit a Cox model separately for each AP-risperidone pair. The Cox model will include an indicator variable for drug exposure (e.g., 1 quetiapine 0 for risperidone) as the only independent variable. In both the crude and adjusted analyses, as well as both the site-specific and MS-wide analyses, the time scale for the Cox models will be time since the index date. The Data Partners will run the distributed program, and then send the SAS output and log files, and a pre-specified aggregate-level dataset to the MSOC for further analyses. The aggregate-level dataset will include one record per risk set, each is anchored by a type 2 diabetes case, and will be used in both the crude and adjusted analyses described below.

b. MS-wide estimates

We will use two methods to obtain the "crude" MS-wide estimates. (Note: Because the MS-wide analysis will adjust for Data Partner site, the estimates are not strictly "crude".) The first method is based on the case-centered logistic regression approach developed by Fireman et al. In this approach, we will use the pre-specified summary-level dataset sent by the Data Partners to fit a logistic model, separately for each drug pair of interest. In the quetiapine-risperidone pair, for example, the outcome variable in the logistic model will be whether the type 2 diabetes case was exposed to quetiapine, the independent variable – to be specified as an offset in the model – will be the log odds of the site-specific proportion of individuals in the risk set who were quetiapine users. The model will also include Data Partner site as a stratification variable. As shown by Fireman et al, such model maximizes the same likelihood as a stratified Cox regression model, and both yield the same parameter estimates.
In the second method, we will perform a meta-analysis using both fixed-effect and random-effects model to pool the crude site-specific estimates obtained from the SAS output files. The MS-wide HR will be calculated as a weighted average of the site-specific HRs using the inverse of the site-specific variance as the weight. As a secondary analysis, we will use the site-specific sample size as the weight.

4. Adjusted analysis comparing the risk of type 2 diabetes between individual SGAs (referent: risperidone)

a. Site-specific estimates

We will use a propensity score (PS)-stratified approach to obtain the adjusted site-specific estimates. The PS will be the probability of initiating risperidone, which will be estimated by a logistic regression model fit separately for each AP-risperidone pair at each site. Risperidone was chosen as the referent agent because it was the most commonly used SGA during the period from 2001 to 2005 and thus served as the referent agent in the Medicaid study. The PS model will include the variables referenced in section E as well as demographic and baseline healthcare utilization variables and will be common

across all Data Partners. This approach lets each site fit the same PS model but allows the coefficients to vary by site. Two propensity score specifications were developed 1) a comprehensive model and a more limited model (see Appendix B).

We will work with the MSOC to develop a distributed SAS program that will allow each site to fit 1) the PS model; 2) a PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in quintiles) as a stratification variable; and 3) a case-centered logistic model with the risk set of each type 2 diabetes case identified from individuals with the same PS quintile as the case.

All pre-specified subgroup analyses will use the PS estimated from the entire study cohort. The Data Partners will run the distributed program, and then send the SAS output and log files from these models to the MSOC.

b. MS-wide estimates

We will use the pre-specified aggregate-level dataset described above to fit a case-centered logistic regression model (which is equivalent to a stratified Cox model), separately for each drug pair of interest. The model will be identical to the one described in the "crude" MS-wide analysis, except that the log odds will be calculated at each site among individuals in the same PS quintile as the case who were at risk of type 2 diabetes at the time the case occurred.

G. SUBGROUP/SENSITIVITY/DOSE-RESPONSE ANALYSES

1. Sensitivity analyses for exposure definition:
   (1) 30 days follow-up added after index AP discontinuation (base case)
   (2) 30 days follow-up added after index AP discontinuation or 2nd APM/APM switch
   (3) 90 days follow-up added after index AP discontinuation
   (4) No days added after index AP discontinuation or 2nd APM/APM switch
   (5) 180 day intent to treat (index exposure carried forward until day 180)
   (6) 365 day intent to treat (index exposure carried forward until day 365)
   (7) base case with secondary type 2 diabetes definition
   (8) base case based on secondary propensity score

2. 365 day look-back period (base case only)

3. Subgroup analyses:
   - Age group (2-5, 6-12, 13-17, 18-24 years of age)
   - Sex
   - Excluding patients with a hospitalization in the 29 days immediately prior to the index date.
   - APM Indication (ADHD/conduct disorder, schizophrenia, bipolar disorder, PDD/MR, tic disorder)
   - Index Dose
   - low vs. high > 75mg CPZ equivalent (reflects median dose of all study APMs; conversion factors: Andreasen, 2010: aripiprazole: 15.6, olanzapine: 21.1, quetiapine: 0.7, risperidone: 75.8, ziprasidone: 1.98)

4. Dose Response
   - (APM specific tertiles APM; computed for index dose and last observed dose)

END OF WORKPLAN 2

III. SUBPROJECT 2A

A. STUDY COHORT

The study cohort for exploratory Subproject 2A is entirely nested within the APY cohort developed in Subproject 1. The APY Subproject 2A cohort is comprised of patients between the ages of 2 and 24 who newly-initiated an AP between January 1, 2006 and December 31, 2011 and who meet the Subproject 1 inclusion and exclusion criteria (see section B.II). MSN DPs contributing MSDD patients to the APY cohort are shown in Table 16. The timeframe of the APY cohort for Subproject 2A is more restrictive than the timeframe for Subproject 1 because January 1, 2006 is the earliest date laboratory results and BMI data are available in the MSDD.

B. EXPOSURE ASSESSMENT

New initiation of an AP is the exposure of interest. The definition and assessment of new initiation of an AP for Subproject 2A is the same as used in Subproject 1. The index date is defined as the date of first dispensing of the newly-initiated AP.

Table 16. Subprojects 1 and 2A Data Availability in the MSDD by Data Partner

Data Partner	Contributed to Subproject 1A APY Cohort	Contributed to Subproject 2A Cohort Data		
		Height/ Weight	HbA1c	Glucose, fasting and/or random
#1	√		√	√
#2	√		√	√
#3	√			
#4	√	√	√	√
#5	√			
#6	√			
#7	√			
#8	√			
#9	√	√	√	√
#10	√	√	√*	√*
#11	√	√	√	√
#12	√	√	√	√
#13	√	√	√	√
#14	√	√	√	√
#15	Did not participate in this Workgroup activity			
#16	√	√	√	√
#17	√			
* Anticipated to be available prior to date needed				

C. CRUDE OUTCOME ASSESSMENT

The "outcome" of interest is the presence (and frequency) or absence of BMI and GLU results among APY cohort members. As the number of APY cohort members with the potential to have BMI and/or GLU data in the MSDD is less than the total number of members in the APY cohort (partly because not all DPs can provide BMI or laboratory data and partly because of the date range of BMI and laboratory data available in the MSDD), the count of all members entering the APY cohort between January 1, 2006 and December 31, 2011 will first be identified at each DP and summed across DPs to yield the total number of members in the APY Subproject 2A sub-cohort (Figure 1). Second, the count of members in the APY sub-cohort at DPs with GLU and with BMI+GLU results data potentially available in the MSDD with be identified (from DP that have populated the MSDD with BMI and/or GLU results data)(Table 16.). These counts will be summed across DPs to yield the denominators of the APY GLU and the APY BMI+GLU sub-cohorts (Figure 1). Note that BMI and GLU are considered outcomes for this current work (Subproject 2A). However, for the planned extension of Subproject 1 that includes BMI and GLU result values as baseline confounders (i.e., Subproject 2B), BMI and GLU values would be covariates.

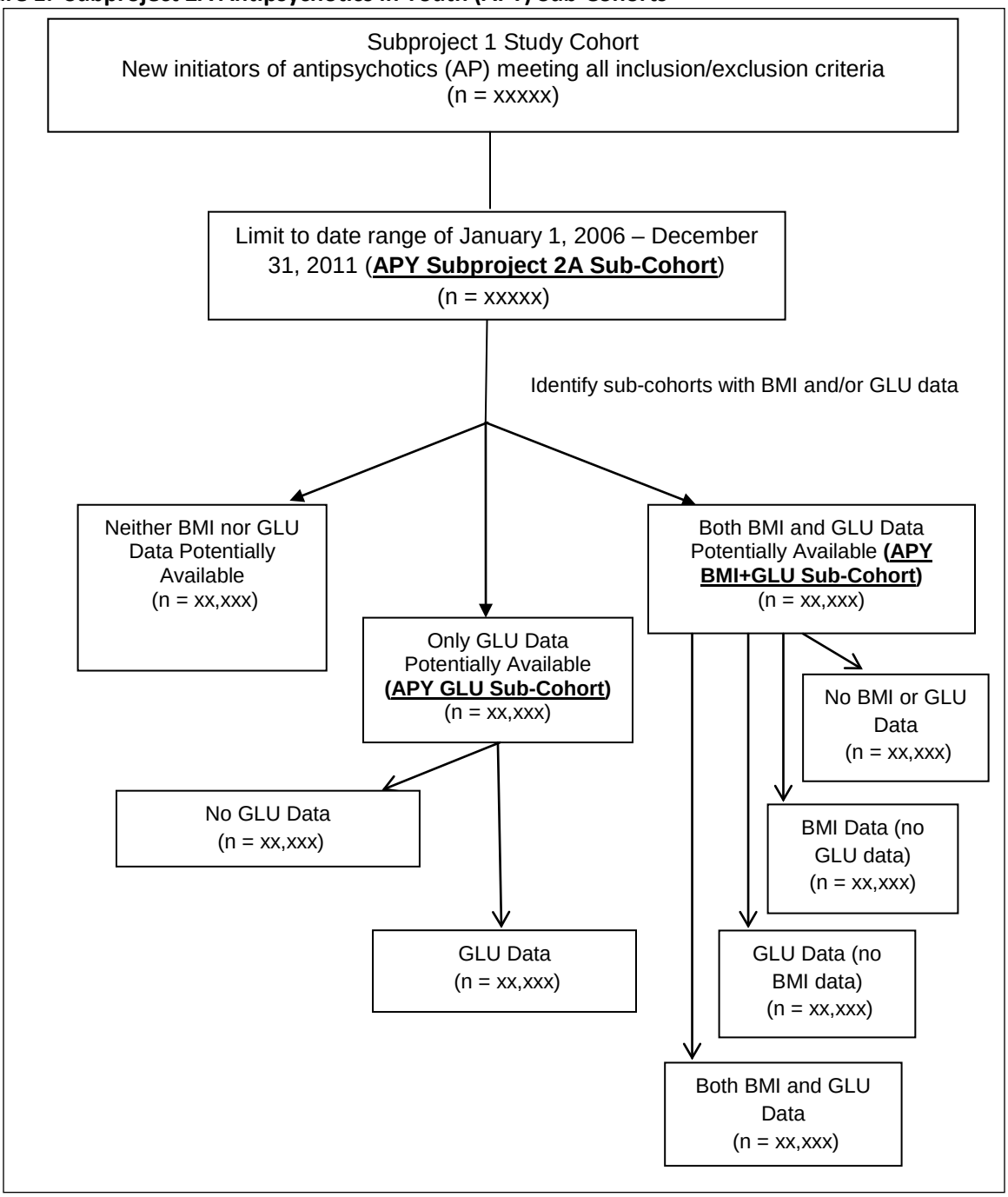
Height and weight data needed to compute BMI, as well as HbA1c and fasting/random blood glucose data, for sub-cohort members will then be requested from applicable DPs (Table 16.). This step provides both the outcomes data to be explored and the crude numerators of APY BMI+BLU and APY GLU sub-cohort members with at least one weight, height, HbA1c, and/or fasting/random blood glucose.

D. OUTCOME DATA EXPLORATION

Distributed SAS code will be developed (by KPCO and KPNW DCC), tested (by willing DP), quality checked (MSOC to contract) and implemented (at DPs shown in Table 16. to return the data needed for the crude outcome assessment detailed above. Implementation of the programming code will also result in return of the data files needed to explore the completeness and timing of BMI and GLU data relative to the index date.

To maintain deidentified data, although the SAS programs will access individual-level data at the participating DPs, the code will be written such that only relative dates will be returned for analysis. That is, all BMI or GLU result dates will be calculated relative to the index date (initiation of AP agent) for each cohort member. In the dataset returned for analysis, all BMI and GLU result dates will be identified only by the number of days prior to or after (relative to) the index date.

Figure 1. Subproject 2A Antipsychotics in Youth (APY) Sub-Cohorts



1. Exploration of baseline BMI data availability, completeness, and timing

In addition to completing the crude outcome assessment of data availability detailed above, use the height and weight values obtained on the date(s) closest to the date of AP initiation (e.g., the index date) to explore the availability of BMI data according to each of the following definitions:

Primary Definition: Numbers and proportion of members of the ASY sub-cohort with baseline height and weight taken on

1. The same day and within the date range inclusive of 31 days prior to through 3 days after the index date.

Secondary Definitions: Numbers and proportion of members of the ASY sub-cohort with baseline height and weight taken on

2. The same day and within the date range of 60 days prior to through 3 days after the index date.
3. The same day and within the date range of 90 days prior to through 3 days after the index date.
4. Different days and within the date range of 31 days prior to through 3 days after the index date.
5. Different days and within the date range of 60 days prior to through 3 days after the index date.
6. Different days and within the date range of 90 days prior to through 3 days after the index date.
7. The same or different days and within the date range of 31 days prior to through 31 days after the index date.
8. The same or different days and within the date range of 60 days prior to through 31 days after the index date.
9. The same or different days and within the date range of 90 days prior to through 31 days after the index date

Tertiary Definitions: Applying definitions 1 – 3 and 7 – 9 above, determine the additional members of the ASY sub-cohort that would be included if only baseline weight (no height) was required.

Prepare Tables to display the results obtained from the BMI data availability and the primary, secondary, and tertiary BMI data completeness and timing explorations. The Tables should provide data availability based on the entire date range of interest, by year, by individual drug initiated, by individual DP, across all DPs, by age, and by gender. Examples of these result tables are shown below. Comparisons of all the potential BMI/weight definitions may not be needed in all the tables that follow as data explorations in early tables may suggest a more limited number to explore more fully.

Example Table a. BMI Data Availability across all AP Agents by Individual DP (could reverse row/column headers)

BMI	DP without BMI	DP with BMI Available			Total Across all ASY Cohort (n = xxx)	Total Across DP with BMI Available (n = xxx)
	DP1 (n = xxx)	DP1 (n = xxx)	DP 2 (n = xxx)	DP…N (n = xxx)		
Same day, 31 d prior through 3 d after	N (%)					
Same day 60 d prior through 3 d after						
Etc, based on secondary definitions						
Weight only						
Same day, 31 d prior through 3 days after						
Same day, 60 days prior through 3 days after						
Etc base on secondary definitions						

Example Table b. BMI Data Availability across all DP with BMI in MSCDM by individual AP Agent

BMI	Risperidone (n =xxx)	Quetiapine (n = xxx)	Olanzapine	Aripiprazole	Ziprasidone	Total Across All AP Agents with BMI Available (n = xxx)
Same day, 31 d prior to 3 days after	N (%)					
Same day, 60 days prior through 3 days after						
ETC. (same as Table a)						

Example Table c. BMI Availability across DP with BMI in MSCDM by Age Group (note: Age categories are draft. Categories are subject to change based on results of cohort creation in Subproject 1)

BMI	Age in Years 2 - 4	Age in Years 5 - 9	Age in Years 10 - 12	Age in Years 13 - 15	Age in Years 16 - 18	Age in Years 19 - 24	Total Across all DP with BMI Available (n = xxx)
Same day, 31 d prior to 3 days after	N (%)						
Same day, 60 days prior through 3 days after							
ETC. (Same as Table a)							

Example Table d. BMI Availability across DP with BMI in MSCDM by Gender

BMI	Male	Female	Unknown	Total Across all DP with BMI Available (n = xxx)
Same day, 31 d prior to 3 days after	N (%)			
Same day, 60 days prior through 3 days after				
ETC. (Same as Table a)				

Example Table e. BMI Availability by Individual Drugs by Year (anticipate separate tables for each of risperidone, quetiapine, olanzapine aripiprazole, and ziprazidone if sufficient n for each)

BMI	2006 (n =xxx)	2007	2008	2009	2010	Total Across All AP Agents with BMI Available (n = xxx)
Same day, 31 d prior to 3 days after	N (%)					
Same day, 60 days prior through 3 days after						
ETC. (same as Table a)						

2. Exploration of baseline HbA1c, fasting glucose, and random glucose data availability, completeness, and timing

In addition to completing the crude outcome assessment of data availability detailed above, use the HbA1c, fasting glucose, and random glucose values obtained on the date(s) closest to the index date (if more than one result or set of results is available) and within the hierarchy of HbA1c > fasting glucose > random glucose to explore the availability of GLU data according to each of the definitions provided below. Further, if two GLU result values are obtained on days equally distant from the index date (e.g., results obtained 1 day pre-index and also 1 day post-index), the pre-index result value will be used, applied after the hierarchy of HbA1c > fasting glucose > random glucose has been applied.

Primary Definitions: Numbers and proportion of members of the ASY sub-cohort with the following baseline GLU data

1. HbA1c obtained within the date range inclusive of 14 days prior to through 3 days after the index date.
2. Fasting glucose obtained within the date range inclusive of 14 days prior to through 3 days after the index date.
3. Random glucose obtained within the date range inclusive of 14 days prior to through 3 days after the index date.

Secondary Definitions: Numbers and proportion of members of the ASY sub-cohort with the following baseline GLU data

4. HbA1c obtained within the date range inclusive of 45 days prior to through 3 days after the index date.
5. Fasting glucose obtained within the date range inclusive of 45 days prior to through 3 days after the index date.
6. Random glucose obtained within the date range inclusive of 45 days prior to through 3 days after the index date.
7. HbA1c obtained within the date range inclusive of 90 days prior to through 3 days after the index date.
8. Fasting glucose obtained within the date range inclusive of 90 days prior to through 3 days after the index date.
9. Random glucose obtained within the date range inclusive of 90 days prior to through 3 days after the index date.

Prepare Tables to display the results obtained from the GLU data availability and the primary and secondary GLU data completeness and timing explorations. The Tables should provide data availability based on the entire date range of interest, by year, by individual drug initiated, by individual DP, across all DPs, by age, and by gender. Examples of these result tables are shown below.

Example Table f. GLU Data Availability across all AP Agents by Individual DP (could reverse row/column headers)

GLU	DP without GLU	DP with GLU Available			Total Across all ASY Cohort (n = xxx)	Total Across DP with GLU Available (n = xxx)
	DP1 (n = xxx)	DP1 (n = xxx)	DP 2 (n = xxx)	DP…N (n = xxx)		
14 days prior to through 3 days after index date						
HbA1c only	N (%)					
Fasting glucose only						
Random glucose only						
HbA1c and fasting glucose						
HbA1c and random glucose						
HbA1c, fasting glucose, and random glucose						
Fasting glucose and random						

GLU	DP without GLU	DP with GLU Available			Total Across all	Total Across
glucose						
Any HbA1c (with or without other glucose)						
Any fasting glucose (without HbA1c)						
Any random glucose (without HbA1c or fasting glucose)						
45 days prior to through 3 days after the index date						
HbA1c only						
Fasting glucose only						
Random glucose only						
HbA1c and fasting glucose						
ETC. using row descriptions as above						
90 days prior to through 3 days after the index date						
HbA1c only						
Fasting glucose only						
Random glucose only						
HbA1c and fasting glucose						
ETC. using row descriptions as above						

Example Table g. GLU Data Availability across all DP with GLU in MSCDM by individual AP Agent

GLU	Risperidone (n =xxx)	Quetiapine	Olanzapine	Aripiprazole	Ziprasidone	Total Across All AP Agents with GLU Available (n = xxx)
14 days prior to through 3 days after index date						
HbA1c only						
Fasting glucose only						
Etc., as in Table f						

Example Table h. GLU Availability across DP with GLU in MSCDM by Age Group (note: Age categories are draft. Categories are subject to change based on results of cohort creation in Subproject 1)

GLU	Age in Years 2 - 4	Age in Years 5 - 9	Age in Years 10 - 12	Age in Years 13 - 15	Age in Years 16 - 18	Age in Years 19 - 24	Total Across all DP with GLU Available (n = xxx)
14 days prior to through 3 days after index date							
HbA1c only							
Fasting glucose only							
Etc., as in Table f							

Example Table i. GLU Availability across DP with GLU in MSCDM by Gender

BMI	Male	Female	Unknown	Total Across all DP with GLU Available (n = xxx)
14 days prior to through 3 days after index date				
HbA1c only				
Fasting glucose only				
Etc., as in Table f				

Example Table j. GLU Availability by Individual Drugs by Year (anticipate separate tables for each of risperidone, quetiapine, olanzapine aripiprazole, and ziprazidone if sufficient n for each)

BMI	2006 (n =xxx)	2007	2008	2009	2010	Total Across All AP Agents with GLU Available (n = xxx)
14 days prior to through 3 days after index date						
HbA1c only	N (%)					
Fasting glucose only						
Etc., as in Table f						

3. Exploration of baseline HbA1c, fasting glucose, and random glucose baseline data availability, completeness, and timing in conjunction with baseline BMI data availability, completeness, and timing

In addition to completing the separate assessments of GLU and BMI data availability detailed above, use the available data to explore the availability of both BMI and GLU data, BMI data alone, GLU data alone, and neither BMI nor GLU data in the cohort. To this end, we will request BMI and GLU data both prior to antipsychotic drug initiation up to -365 days and post antipsychotic drug initiation up to + 365 days from participating DPs as part of data quality checks. The data post antipsychotic drug initiation will additionally serve as an initial feasibility assessment of subproject 2B.

Prepare Tables to display the results obtained from the BMI and GLU data availability and the primary BMI and GLU data completeness and timing explorations. The Tables should provide data availability based on the entire date range of interest, by year, by individual drug initiated, by individual DP, across all DPs, by age, and by gender. Examples of these result tables are shown below. Comparisons of all the potential definitions may not be needed in all the tables that follow as data explorations will likely suggest a limited number to explore more fully.

Example Table k. BMI and GLU Data Availability across all AP Agents by Individual DP (could reverse row/column headers)

BMI and GLU	DP without BMI or GLU Available	DP with BMI and GLU Available		DP with only GLU Available		Total Across all ASY Cohort (n = xxx)
	DP1 (n = xxx)	DP1 (n = xxx)	DP 2 (n = xxx)	DP1 (n = xxx)	DP1 (n= xxx)	
BMI same day, 31 d prior through 3 d after; HbA1c 14 days prior to through 3 days after	N (%)					
BMI same day, 31 d prior through 3 d after; fasting glucose 14 days prior to through 3 days after						
BMI same day, 31 d prior through 3 d after; random glucose 14 days prior to through 3 days after						

Example Table l. BMI and GLU Data Availability across all DP with BMI and GLU in MSCDM by individual AP Agent

BMI and GLU	Risperidone (n =xxx)	Quetiapine (n = xxx)	Olanzapine	Aripiprazole	Ziprasidone	Total Across All AP Agents with BMI and GLU Available (n = xxx)
BMI same day, 31 d prior through 3 d after; HbA1c 14 days prior to through 3 days after	N (%)					
BMI same day, 31 d prior through 3 d after; fasting glucose 14 days prior to through 3 days after						
BMI same day, 31 d prior through 3 d after; random glucose 14 days prior to through 3 days after						

Example Table m. BMI and GLU Availability across DP with BMI and GLU in MSCDM by Age Group (note: Age categories are draft. Categories are subject to change based on results of cohort creation in Subproject 1)

BMI and GLU	Age in Years 2 - 4	Age in Years 5 - 9	Age in Years 10 - 12	Age in Years 13 - 15	Age in Years 16 - 18	Age in Years 19 - 24	Total Across all DP with BMI and GLU Available (n = xxx)
BMI same day, 31 d prior through 3 d after; HbA1c 14 days prior to through 3 days after	N (%)						
BMI same day, 31 d prior through 3 d after; fasting glucose 14 days prior to through 3 days after							
BMI same day, 31 d prior through 3 d after; random glucose 14 days prior to through 3 days after							

Example Table n. BMI and GLU Availability across DP with BMI and GLU in MSCDM by Gender

BMI and GLU	Male	Female	Unknown	Total Across all DP with BMI and GLU Available (n = xxx)
BMI same day, 31 d prior through 3 d after; HbA1c 14 days prior to through 3 days after	N (%)			
BMI same day, 31 d prior through 3 d after; fasting glucose 14 days prior to through 3 days after				
BMI same day, 31 d prior through 3 d after; random glucose 14 days prior to through 3 days after				

Example Table o. BMI and GLUD Availability by Individual Drugs by Year (anticipate separate tables for each of risperidone, quetiapine, olanzapine aripiprazole, and ziprazidone if sufficient n for each)

BMI and GLU	2006 (n =xxx)	2007	2008	2009	2010	Total Across All AP Agents with BMI and GLU Available (n = xxx)
BMI same day, 31 d prior through 3 d after; HbA1c 14 days prior to through 3 days after	N (%)					
BMI same day, 31 d prior through 3 d after; fasting glucose 14 days prior to through 3 days after						
BMI same day, 31 d prior through 3 d after; random glucose 14 days prior to through 3 days after						

E. ASSESSMENT OF MISSING DATA AND METHODS TO HANDLE MISSING DATA

Based on the results of the data exploration detailed above and discussion among workgroup members, we will provide written assessments and recommendations of:

1. Whether BMI data are adequate for use as covariates in adjusted models of AP and risk of type 2 diabetes
2. Whether GLU data are adequate for use as covariates in adjusted models of AP and risk of type 2 diabetes
3. For each of the data elements, BMI and GLU, specific recommendations will include
    - DP selection (if not all will be included and rationale).
    - Discussions (with Work Group) of limitations any selections may impose on subsequent analyses.
    - Analytic methods and potential implications for distributed methods.

Recommendations about whether BMI and/or GLU data are adequate to use in further analysis will be based on the following:

1. Whether the proportion of missing data differs by DP, year, age, gender, and/or individual AP agent, suggesting that data are not missing at random (MAR).
2. Whether the resulting proportion of missing and the proposed method of analysis are likely to be acceptable in a publication (based on discussions with the Work Group, we will consider defining an apriori proportion of acceptable data missing overall and by DP (e.g., 10%, 20%, 30%).
3. Impacts of limiting data to selected DPs, years, and/or select antipsychotic agents.
4. Consideration of reasons for missing data. This can include for example, illogical result values, variation in data capture within individual DPs (e.g., selected DPs may not have lab data from all vendors), and variability in treatment protocols/practices across DPs.
5. Potential for missing data to bias the results and/or restrict inferences that can be made about the results.

Although final recommendations for handling missing data will be predicated upon the results of the assessment of missingness (e.g., the pattern of missingness), recommendations for methods to handle missing data will be provided. It is feasible that both a complete case analysis and an analysis using multiple imputation techniques, or maximum likelihood estimation methods may be worth comparing. Missing data models will need to be adapted for implementation using distributed data programs and that requirement may influence decisions.

IV. APPENDIX A

A. EXCLUSION CONDITIONS AND ILLNESSES

1. Somatic exclusion illness
2. Endpoint-related exclusion illness
3. Pregnancy and polycystic ovarian syndrome exclusion

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
1. Somatic exclusion illness				
		ICD-9 Code(s)	**Medication(s)**	**Procedure Code(s)**
Sickle cell disease	7a	282.6x		
Cystic fibrosis	7a	277.0x	DORNASE-ALFA	
Cerebral palsy	7a	343.x		
Cancer	7a	140.xx – 172.xx 174.xx – 209.xx 230.xx – 239.xx (EXCEPT 237.7x [neurofibromatosis] and 233.1x [cervical cancer *in situ*], V58.1x)	Antineoplastic agents (systemic only): **ALKYLATING AGENTS**: BUSULFAN, CHLORAMBUCIL, CYCLOPHOSPHAMIDE, MECHLORETHAMINE HYDROCHLORIDE, MITOMYCIN, CISPLATIN, CARMUSTINE, DACARBAZINE, URACIL MUSTARD, PIPOBROMAN, IFOSFAMIDE, TEMOZOLOMIDE, STREPTOZOCIN **ANTIMETABOLITES:** MERCAPTOPURINE, CYTARABINE, MELPHALAN HYDROCHLORIDE, THIOGUANINE, FLUOROURACIL, FLOXURIDINE, ETOPOSIDE, FLUDARABINE PHOSPHATE, CAPECITABINE, GEMCITABINE **ANTIBIOTICS:** BLEOMYCIN SULFATE, DOXORUBICIN HYDROCHLORIDE, DAUNORUBICIN HYDROCHLORIDE, IDARUBICIN HYDROCHLORIDE, MITHRAMYCIN, ACTINOMYCIN, MITOXANTRONE	**CPT:** 36640, 51720, 61517, 96450, 36823, 99601, 99602, 96420, 96421, 96422, 96423, 96424, 96425, 96405, 96406, 96400, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 50391, 96445, 96440, 96530, 95990, 95991, 96520, 96542, 96400, 96545, 96549, 50391

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
			HYDROCHLORIDE **PLANT ALKALOIDS:** VINCRISTINE SULFATE, VINBLASTINE SULFATE, PACLITAXEL, VINORELBINE, DOCETAXEL, INTERFERON ALPHA, ASPARAGINASE, PROCARBAZINE HYDROCHLORIDE, LOMUSTINE, MITOTANE, TESTOLACTONE, AMINOGLUTETHIMIDE, CALUSTERONE, LEUPROLIDE ACETATE, FLUTAMIDE, NILUTAMIDE, CARBOPLATIN, GOSERELIN ACETATE, LEVAMISOLE, ESTRAMUSTINE PHOSPHATE SODIUM, ALTRETAMINE, PIPOBROMAN, PENTOSTATIN, ALDESLEUKIN, TENIPOSIDE, CLADRIBINE, BICALUTAMIDE, ANASTROZOLE, TRIMETREXATE, LETROZOLE, ALITRETINOIN, IRINOTECAN,HCL, BEXAROTENE, TRETINOIN, IMATINIB, TOPOTECAN, PEGASPARGASE, PORFIMER, ARSENIC TRIOXIDE, FULVESTRANT, GEFITINIB, RITUXIMAB, OXALIPLATIN, ALEMTUZUMAB, ALTRETAMINE,PORFIMER **ANTIESTROGEN:** TOREMIFENE CITRATE, TAMOXIFENE CITRATE **OTHER ANTINEOPLASTICS:** AZACITIDINE, BORTEZOMIB, CETUXIMAB, EPIRUBICIN, ERLOTINIB, PEMETREXED, TRASTUZUMAB, SORAFENIB, SUNITINIB, THIOTEPA, VALRUBICIN, URACIL MUSTARD A.K.A. URAMUSTINE, TRIPTORELIN, EXEMESTANE, DENILEUKIN, DIFTITOX, THALIDOMIDE, IBRITUMOMAB, GEMTUZUMAB , CLOFARABINE **Cyto-protective agents:** AMIFOSTINE, DEXRAZOXANE, MESNA	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
HIV	7a	042, 043, 044, 079.53, V08	Antiretrovirals (systemic only) **NON-NUCLEOSIDE REVERSE-TRANSCPRIPTASE INHIBITORS** NEVIRAPINE DELAVIRDINE MESYLATE EFAVIRENZ **NUCLEOSIDE REVERSE-TRANSCPRIPTASE INHIBITORS** ZIDOVUDINE DIDANOSINE ZALCITABINE (DDC) STAVUDINE LAMIVUDINE ABACAVIR TENOFOVIR EMTRICITABINE EMTRICITABINE-TENOFOVIR ABACAVIR-LAMIVUDINE LAMIVUDINE-ZIDOVUDINE ABACAVIR-LAMIVUDINE- ZIDOVUDINE **PROTEASE INHIBITORS** INDINAVIR SULFATE RITONAVIR SAQUINAVIR SAQUINAVIR MESYLATE NELFINAVIR MESYLATE AMPRENAVIR LOPINAVIR-RITONAVIR ATAZANAVIR SULFATE FOSAMPRENAVIR CALCIUM TIPRANAVIR **INFUSION INHIBITORS** ENFUVIRTIDE	
Hepatitis B,C	7a	070.2x, 070.3x, 070.51, 070.54, 070.7x	INTERFERON ALFA-2A, INTERFERON ALPHA-2B, INTERFERON ALFA-1, PEGINTERFERON ALPHA-2B, PEGINTERFERON ALPHA-2A, TELBIVUDINE, ENTECAVIR, LAMIVUDING, ADEFOVIR	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
Tuberculosis	7a	010.x-018.x	ISONIAZID, RIFAMPIN, PYRAZINAMIDE, ETHAMBUTOL, RIFAPENTINE,ETHIONAMIDE, KANAMYCIN,CAPREOMYCIN, PARA-AMINOSALICYLIC, CYCLOSERINE	
Organ transplant	7a	996.8x, V42.1x, V42.6x, V42.7x, V42.81, V42.83, V42.0x	Immunosuppressives (systemic only): AZATHIOPRINE CYCLOSPORINE TACROLIMUS (EXCEPT DERM PREPARATION) MYCOPHENOLATE SIROLIMUS DACLIZUMAB ANTITHYMOCYTE IMMUNE BEVACIZUMAB , BASILIXIMAB MUROMONAB	**CPT:** 32851, 32852, 32853, 32854, 33935, 33940, 33945, 38240, 38241, 47135, 47136, 48554, 48556, 50320, 50360, 50365, 50370, 50380 **ICD-9-CM:** 33.5x, 33.6, 37.5x, 50.5x, 52.8x, 55.6x
Liver failure	7a	570, 571.xx, 572.x, 573.x, 997.4		
Renal dialysis/ ESRD	7a	285.21, 585.5, 585.6, 996.1, 996.73, V45.1, V56.0		**CPT:** 36832, 36833, 36831, 90918-90925, 90989, 90993, 90937, 90999, 90935, 90937, 90945, 90947, 90980 **ICD-9-CM:** 39.95, 54.98
Respiratory failure	7a	518.81, 518.5, 518.82, 518.83, 518.84, 519.0x, V44.0, V55.0, 427.50, 799.10, 415.0x, 416.xx		**CPT:** 31500, 94656, 94657, 94005 **ICD-9-CM:** 96.70, 96.71, 96.72

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
Fatal metabolic disease	7a	270.xx, 271.xx (except 271.3 [lactose intolerance])		
Aplastic anemia	7a	284.xx		
Congenital immune deficiencies	7a	279.04, 279.06, 279.2x		
Down syndrome	7a	758.0x		
Lethal chromosomal abnormalities	7a	758.1x, 758.2x, 758.3 x (note, individual disorders listed separately below)		
Trisomy 13	7a	758.1		
Trisomy 18	7a	758.2		
Autosomal deletion syndrome	7a	758.3x		
serious neuromuscular	7a	340, 335.20, 335.21, 333.4, 344.0x, 344.1, 344.89, 344.9		
Hospice care	7a	V667		**CPT:** G0182, G0065, 99377, 99378
2. Endpoint-related exclusion illness				
Diabetes	7c	250.xx 357.2	**INSULIN** INSULIN INJ INSULIN BEEF LENTE BEEF PROTAMINE ZINC REGULAR LENTE	Diabetes monitoring: **CPT:** 83036 83037 82985

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
			SEMILENTE	86341
			ULTRALENTE	83525
			ISOPHANE (NPH)	82943
			PORK REGULAR	82945-82948
			PORK LENTE	82950-82953
			PORK NPH	80047-80050
			PORK PROTAMINE ZINC	80053
			PROTAMINE ZINC	80054
			GLOBIN ZINC	80069
			HUMAN INSULIN (SEMI-SYNTHETIC)	S9140
			MISC INSLULIN PREPARATIONS	S9141
			INSULIN GLARGINE	S9455
			INJECTIBLE NON-INSULIN HYPO-	S9460
			GLYCEMIC AGENTS	S9465
			PRAMLINTIDE ACETATE	G0108
			ORAL HYPOGLYCEMICS	G0109
			METFORMIN	E0607
			PHENFORMIN	E0609
			CHLORPROPAMIDE	E0784
			TOLAZAMIDE	E2100
			TOLBUTAMIDE	E2101
			ACETOHEXAMIDE	
			GYLBURIDE	
			GLIPIZIDE	
			ACARBOSE	
			GLIMEPIRIDE	
			TROGLITAZONE	
			REPAGLINIDE	
			MIGLITOL	
			ROSIGLITAZONE MALEATE	
			PIOGLITAZONE	
			MATEGLINIDE	
			EXENATIDE	
			SITAGLIPTIN PHOSPHATE	
			ORAL HYPOGLYCEMIC COMBINATIONS	
			GLYBURIDE-METFORMIN	
			ROSIGLITAZONE-METFORMIN	
			METFORMIN-GLIPIZIDE	
			METFORMIN-PIOGLITAZONE	
			ROSIGLITAZONE-GLIMEPIRIDE	
			SITAGLIPTIN-METFORMIN	
			INSULIN-INH	
			REGULAR HUMAN INSULIN	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
3. Pregnancy and polycystic ovarian syndrome exclusion				
Pregnancy	7d	779.6, 630-632, 633.xx-677.xx, 760.xx-763.xx, V30.xx-V39.xx, V22.x-V24.x, V27.x, V28.x,		**CPT:** 36460,76946, 59000-59899, 76801-76828 **ICD-9-CM:** 66.62, 66.11, 69.0x, 69.51, 72.xx-75.xx, 87.71,88.78
Polycystic ovarian syndrome	7e	256.4x		

V. APPENDIX B

A. PROPENSITY SCORE VARIABLES

1. Comprehensive propensity score

Row #	Variable	Definition
	Demographic	
4	Sex (female	Table 14
5	Race/Ethnicity (white, non-hispanic)	Table 14
6	Race/Etnicity (black, non-hispanic)	Table 14
7	Race/Etnicity (hispanic)	Table 14
8	Race/Etnicity (other)	Table 14
9	age (11 categories; 10 dummy variables)	n/a
	Psychiatric Diagnoses	
11	Bipolar Disorder	Table 4
12	Mood disorders, major depression	Table 4
13	Other mood disorders	Table 4
14	ADHD	Table 4
15	Other disruptive behavior disorders	Table 4
16	Impulse control disorders	Table 4
17	Learning disability, other	Table 4
18	Sleep disorder	Table 4
19	Anxiety disorder/phobia	Table 4
20	Personality disorders	Table 4
21	Acute stress, adjustment disorder	Table 4
22	Ethanol, diagnosed	Table 4
23	Other substance abuse, diagnosed	Table 4
24	Somatoform spectrum disorders	Table 4
25	Learning disorder/ developmental delay (non-PDD, non-MR)	Table 4
26	Other psychiatric	Table 4
27	Psychiatric symptoms	Table 4
28	Injury, self-inflicted or undetermined intent	Table 4
29	Schizophrenia, schizophrenia-like psychotic disorders	Table 4
30	Tic disorder	Table 4
31	Pervasive developmental disorders	Table 4
32	Mental Retardation	Table 4
33	Organic Psychosis	Table 4
34	Tourette's	Table 4

Row #	Variable	Definition
	Somatic Medical Care Encounters	
36	**OB/GYN**	
37	Pregnancy, prior	Table 5a
38	Pregnancy, screen	Table 5a
39	Sterilization	Table 5a
40	Contraception management	Table 5a
41	Menstruation, absence	Table 5a
42	Menstruation, infrequent	Table 5a
43	Menstruation, irregular	Table 5a
44	Menstruation, heavy/frequent	Table 5a
45	Menstruation, other disorder	Table 5a
46	Cervical cancer screening	Table 5a
47	Cervical dysplasia	Table 5a
48	Ovarian cysts	Table 5a
49	Other OB/GYN	Table 5a
50	**Metabolic and related**	
51	Obesity, not morbid	Table 6a
52	Obesity, morbid	Table 6a
53	Abnormal weight gain	Table 6a
54	Acanthosis nigricans	Table 6a
55	Weight management program	Table 6a
56	Insulin resistance/metabolic syndrome	Table 6a
57	Metabolic panel	Table 6a
58	Diabetes screen	Table 6a
59	Hyperlipidemia	Table 6a
60	Hyperlipidemia screen	Table 6a
61	Hypothyroidism	Table 6a
62	Hypothyroid screen	Table 6a
63	Hyperthyroidism	Table 6a
64	Other endocrine	Table 6a
65	**Cardiovascular**	
66	Hypertension	Table 7a
67	Other cardiovascular disease	Table 7a
68	Symptoms, possibly cardiovascular	Table 7a
69	**Respiratory/allergy**	
70	Anaphylaxis	Table 8a
71	Allergic reaction	Table 8a
72	Asthma	Table 8a
73	Wheezing	Table 8a
74	Asphyxia	Table 8a
75	Sleep apnea	Table 8a
76	Shortness of breath	Table 8a

Row #	Variable	Definition
77	Smoking, diagnosed	Table 8a
78	**Gastrointestinal disease**	
79	Abdominal pain	Table 9a
80	Gastroesophageal reflux	Table 9a
81	Other upper GI disease	Table 9a
82	**Neurologic/musculoskeletal**	
83	Seizure disorder	Table 10a
84	Migraine	Table 10a
85	Neuropathic pain	Table 10a
86	Back pain	Table 10a
87	Osteoarthritis	Table 10a
88	Other musculoskeletal symptoms	Table 10a
89	Other rheumatologic disease	Table 10a
90	Injury, other	Table 10a
91	**Other**	
92	Urinary tract infection	Table 12
93	Other infections	Table 12
94	Malaise and Fatigue	Table 12
95	Hypersomnia	Table 12
96	Other organic sleep disorder	Table 12
97	Edema	Table 12
98	Cholecystitis, cholelithiasis	Table 12
99	Nephrotic syndrome	Table 12
	Prescription Fills	
101	**Psychotropic**	
102	Lithium	Table 13
103	Anticonvulsant, primary	Table 13
104	Anticonvulsant, secondary	Table 13
105	SSRI/SNRI/mirtazapine	Table 13
106	TCA and heterocyclic compounds	Table 13
107	Antidepressants, MAOI	Table 13
108	Antidepressants, trazodone-related	Table 13
109	Antidepressants, bupropion	Table 13
110	Psychostimulants	Table 13
111	Alpha-agonists, used for ADHD	Table 13
112	Benzodiazepines	Table 13
113	Other GABA agonists	Table 13
114	Other anxiolytic/hypnotic, newer	Table 13
115	Other anxiolytic/hypnotic, older	Table 13
116	Other psychiatric drugs	Table 13
117	**OB/GYN**	
118	Oral contraceptives	Table 5b

Row #	Variable	Definition
119	Other contraception	Table 5b
120	Medroxyprogesterone	Table 5b
121	**Metabolic and related**	
122	Lipid-lowering drugs	Table 6b
123	Hypothyroid treatment	Table 6b
124	Antithyroid agents	Table 6b
125	Anorexiants	Table 6b
126	**Cardiovascular**	
127	Thiazide diuretic	Table 7b
128	ACE inhibitor/ARBs	Table 7b
129	Anti-hypertensives, other	Table 7b
130	Other cardiovascular	Table 7b
131	**Respiratory/allergy**	
132	Antihistamines, non-sedating	Table 8b
133	Antihistamines, other	Table 8b
134	Corticosteroids	Table 8b
135	Asthma medications, other	Table 8b
136	Smoking cessation	Table 8b
137	**Gastrointestinal disease**	
138	Histamine 2 receptor antagonists	Table 9b
139	Proton-pump inhibitors	Table 9b
140	Other prescription dyspepsia	Table 9b
141	Antacids	Table 9b
142	Anti *H pylori*	Table 9b
143	Phenothiazine antiemetics	Table 9b
144	Ulcerative colitis treatment	Table 9b
145	**Neurologic/musculoskeletal**	
146	Migraine treatment/prevention	Table 11
147	NSAID, includes coxibs	Table 11
148	Narcotic analgesic	Table 11
149	Non-narcotic analgesic (acetaminophen)	Table 11
150	Cyclobenzaprine	Table 11
151	Other skeletal muscle relaxants	Table 11
152	Other rheumatologic	Table 11
153	**Other**	
154	Antibiotics	Table 12b
	Utilization	
156	Inpatient days during the baseline period (0, 1-2, 3+)	Table 14
157	Emergency department visits during the baseline period (0,1-2,3+)	Table 14
158	Outpatient visits during the baseline period (0-5, 6-25, 26+)	Table 14

2. Limited propensity score

Proposed PS category	Row #s from Comprehensive PS Table
A. DEMOGRAPHIC	
Sex	4
Race (4 levels)	5,6,7,8
Age	9

B. PSYCHIATRIC	
Mood	11, 12, 13
Impulsivity/externalizing	14, 15, 16
LD/dev delay	17, 25
Anxiety	19
Stress/adjustment	21
Diagnosed SUD	22, 23, 77, 136
Primary psychotic	29
PDD/MR	31, 32
Other psychiatric	18, 20, 24, 26-30, 33, 34

C. OBESITY AND RELATED	
Obesity/wtgn, dx and tx	51-53, 55, 125
Obesity rel dx	59, 66, 67 (acute MI, ischemic HD, cardiomyopathy, heart failure, TIA, selected 437x, PVD), 72, 75, 80, 86-88, 94, 98, 122, 138, 139
Insulin resistance/glycemic	54, 56

D. POTENTIALLY DIABETOGENIC MEDICATIONS (NON-APD)	
Orexigenic mood stabilizer	102, VPA, DVPX sodium
Somatic	118, 127, 129, 134, phenytoin, niacin, aluminum nicotinate
E. PSYCHOTROPIC MEDICATIONS	
Antidepressants	105-109
ADHD	110, 111
Other MS	104, CBMZ, LTG
Anx/sed/hypnotic	112, 114, 115
Other psychotropic	113, 116

Proposed PS category	Row #s from Comprehensive PS Table
F. MEDICAL AND METABOLIC SURVEILLANCE/SERVICE USE	
Inpatient days during the baseline period (0, 1-2, 3+)	156
Emergency department visits during the baseline period (0,1-2,3+)	157
Outpatient visits during the baseline period (0-5, 6-25, 26+)	158
Number of prescription fills during the baseline period (0-5, 6-20, 21+)	159
Metabolic surveillance	57, 58, 60, 62

G. SELECTED GENERAL MEDICAL COMORBIDITIES (INCL TX)	
OBGYN	41-45, 48
Endocrine	61, 64, 123
Neuro	83, 84, 85, 146
Injury	90
Infectious	92, 93, 154
Rheumatologic	89, 152