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

SUBPROJECT 3

EXAMINING LONGITUDINAL CHANGE IN WEIGHT FOR YOUTH INITIATING TREATMENT WITH SECOND GENERATION ANTIPSYCHOTIC MEDICATIONS

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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	7/7/2015	Covariates were expanded to include: • Prader-Willi Syndrome • Weight-loss medications (including orlistat, benzphetamine, phendimetrazine, diethylpropion, phentermine, lorcaserin) • Other GI medications (including azathioprine, mercaptopurine, infliximab, golimumab) • Second-generation antipsychotics (including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, asenapine, clozapine, iloperidone, paliperidone, lurasidone)	A. Mini-Sentinel APY Workgroup
V3	1/14/2016	Workgroup decided to use weight as the primary outcome measure in the main analysis, and BMI as the outcome in a sensitivity analysis (the protocol previously stated the reverse). The decision to select standardized weight as the primary outcome measure was based on (1) a higher percentage of youth had weight available at the baseline and outcome time periods; (2) increased sample size; (3) increased power; (4) more reliable measurements due to a large amount of missing height data. Possible implications of this outcome change are discussed under Section F. Olanzapine was removed from the analysis because there were only 53 youths using olanzapine at baseline. The sample size was not large enough to generate unbiased estiamtes of the potential weight gain associated with olanzapine use compared to aripiprazole.	B. Mini-Sentinel APY Workgroup

This protocol is modified periodically to document major changes made during protocol implementation.

Mini-Sentinel Assessment Protocol

Metabolic Effects of Second Generation Antipsychotics in Youth

Subproject 3

Examining Longitudinal Change in Weight for Youth Initiating Treatment with Second Generation Antipsychotic Medications

Table of Contents

I. BACKGROUND

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 SGA 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 aimed to replicate the findings of a study (conducted in a national sample of Medicaid insured youth) regarding risk of Type 2 Diabetes among youth initiating treatment with second generation antipsychotic medications using the Mini-Sentinel patient cohort of youth - referred to as the Antipsychotics in Youth (APY) cohort. Subproject 2 explored the feasibility of using BMI and laboratory data for baseline confounding adjustment in the APY cohort for MSN Data Partners with BMI data available. These subprojects prepared the workgroup to undertake subproject 3 regarding changes in BMI among youth in the APY cohort. Subproject 3 aims to examine longitudinal changes in weight between individuals initiated on select SGA medications in the APY cohort. This document describes Subproject 3 in detail.

II. SUBPROJECT 3: EXAMINING LONGITUDINAL CHANGE IN WEIGHT FOR YOUTH INITIATING TREATMENT WITH SECOND GENERATION ANTIPSYCHOTIC MEDICATIONS

A. SPECIFIC AIMS

Use of second generation antipsychotic medications (SGAs) is associated with significant weight gain and this weight gain is associated with incident diabetes mellitus, cardiovascular disease, and premature mortality.(1-7) Individual SGAs carry different risks with olanzapine being most strongly associated with weight gain and aripiprazole being the most metabolically neutral.(8) While there have been extensive studies in adults, the magnitude and trajectory of weight gain in youth is less well understood. Recent studies in youth suggest that SGAs are associated with an absolute increase in BMI percentile between 8% (aripiprazole) and 24% (olanzapine) in the three months following initiation.(9) There is deep concern that youth may be more vulnerable to the metabolic side effects of these medications and that, with continued treatment, these negative side effects propagate through the lifespan – potentially leading to higher risk of cardiovascular disease and increased premature mortality.(10-13)

The specific aim for subproject 3 is to determine the average change in weight z-score among youth initiating monotherapy treatment with quetiapine or risperidone compared to aripiprazole between baseline (treatment initiation) and: (i) 12 weeks (+/- 2 weeks), and (ii) 52 weeks (+/- 8 weeks) in the Mini-Sentinel Distributed Database (MSDD) population.

B. DATA SOURCE

We propose to use Electronic Health Records (EHR) and administrative claims from the Mini-Sentinel Distributed Database (MSDD). The MSDD refers to data held and maintained by Data Partners in the Mini-Sentinel Common Data Model (MSCDM) format. The MSCDM was developed in accordance with the MSCDM Guiding Principles and was modeled after the HMO Research Network Virual Data Warehouse. The MSCDM currently includes 11 tables that represent information for the data elements needed for Mini-Sentinel activities. Records are linked across tables by a unique personal identifier.

The time period for the analyses will be January 1, 2006 to December 31, 2012.

1. Preliminary Data

The results of Subproject 2 made it clear that we have sufficient data to undertake the proposed statistical analysis plan successfully. There were 4,348 youth meeting study criteria (see Section C) with respect to baseline BMI measurement. Of these, 964 had at least one BMI measurement at 12 weeks (+/- 2 weeks). Among the 964 youth with both baseline and 12 week follow-up BMI measurement, 207 used aripiprazole, 59 used olanzapine, 245 used quetiapine, and 437 used risperidone. There were 1,191 youth with BMI measured at both baseline and 52 weeks (+/- 8 weeks); 256 used aripiprazole, 73 used olanzapine, 304 used quetiapine, and 540 used risperidone. However, we decided to use standardized weight as the primary outcome after evaluating the missingness of BMI data. Missing BMI was mostly due to missing height measurements. We substantially increase our sample size by using standardized weight rather than BMI.

2. Statistical Power

We conducted a conservative power estimate based on a complete case analysis where both baseline and follow-up BMI measures were non-missing. We further reduced our available sample sizes in each of the treatment groups by 30% to allow for the additional sample size that is needed in observational studies to account for confounding. We conducted power estimates based on a two-sample t-test with an alpha level of 0.05. We assumed the same standard deviation (0.89, derived from Subproject 2A) for change in BMI from baseline to 12 weeks for all groups. Comparing all three treatments to aripiprazole, we have 80% power to detect a 0.4 difference in the mean change from baseline to 12 week BMI z-score for children treated with olanzapine, a 0.3 difference for children treated with quetiapine, and a 0.2 difference for children treated with risperidone. Conducting similar power estimates for the 52 week analyses, we have 80% power to detect a 0.4 difference in the mean change from baseline to 52 week BMI z-score in children treated with olanzapine compared to children treated with aripiprazole, and a 0.2 difference for children treated with quetiapine and risperidone, (again compared to children treated with aripiprazole).

While our baseline preliminary data suggested sufficient power to conduct an analysis of change in BMI, we will conduct our primary analysis using change in standardized weight. There was much more missing follow-up BMI data than anticipated – particularly for olanzapine. The reason for missing BMI data was missing height measurements rather than weight measurements, thus, we made weight our primary outcome.

In weight loss studies, previous authors have argued that the minimum change in BMI z-score considered clinically significant is a reduction of at least 0.5, at which cardiovascular risk is reduced and insulin resistance is improved,(14-16) although others suggest a reduction of ≥0.25 as the minimum requirement.(17) Thus, for both quetiapine and risperidone we have sufficient power to detect a strictly clinically meaningful change in BMI z-score. Due to the smaller sample size in the olanzapine group we have power to detect a larger difference (0.4), and this compares favorably to the 0.5 clinical criterion used in weight loss studies. In addition, olanzapine is known to have a larger impact on weight, thus, it is likely that the increases in this group will be sufficiently large such that we can detect a difference.

C. STUDY COHORT

The study cohort includes individuals initiating monotherapy treatment with SGAs meeting all inclusion/exclusion criteria. All inclusion/exclusion criteria are identical to the original project with a few relevant events added (e.g., eating disorder diagnosis).

1. Inclusion Criteria

- Aged greater than 2 and less than 18 years at baseline (initiation of monotherapy SGA), known date of birth and gender. See Covariates section F for further details regarding the specification of age.
- Enrollment with both medical and prescription drug coverage for 365 days preceding baseline, allowing enrollment lapses of ≤45 days.
- Current use of a study SGA (see section F) at baseline, which includes depot antipsychotics, but excludes non-depot injections (identified by NDC).
- At least 180 consecutive days with no current use of any antipsychotics (see "all antipsychotics" section F), except for non-depot injections, in the 180 days prior to baseline.
- At least one medical care encounter (inpatient, ED, physician or other outpatient) in the 365 days preceding baseline.
- Not in long-term care institution at baseline or in the preceding 180 days.

2. Exclusion Criteria

- BMI percentile greater than 95% at baseline. These youth are excluded due to statistical ceiling effects in ability to model change in BMI z-score.
- No claim with an ICD9CM code corresponding to a somatic exclusion illness at baseline in the 365 days preceding baseline (Table 1; Appendix A1).
- Other condition exclusion: pregnancy, polycystic ovarian syndrome
- Eating disorder diagnosis other than binge eating (new binge eating code may be used in conjunction with reason for weight gain).
- Crohn's or Ulcerative Colitis diagnosis in 365 days prior to baseline
- Claims with a CPT for bariatric weight loss surgery of any type
- Less than one day of study follow-up
- Initiation of more than one SGA at baseline
- Index SGA with 0 day supply

We will create a consort-type attrition table to document the number of individuals lost due to exclusion criteria.

3. Reference group

Individuals initiating on monotherapy with aripiprazole will be the reference group. Aripiprazole is most metabolically neutral of all SGAs.(18, 19) The reference group also has to meet the inclusion and exclusion criteria.

D. OUTCOME OF INTEREST

We will model the average change in weight z-score from baseline to 12 weeks and separately for baseline to 52 weeks. From a modeling perspective, this means that each individual will have one observation (row) in the weight z-score model. Prior versions of this protocol had listed BMI as the

outcome of interest, but this was changed to standardized weight, given that a higher percentage of youth has weight available at the baseline and outcome time periods.

E. EXPOSURE AND FOLLOW-UP

Subproject 3 includes all of the SGAs with significant utilization in the MSDD population of youth. Clozapine, asenapine, lurasidone, iloperidone, paliperidone, and ziprasidone are excluded due to low prevalence of utilization.

The first step is to create a calendar of 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.

Breaks of up to 14 days are considered continuous use. The index SGA is considered to be discontinued (at the last day of supply) if there is a break in supply of >14 days.

1. Censoring Date

Follow up begins at baseline. End of follow-up (censoring date) is defined as the first of the following dates:

- SGA discontinuation
- Addition of 2nd SGA
- Switch to a different SGA or first generation antipsychotic

- Day prior to 18th birthday
- No medical care encounters within the year of treatment initiation (day 365 without at least one medical encounters)
- Pregnancy (defined in covariates Table 3a)
- Polycystic ovarian syndrome (defined in covariates Table 3a)
- Serious somatic illness (defined in covariates Table 9a)
- 365 days from index date (end of follow-up for study)

F. COVARIATES AND CONFOUNDING CONTROL

- Covariates (assessed during both the 365 day pre-index and post-index periods) include age, sex, other psychotropic medication use, mental health diagnoses, somatic diagnoses, (see **Tables 2a-9b).**
- Concurrent use of medications associated with weight gain. (e.g., corticosteroids, antidepressants, anticonvulsants, lithium)
- Concurrent use of medication associated with weight loss
- Concurrent use of other psychotropic medications (see Table 2b)

G. ANALYTIC APPROACH

We will calculate descriptive statistics for all dependent and independent variables proposed in the analysis. We will evaluate the level and nature of missing data (e.g., weight at baseline, 12 weeks and 52 weeks) and produce tables of attrition according to exclusion criteria. We evaluated the potential for

bias associated with differential measurement of height and weight by medication exposure group. Missing height data led us to use weight as the primary outcome.

We will use ordinary least squares (OLS) regression to model the change in weight z-score. Two-sided Wald test, using robust variance estimators(20), will be applied to test the significance of the change in weight z-score with a 0.05 type I error. We will adjust for baseline covariates and use inverse probability weighting (IPW) to control for antipsychotic selection, missing weight z scores, and censoring events.

1. Inverse Probability Weighting

We propose to use the inverse probability weighting (IPW) approach to attenuate confounding using the following weights:

- Inverse probability of treatment weights to account for antipsychotic medication selection at baseline,
- Inverse probability of missing weights (IPW) for weight measured at: baseline, 12, and 52 weeks,
- Inverse probability of censoring weights (IPW) for incident events (e.g., large weight gain is associated with discontinuation and/or switching).

Three separate models are estimated for treatment selection weights, missing weights, and censoring weights. These weights are then multiplied to generate a single weight for each individual in the weight change (outcome) model.

a. Why Use IPW?

There is a differential likelihood of weight being measured at baseline and follow-up. A high weight at baseline is probably associated with closer monitoring. Observed weight (particularly if it increases significantly) is likely to alter the treatment exposure. Youth that don't gain significant weight are more likely to continue treatment with the baseline medication.

IPW allows us to address significant potential for biased estimates of the impact of SGAs on weight gain. In particular, there is confounding by indication (i.e., which SGA an individual is prescribed at baseline depending on baseline weight) and time-dependent confounding involved in treatment assignment post-baseline depending on changes in BMI (e.g., switch SGA, discontinuation of SGA). Use of IPW allows these effects to be modeled explicitly and the associated bias attenuated.

b. Treatment Selection Weights

It is likely that clinicians choose antipsychotic medications purposefully at treatment initiation. For example, youth who are overweight at baseline may be less likely to be prescribed olanzapine (which is known to have the largest effects on weight gain in adults).

We will estimate the treatment selection model using multinomial logistic regression. The reference medication will be aripiprazole. Covariates (**Tables 2a-9b**) include: age, sex, other psychotropic medication use, diagnosis of autism spectrum disorder, diagnosis of a psychotic disorder, diagnosis of bipolar disorder, diagnosis of diabetes mellitus, and weight z-score. Models for treatment selection weights will use values for covariates measured at baseline only.

2. Missing Weight Measurement

Youth missing weight measurement at baseline and/or follow-up are likely different than youth whose weight was measured. For example, youth with normal or lower than average weight at baseline may be less likely than those who are overweight at baseline to have their weight measured. In other words, clinicians may be more attentive to potential weight gain in youth who are already overweight or obese at baseline.

We will estimate the likelihood of weight being measured at baseline, 12, and 52 weeks using separate logistic regression models. We will use the same covariates as used in the treatment selection model above, excluding weight z-score at baseline. The model for missingness will use both baseline and post-baseline covariates. Inverse probability weights calculated for missingness are conditional on individuals not being censored.

3. Censoring Events

Treatment switching and discontinuation are the norm rather than the exception in antipsychotic medication therapy. Youth that continue use of SGAs are likely to experience milder side effects such as less weight gain. In order to capture the effects of each agent (relative to aripiprazole) on weight gain, we will censor individuals that switch SGA treatment. We will also censor individuals, post baseline, at the occurrence of a diagnosis or procedure associated with weight gain or serious somatic illness (e.g., polycystic ovarian syndrome, ulcerative colitis, etc). We will conduct a sensitivity analysis which does not censor individuals that switch medications. This approach is consistent with an intent-to-treat analysis.

We will estimate the censoring weights using a longitudinal logistic regression model. Each individual contributes as much time on treatment as is available. We will use covariates as defined in the treatment selection and missingness models. Both baseline and post-baseline values of covariates will be used to estimate the censoring models. We will also include all the censoring event indicators listed under Censoring Date above.

H. SUBGROUP AND SENSITIVITY ANALYSES

1. Subgroup Analyses:

We propose to conduct 3 subgroup analyses as time permits:

a. Age group (2-12, 13-17 years of age)
b. Sex
c. Diagnosis of ADHD + disruptive behavior

2. Sensitivity Analyses

a. Age

The primary cohort includes youth aged greater than 2 and less than 18 years. Depending on the sample size for children aged less than 13 years, we will explore alternative specifications of age in the outcome model where age will be defined categorically for youth aged 2-12 years and 13-18 years.

We will conduct sensitivity analyses that include individuals aged greater than 18 and less than 24 years. These individuals meet the World Health Organization definition of youth. Individuals in this older age

group will be used as a reference group to determine the magnitude of any difference in weight gain for the 2-12 and 13-18 groups of youth.

b. BMI

We will conduct sensitivity analyses that include youth with BMI greater than the 95 percentile at baseline. Depending on longitudinal availability and quality of BMI data and study resources, we will potentially examine change in weight z score as an outcome variable.

c. Censoring

We will conduct intent-to-treat sensitivity analyses where youth are not censored for SGA addition of a second SGA, or SGA switching.

III. TABLES AND FIGURES

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
Prader Willi Syndrome: 759.81

*See APPENDIX for detailed definitions.

A. COVARIATES[1]

Table 2a. Psychiatric diagnoses

Variable	ICD9CM diagnosis
1. Bipolar disorder	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7, 296.8x, 301.13
2. Mood disorders, major depression	296.2x, 296.3x, 296*, 298.0
3. Mood disorders, other	296.9x, 300.4, 301.10, 301.12, 309.0, 309.1, 311
4. ADHD, hyperkinetic syndrome	314.0x, 314.2, 314.8, 314.9
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, 315.1, 315.2, 315.9
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, 300.3, 309.81
10. Personality disorders	301.0, 301.11, 301.20, 301.22, 301.4, 301.50, 301.59, 301.6, 301.7, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9
11. Acute stress, adjustment disorder	308.x, 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, 307.9
15. Learning disorder/ developmental delay (non-PDD, non-MR)	315.xx, 314.1
16. Other psychiatric	293.xx, 294.0, 294.8, 295.xx-319.xx, not above
17. Psychiatric symptoms	780.1, 780.71, 799.2
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.x, 298.3, 298.4, 298.8, 298.9
20. Tourette's disorder	307.20, 307.21, 307.22, 307.23
21. Pervasive developmental disorders	299.xx
22. Mental retardation	317.xx-319.xx, V79.2
23. Eating disorder	307.1; 307.5x;
24. Prader-Willi Syndrome	759.81

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

[1] Listed medications may constitute a group. The drug list includes all combinations and formulations.

Table 2b. Psychiatric Medication

Psychiatric Medications	
ANTIDEPRESSANT	
amitriptyline	
amitriptyline/chlordiazepoxide	
amitriptyline/perphenazine	
amoxapine	
bupropion	
citalopram	
clomipramine	
desipramine	
desvenlafaxine	
doxepin	
duloxetine	
escitalopram	
fluoxetine	
fluoxetine/olanzapine	
fluvoxamine	
imipramine	
isocarboxazid	
maprotiline	
milnacipran	
mirtazapine	
nefazodone	
nomifensine	
nortriptyline	
paroxetine	
phenelzine	
protriptyline	
selegiline	
sertraline	
tranylcypromine	
trazodone	
trimipramine	
venlafaxine	
STIMULANT	
methylphenidate	ritalin
methylphenidate	concerta
methylphenidate	methylin
methylphenidate	metadate
dextroamphetamine	dexedrine
dextroamphetamine	dextrostat
dexmethylphenidate	focalin
aphetamine salts	adderall
lisdexamfetamine	vyvanase
OTHER ADD	

Psychiatric Medications	
atomoxetine	strattera
modafinil	provigil
clonidine	catapres
guanfacine	tenex
armodafinil	nuvigil
LITHIUM	
Lithium	Lithobid
Lithium	Eskalith
Lithium	Lithonate
Lithium	Lithotabs
ANTICONVULSANT	
Valproic Acid	
Valproate	
Divalproex	Depakote
Carbamazepine	Tegretol
Carbamazepine	Carbatrol
Lamotrigine	Lamictal
Oxcarbazepine	Trileptal
Gabapentin	Neurontin
Topiramate	Topamax
Tiagabine	Gabatril
Zonisamide	Zonegran
FIRST GENERATION ANTIPSYCHOTIC	
chlorpromazine	thorazine
chlorprothixene	taracten
flupenthixol	fluanxol
fluphenazine	prolixin
haloperidol	haldol
loxapine	loxitane
mesoridazine	serentil
molindone	moban
thiothixene	navane
perphenazine	trilafon
pimozide	orap
prochlorperazine	compazine
promazine	sparine
thioridazine	mellaril
thiothixene	navane
trifluoperazine	stelazine
SECOND GENERATION ANTIPSYCHOTIC	
aripiprazole	abilify
olanzapine	zyprexa
olanzapine/fluoxetine	symbyax
quetiapine	seroquel
risperidone	risperdal

Psychiatric Medications	
OTHER SGA	
ziprasidone	geodon
asenapine	saphris
clozapine	clozaril
clozapine	fazaclo
clozapine	versacloz
iloperidone	fanapt
paliperidone	invega
lurasidone	latuda
BENZODIAZEPINE	
alprazolam	xanax
chlordiazepoxide	librium
clonazepam	klonopin
clorazepate	tranxene
diazepam	valium
estazolam	prosom
flurazepam	dalmane
halazepam	paxipam
lorazepam	ativan
oxazepam	serax
prazepam	centrax
quazepam	doral
temazepam	restoril
triazolam	halcion
OTHER HYPNOTIC	
zolpidem	ambien
eszopiclone	lunesta
zaleplon	sonata
ramelteon	rozerem
OTHER ANTI-ANXIETY	
buspirone	Buspar
hydroxyzine	Atarax
meprobamate	Miltown
meprobamate	Equanil
pregabalin	Lyrica

Table 3a. 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	626.0		
Menstruation, infrequent	626.1		
Menstruation, irregular	626.4		
Menstruation, heavy/frequent	626.2		
Menstruation, other disorder	626.8, 626.9		
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		
Polycystic Ovarian Syndrome	256.4x		

Table 3b. Obstetric/Gynecologic Medications

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

Table 4a. Metabolic Related Medical Care Encounters

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

Table 4b. 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 hormone desiccated thyroid levothyroxine liothyronine and liotrix
Antithyroid agents	propylthiouracil(PTU) methimazole sodium iodide
Anorexiants	phentermine sibutramine orlistat
Weight loss medications	Orlistat Benzphetamine Phendimetrazine Diethylpropion Phentermine Lorcaserin

Table 5a. Cardiovascular Medical Care Encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Hypertension	401.x-403.x, 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 of cerebral arteries (430, 431, 432.x, 433.xx, 434.xx, and 436), TIA (435.x); Other cerebrovscular disease: 437.x, 438.xx; Peripheral vascular disease: 440.2x, 440.3, 443.xx, 444.2x, 444.8x, 445.0x, 785.4;; 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)	Note: prior cardiovascular hospitalization is exclusion criteria, thus, won't have valve repair procedures, etc as these are inpatient	
Symptoms, possibly cardiovascular	Cardiovascular symptoms (in absence of any of the above): 780.2, 785.0-785.3, 785.50, 785.51,785.9, 786.5x;		

Table 5b. 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

Cardiovascular Medications	
	fosinopril lisinopril moexipril perindopril quinapril ramipril trandolapril losartan valsartan irbesartan telmisartan candesartan 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

Cardiovascular Medications	
	spironolactone eplerenone) acetazolamide dichlorphenamide mercaptomerin mannitol ethoxzolamide mersalyl theophylline merethoxylline theophyllin
Other cardiovascular	warfarin heparin **LMW heparin** (dalteparin enoxaparin) **Factor Xa inhibitor** (fondaparinux idraparinux razaxaban) hirudin lepirudin argatroban ximelagatran thrombin inhibitors (bivalirudin) 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

Cardiovascular Medications	
	ibutilide dofetilide sotalol azimilide) digoxin amrinone milrinone enoximone vesnarinone pimobendan, levosimendan dopamine dobutamine ibopamine xamoterol metaraminol bitartrate digotoxin digitalis NF gitalin lanatoside C deslanoside midodrine inamrinone furosemide bumetanide torsemide ethacrynic acid nitroglycerin isosorbide dinitrate isosorbide mononitrate pentaerythroid tetranitrate erythritol tetranitrate amyl nitrate dipyridamole cilostazol **PLT inhibitors** (abciximab clopidogrel eptifibatide tirofiban ticlopidine)

Table 6a. Respiratory/Allergy Medical Care Encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Anaphylaxis	995.0		
Allergic reaction	995.2x, 995.3		
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	305.1 , 649.0x (tobacco use disorder complicating pregnancy), 989.84 (toxic effect of other substances, incl. tobacco)	99406, 99407	

Table 6b. Respiratory/Allergy Medications

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

Respiratory/Allergy Medications	
Asthma medications, other	metaproterenol albuterol levalbuterol bitolterol pirbuterol terbutaline salmeterol inhaled formoterol inhaled aminophylline dyphylline oxtriphylline theophylline beclomethasone inhaled budesonide inhaled flunisolide inhaled fluticasone inhaled triamcinolone inhaled betamethasone inhaled mometasone inhaled ipratroprium bromide tiotropium montelukast zafirlukast zileuton cromolyn inhaled nedocromil inhaled epinephrine omalizumab
Smoking cessation	varenicline nicotine

Table 7a. Gastrointestinal Disease Medical Care Encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Abdominal pain	789.0x		
Gastroesophageal reflux	530.1x, 530.8x		
Crohn's Disease	555.0, 555.1, 555.2, 555.9		
Ulcerative Colitis	556.0 – 556.9		
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 7b. Gastrointestinal Disease Medications

Gastrointestinal Medications	
Histamine 2 receptor antagonists	Cimetidine famotidine nizatidine famotidine+calcium carbonate+magnesium hydroxide) ranitidine
Proton-pump inhibitors	Esomeprazole lansoprazole omeprazole pantoprazole rabeprazole omperazole + bicarbonate
Other prescription dyspepsia	Misoprostol Sucralfate
Antacids	Alka-seltzer aluminum hydroxide bicarbonate+citrate aluminum hydroxide+magnesium carbonate aluminum hydroxide+magnesium hydroxide magaldrate aluminum hydroxide_magnesium hydroxide_simethicone 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 adalimumab
Other GI medications	Azathioprine Mercaptopurine Infliximab Golimumab

Table 8a. 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	724.2, 724.3, 724.5		
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, 78.10-78.19
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 8b. Neurologic/Musculoskeletal Medications

Neurologic/Musculoskeletal Medications	
Migraine treatment/prevention	methysergide dihydroergotamine mesylate ergotamine tartrate 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 gold sodium thiomalate hydroxychloroquine leflunomide methotrexate

Table 9a. Other Somatic Medical Encounters

Variable	ICD9CM diagnoses	CPT4 procedures	ICD9CM procedure
Urinary tract infection	599.0		
Other infections	001.xx-139.xx, 480.x, 481, 482.xx, 483.x, 484.x, 485, 486, 487.x, 507.x, 510.x, 513.x		
Malaise and Fatigue	780.79		
Hypersomnia	780.54, 327.11, 327.12		
Other organic sleep disorder	327.00-327.09, 327.20-327.29, 327.51-327.59, 327.10-327.19, 327.30		
Edema	782.3		
Cholecystitis, cholelithiasis	574.1x-574.9x, 575.0-575.1x		
Nephrotic syndrome	581.81, 581.9		

Table 9b. 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 cefazolin cephalexin cefaclor cefotetan cefoxitin cefprozil

Other Somatic Medications	
	cefuroxime cefidinir cefoperazone cefotaxime cefditoren cefixime cefpodoxime ceftazidime cefibuten deftizoxime ceftriaxone penicillin dicloxacillin nafcillin oxacillin amoxicillin ampicillin amoxicillin-clavulanate pivampicillin piperacillin ticarcillin naldixic acid ciprofloxacin lomefloxacin norfloxacin orfloxacin levofloxacin gemifloxacin moxifloxacin sulfadiazine sulfisoxazole trimethoprim-sulfamethoxazole demeclocycline doxycycline minocycline oxytetracycline tetracycline clindamycin metronidazole nitrofurantoin rifaximine telithromycin,

IV. APPENDIX

A. EXCLUSION CONDITIONS AND ILLNESSES

1. Somatic Exclusion Illnesses
2. Endpoint-related Exclusion Illness
3. Pregnancy and Polycystic ovarian syndrome exclusion
4. Weight Loss Surgery exclusion/censoring event

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
1. Somatic Exclusion Illnesses				
		ICD-9 Code(s)	**Medication(s)**	**Procedure Code(s)**
Sickle cell disease		282.6x		
Cystic fibrosis		277.0x	DORNASE-ALFA	
Cerebral palsy		343.x		
Cancer		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,

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	96440, 96530, 95990, 95991, 96520, 96542, 96400, 96545, 96549, 50391

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
			Cyto-protective agents: AMIFOSTINE, DEXRAZOXANE, MESNA	
HIV		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	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
Hepatitis B,C		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	
Tuberculosis		010.x-018.x	ISONIAZID, RIFAMPIN, PYRAZINAMIDE, ETHAMBUTOL, RIFAPENTINE,ETHIONAMIDE, KANAMYCIN,CAPREOMYCIN, PARA-AMINOSALICYLIC, CYCLOSERINE	
Organ transplant		996.8x, V42.1x, V42.6x, V42.7x, V42.81, V42.83, V42.0x	Immunosuppressives (systemic only): AZATHIOPRINE CYCLOSPORINE TACROLIMUS (EXCEPT DERM PREPARATION) MYCOPHENOLATE MOFETIL MYCOPHENOLATE SODIUM 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		570, 571.xx, 572.x, 573.x, 997.4		

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
Renal dialysis/ ESRD		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		518.81, 518.5, 518.82, 518.83, 518.84, 519.0x, V44.0, V55.0, 427.50, 799.10, 415.0, 416.x		**CPT:** 31500, 94656, 94657, 94005 **ICD-9-CM:** 96.70, 96.71, 96.72
Fatal metabolic disease		270.x, 271.x (except 271.3 [lactose intolerance])		
Aplastic anemia		284		
Congenital immune deficiencies		279.04, 279.06, 279.2		
Down syndrome		758.0		
Lethal chromosomal		758.1, 758.2, 758.3 x		

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
abnormalities		(note, individual disorders listed separately below)		
Trisomy 13		758.1		
Trisomy 18		758.2		
Autosomal deletion syndrome		758.3x		
serious neuromuscular		340, 335.20, 335.21, 333.4, 344.0x, 344.1, 344.89, 344.9		
Hospice care		V667		**CPT:** G0182, G0065, 99377, 99378
2. Endpoint-related Exclusion Illness				
Hyperlipidemia		272.0 272.1 272.2 272.3 272.4 272.7	**BILE ACID SEQUESTRANTS** CHOLESTYRAMINE COLESEVELAM COLESTIPOL **HMG-CO-A REDUCTASE INH** LOVASTATIN + NIACIN ATORVASTATIN AMLODIPINE + ATORVASTATIN FLUVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN SIMVASTATIN + EZETIMIBE **OTHER** BEZAFIBRATE EZETIMIBE FENOFIBRATE GEMFIBROZIL	
Diabetes		250.xx 357.2	**INSULIN** INSULIN INJ	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
			INSULIN BEEF LENTE BEEF PROTAMINE ZINC REGULAR LENTE SEMILENTE ULTRALENTE ISOPHANE (NPH) PORK REGULAR PORK LENTE PORK NPH PORK PROTAMINE ZINC PROTAMINE ZINC GLOBIN ZINC HUMAN INSULIN (SEMI-SYNTHETIC) MISC INSLULIN PREPARATIONS INSULIN GLARGINE **INJECTIBLE NON-INSULIN HYPO-GLYCEMIC AGENTS** PRAMLINTIDE ACETATE **ORAL HYPOGLYCEMICS** METFORMIN PHENFORMIN CHLORPROPAMIDE TOLAZAMIDE TOLBUTAMIDE 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	

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
			SITAGLIPTIN-METFORMIN INSULIN-INH REGULAR HUMAN INSULIN	
Parkinson's Disease		332.xx	BENZTROPINE BIPERIDEN PROCYCLIDINE TRIHEXYLPHENIDYL LEVODOPA/BENZERAZIDE LEVODOPA LEVODOPA-CARBIDOPA CARBODOPA ROPINIROLE COMT INHIBITORS TOLCAPONE ENTACAPONE PERGOLIDE MESYLATE PRAMIPEXOLE ROTIGOTINE	
Antipsychotic related movement D/O		307.3, 333.xx, 781.0	DEXETIMIDE ORPHENADRINE	
Serious cardiovascular disease		401.0 – 404.9 410.xx-416.xx, 425.xx-437.xx, 440.xx-447.xx	NOTE: Serious cardiovascular disease cases will be identified based on primary inpatient diagnoses because outpatient diagnoses will not be used to define the serious cardiovascular disease study endpoint.	
Seizures		345.xx 780.3x (not 780.31)	ETHOSUXIMIDE ETHOTOIN FOSPHENYTOIN METHSUXIMIDE PHENOBARBITAL PHENYTOIN	
Organic psychotic disorder		293.81, 293.82		

Exclusion illnesses	Criterion number (Table 2)	Computer case definition		
3. Pregnancy and Polycystic Ovarian Syndrome Exclusion				
Pregnancy		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		256.4x		
4. Weight Loss Surgery Exclusion/Censoring Event				
Gastric Bypass		43644, 43645		
Gastric Banding		43659, 43770, 43771, 43772, 43773, 43774, 43775		
Sleeve Gastrectomy		43775		
Misc. Gastric Procedure		43842, 43843, 43845, 43846, 43847, 43848, 43860, 43865, 43886, 43887, 43888		

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