Incretin-based drugs and Retinopathy risk using Medicare data 2006-2014.

Protocol, Feb 08, 2017

1. Background

The prevalence of diabetes in the elderly Medicare population in the United states has been growing at an alarming rate, with approximately 32% of Medicare spending attributed to diabetes (1). Type 2 diabetes (DM) accounts for 90-95% of all diabetes cases diagnosed in adults (2, 3). With a number of antihyperglycemic drugs now available, there are growing concerns about potential adverse effects associated with these drugs (4). Dipeptidyl peptidase-4 inhibitors (DPP-4i) and GLP-1 receptor agonists (GLP-1RA) are incretin-based therapies (IBRx) used for the management of DM. Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the pancreatic cells, reduce glucagon secretion, regulates gastric emptying and influences satiety/appetite. Exenatide and liraglutide, injectable GLP-1 receptor agonists were approved by the US FDA in 2005 and 2010 respectively (5). Exenatide in its once weekly formulation was approved by FDA in 2012 (5), Dulaglutide (once weekly) and albiglutide (once weekly) were both approved by FDA in 2014 (6, 7). Oral DPP-4i drugs sitagliptin, saxagliptin, linagliptin and alogliptin were approved in 2006, 2009, 2011 and 2013 respectively (5). Lexisenatide was approved by FDA in 2016 and as a result will not be examined in this study (8).

Large randomized trials suggest incretin therapies are associated with an increased risk of retinopathy. In the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes trial (SUSTAIN-6), Marso et al. reported an unexpected and significantly higher rate of retinopathy complications (defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or onset of blindness) with semaglutide versus placebo (hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.11 to 2.78; P=0.02) (9). In the LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes), a non-significant higher incidence of retinopathy events was also reported (HR, 1.15; 95%CI, 0.87 to 1.52; P=0.33) (10). In the TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), a significant higher incidence of diabetic eye disease (including blindness due to diabetes and retinopathy) was reported (RR, 1.25; 95%CI, 1.04 to 1.50) (11).

Improved glycemic control reduces the risk of developing retinopathy and the progression of retinopathy (12, 13). Preclinical data demonstrate the beneficial pleiotropic effects of GLP-1RA and dipeptidyl peptidase-4 inhibitor (DPP-4i) in diabetic retinopathy independent of the glucose-lowering effect by reducing blood–retinal barrier breakdown, inflammation, and neuronal cell death (14). Clinical data also showed an improvement in retinal capillary blood flow with saxagliptin (15). However, in a study of exenatide, there was a transient worsening of diabetic retinopathy associated with a rapid reduction in HbA1c levels (16), which suggests that incretin associated retinopathy risk is biologically plausible.

To our best knowledge, no observational studies have assessed the retinopathy risk associated with incretin therapies. Given the lack of data from randomized trials, further studies are warranted to assess the safety of incretin-based therapies. This is particularly relevant given the high prevalence of DM and the potential for widespread use of IBRx for glucose

management in DM.

It has been proposed that tendency of a higher risk of retinopathy associated with IBRx observed in the trials could be attributed to detection bias. Hypoglycemia is the severe adverse effect in diabetes patients and its risk varies among anti-hyperglycemic drugs. Thus, physician may pay less attention on diabetic complications in patients who are more likely to suffer from hypoglycemia, leading to differential detection among patients receiving different anti-hyperglycemic drugs. In addition, due to unresolved concerns on retinopathy associated with thiazolidinedione, physicians may be more likely to order retinopathy diagnostic workups for patients receiving thiazolidinedione, leading to earlier/increased discovery of retinopathy, compared with those receiving other anti-hyperglycemic drugs. Furthermore, non-retinopathy eye diseases could affect the probability of undergoing eye examinations, but it is unknown whether the prevalence of eye diseases differs between users of different anti-hyperglycemic drug classes in the observational studies. Thus, in this study, we will first examine the probability of receiving retinopathy diagnostic workups across treatment cohorts defined by initiation of different antidiabetic drug classes before initiation and during follow-up. We will also examine the prevalence of eye diseases between treatment groups at baseline and compare the probability of receiving retinopathy diagnostic workups among treatment groups, stratified by eye diseases at baseline.

2. Objectives

Aim: To examine the effect of initiation of incretin-based therapies (IBRx) relative to other antidiabetic therapies (CompRx) on the incidence of retinopathy based on an active comparator new-user study design. The comparisons to be made are listed in section 4.

3. Study design

We will implement an active comparator, new user cohort design. New-user design helps to avoid the biases inherent in the prevalent user designs (17-19). The magnitude of the risks and benefits of drugs often vary over time after the start of treatment, which introduces bias in a prevalent user design. Another difficulty in the analysis of prevalent user designs stems from the fact that disease risk factors can be affected by the treatment itself. In a new user design, this difficulty is addressed because potential confounders can be measured prior to treatment initiation. Although the benefits of the new user design are well understood and attractive, such designs are often not employed because of the logistical complexities of identifying new users and because of the loss of sample size and thus statistical power compared with a prevalent user design.

Using an active comparator will help to balance the comparison groups on diabetes severity and baseline retinopathy risk. Even though diabetes is a risk factor for retinopathy, such a design can therefore be used to examine the retinopathy risk with IBRx (rather than with diabetes itself) adjusting for baseline retinopathy risk.

4. Data source:

Medicare Part A, B and D claims data 2006-2014.

5. Exposure and comparisons

The analysis will be based on new-users of IBRx and active comparators (CompRx) in the table below. The date of dispensing of the first prescription after at least 12 months without a dispensed prescription for any of the drug classes compared will be the index date. Drug use will be defined using National Drug Codes (NDC codes), days supply, and fill dates from pharmacy claims in the Medicare part D data. Patients will be required to fill a second prescription of the same drug within (days-supply + 90 days) of index date. This is to increase the probability that the new users are actually started on the therapy.

Comparisons	IBRx	CompRx
I	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)	Thiazolidinediones (pioglitazone, rosiglitazone)
II	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)	Sulfonylureas (glyburide, glipizide, glimepiride).
III	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)	SGLT2 (canagliflozin, dapagliflozin, empagliflozin).
IV	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)	Thiazolidinediones (pioglitazone, rosiglitazone), Sulfonylureas (glyburide, glipizide, glimepiride), or SGLT2 (canagliflozin, dapagliflozin, empagliflozin).
V	GLP-1RA (Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide)	Long acting insulin (premixed, NPH, glargine, detemir)
VI	GLP-1RA (Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide)	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)
VI	GLP-1RA (Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide)	DPP-4i (Sitagliptin, Saxagliptin, linagliptin, alogliptin)
VII	GLP-1RA (Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide)	Thiazolidinediones (pioglitazone, rosiglitazone)
VIII	GLP-1RA (Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide)	SGLT2 (canagliflozin, dapagliflozin, empagliflozin).

6. Study Population/Inclusion criteria

1. Medicare enrollees >65 years of age
2. Patients will be identified based on their first prescription for IBRx or CompRx; the date of dispensing of the first prescription will be the index date. Frist prescription is defined as having no prescriptions dispensed during the 9 months prior to the first prescription.
3. Patients need to have at least 12 months of continuous Part D enrollment and at least 12 months of continuous enrollment in parts A and B before the index date.
4. Since pharmacy data is available starting from January 1st, 2007, the earliest index date will be January 1st, 2008 (to ensure that the patients have at least 12 months of baseline pharmacy data).
5. Prevalent users of the drugs of interest in the 12 months prior to the index date will be excluded (washout period). For example, in the DPP-4i versus Sulfonylureas (SU) comparison, the patients cannot be prevalent users of DPP4-i or SU, but they can be on other antihyperglycemic drugs during the washout period.
6. Patients will be required to fill a second prescription of the same drug class within (days-supply + 90 days grace period) of the index date. This is to increase the probability that the new users are actually started on and taking the therapy. Follow-up will start from the date of the second prescription fill (cohort entry date). Patients not meeting this criterion and their outcomes (retinopathy) will be enumerated.
7. Patients who had at least one of following diagnosis or procedure codes any time before the start of follow-up (cohort entry date) will be excluded:

    (1) Retinopathy diagnosis: ICD9 Dx: codes 362.0X
    (2) Blindness and low vision: ICD9 Dx: 369.XX
    (3) Treatment for retinopathy, including photocoagulation, intravitreal corticosteroid, intravitreal anti-VEGF agents, and vitrectomy (CPT and HCPCS codes are listed below).
8. Patients who fulfill these inclusion criteria at a later point in time (prevalent users) or more than once (incident users) will be enumerated and included as separate observations depending on their number.

7. Outcomes

The outcome of interest is diabetic retinopathy requiring treatment. The primary definition used to ascertain the case of diabetic retinopathy is receipt of one of the following treatment procedures with at least one retinopathy (ICD-9 DX: 362.0X) or diabetes diagnosis (ICD9 DX: 250.XX) within the same claim of the procedure. Because some of these therapies are also used to treat wet age-related macular degeneration (AMD, ICD9 dx: 362.50, 362.52, 362.42, 362.43), these therapies are not considered to be performed for retinopathy if these procedures with a diagnosis of AMD within the same claim.

Treatment for diabetic retinopathy includes:

(1) Photocoagulation (CPT 67228 or 67210)

(2) Injections of intravitreal corticosteroid and anti-VEGF agents. To be specific to identify intravitreal injection, we require a joint CPT code of 67028 in the same claim of these agents.

a) Intravitreal corticosteroid

- Intravitreal triamcinolone (Triesence®): HCPCS J3300, J3301
- intravitreal dexamethasone (Ozurdex®): HCPCS J7312, C9256
- intravitreal fluocinolone (Iluvien®): HCPCS J7313

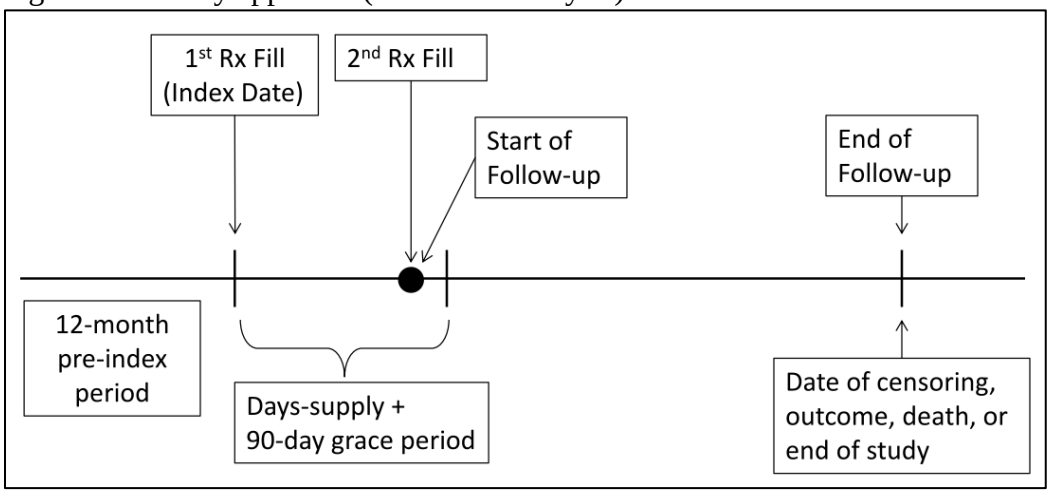
b) Intravitreal anti-VEGF Agents

- Ranibizumab (Lucentis®): HCPCS J2778
- Aflibercept (Eylea®): HCPCS J0178, Q2046, C9291
- Bevacizumab (Avastin®): HCPCS J9035 or C9257

(3) Vitrectomy: CPT 67036, 67038, 67039, 67040, 67041, 67042)

8. Follow-up and analysis

Figure 1: Primary approach (As treated analysis)



Analysis for the primary outcome (incident retinopathy): in the primary "as-treated" analysis, follow-up will start at the date of filling the 2nd IBRx or CompRx prescription (the cohort entry date) and will continue until the outcome occurs or until the date of censoring (death, treatment discontinuation/switching/augmenting, end of study period or Medicare Part A, B, and D enrollment), whichever comes first.

Treatment discontinuation will be defined as no new prescription of a drug from the same drug class within (days-supply + 90 days grace period) after the last prescription. Patients will be censored at the end of drug supply + 90 days grace period. The final grace period for each analysis will be determined based on the observed distribution of days between the end of drug supply and the dispensing of the next prescription. We expect that we will use a longer grace period for the injectable drug classes.

Switching from the study drug will be defined as filling a prescription for a comparison drug without filling another prescription for the study drug within days-supply + the grace period. Patients will be censored at the date of filling the comparison drug. Switching to another drug from the same class (example glimepiride to glyburide with the SU class) or switching doses of the same drug will not be classified as switching.

Augmenting will be defined as adding a prescription of a comparison drug with another prescription of the study drug within days-supply plus the grace period. Patients will be censored at the date of filling the comparison drug.

In addition, we will conduct "initial treatment" (IT) analysis where we do not censor for augmenting, switching, or stopping (i.e., counting all events until death or administrative censoring). This analysis is similar to an intention-to-treat (ITT) analysis in a RCT.

For each cohort, we will calculate incidence rates of retinopathy per 1,000 person-years and use Kaplan-Meier methods to plot cumulative incidence of retinopathy. A Cox proportional regression models will be used to estimate the crude and adjusted hazard ratios of retinopathy and their corresponding 95% confidence intervals with robust variance. The proportional hazard assumption is assessed by an addition of an interaction term between cohort and log survival time and by plotting –ln(ln(estimated survivor function)) as a function of time on the logarithmic scale. We will also perform subgroup analyses, stratified by age, sex, use of statins at baseline, or presence of cardiovascular disease or eye disease at baseline. Additional analyses listed in Section 11 will be performed as sensitivity analyses.

9. Covariates

Drug use and co-morbidity will be measured in the 12 months prior to the index date.

(1) Demographics: age, gender, race/ethnicity, available measures of socioeconomic status, e.g., low-income subsidies

(2) Comorbidity: hypertension, dyslipidemia, nonalcoholic fatty liver disease , renal insufficiency, diabetic nephropathy, diabetic neuropathy, non-retinopathy eye disease, chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), chronic kidney disease (CKD), acute kidney injury (AKI), ischemic heart disease (IHD), cerebrovascular disease (CBD), peripheral artery disease (PVD), cancer, and osteoporosis. All co-morbidity variables are categorized into binary variables (yes or no), defined as at least one diagnosis code.

(3) Medications: statins, bisphosphonates, ACE inhibitors, ARBs, beta blockers, calcium channel blockers, loop diuretics, non-loop diuretics, antidepressant, digoxin, cholesterol absorption inhibitor, and drugs that may induce retinopathy or macular edema (listed in Appendix C) (20, 21). All medication variables are categorized into binary variables (yes or no), defined as at least one prescription or refill records.

(4) Health Care System Use: number and total days of hospitalizations, number of physician encounters, number of emergency department visits, number of lipid tests, number of HbA1c tests, general utilization (flu vaccination, other health screenings), cancer screenings (mammography, endoscopy, PSA, pap

smears). All health care system use variable are treated as both continuous variables and categorical variables.

Propensity score (PS) method will be used to adjust for potential confounding due to channeling between treatments. We will implement the PS using fine stratification and (SMR and IPTW) weighting and compute the adjusted hazard ratios using a Cox proportional hazards (time to event) model. Balance of important covariates will be assessed within deciles of the propensity score and across weighted pseudo populations. Any imbalance will be interpreted according to the potential of the imbalanced covariate to affect the risk for retinopathy. Given balanced covariates and under the assumption of no unmeasured confounding, incidence rates and survival curves are adjusted or unconfounded and thus can be directly compared. The main measure of association will be the hazard ratio estimated using a Cox proportional hazards model controlling for age and sex as well as any covariates remaining imbalanced after implementation of the propensity score.

10. Considerations on potential detection bias

Within the new users of IBRx and CompRx, we will calculate the prevalence of receiving diagnostic work-ups for retinopathy (listed in Appendix C), any eye examinations, and visits to ophthalmology physicians during 12 months prior to initiation. We also examine the frequencies of receiving diagnostic work-ups and ophthalmology physician visits after initiation, overall and stratified by follow-up time with sequential 6-month intervals. To minimize the impact from varying follow-up time, we will restrict the study population to those who have follow-up more than 12 months and repeat the descriptive analysis within 12 months since initiation. Receipt of diagnostic procedures for retinopathy may be affected by prevalent eye disease. Thus, we will repeat above analyses in new user cohort with and without eye diseases, separately.

11. Sensitivity analyses

We plan several sensitivity analyses to examine the robustness of the estimation of the association between IBRx and retinopathy.

(1) As retinopathy is prevalent among older diabetic patients and mild retinopathy usually does not require active treatment, we will repeat all analysis in diabetic patients who do not receive the treatment for retinopathy (includes photocoagulation, injections of intravitreal agents including corticosteroid or anti-VEGF therapy, and vitrectomy) and do not have diagnosis code for blindness (369.xx), irrespective of retinopathy diagnosis.

(2) In the main study, follow-up will start at the date of filling of the 2nd prescription and stop when the patients are censored as described above for the "as treated" analysis. Time trends in incidence rates and relative hazards will be assessed by stratifying on months of follow-up time (0-6, 7-12, 23-24, and 24+). Sensitivity analyses will be conducted to account for varying induction and carryover effects. Induction period is defined as the time between causation and disease initiation (Rothman 1981). To allow for time-varying hazard ratios (e.g., varying induction periods), we will do

sensitivity analyses starting follow-up at different times after baseline (e.g., 6 months, 9 months, 12 months, and 24 months). This will be achieved by subtracting the corresponding days from the days of follow-up. Sensitivity analysis will also be conducted to account for carry-over effects (persistent effect of the drug). To do so, we will have additional censoring variables, censoring follow-up time at 3 months, 6 months, 12 months, and 24 months after the exposure defined censoring event as describe in Section 8. In these analyses, events and person-time during these lag times after stopping, switching, augmenting will be counted. The final range of induction periods and carryover effects analyzed will be determined based on availability of (outcome) data for these analyses.

(3) In the main study, the new users will be allowed to be on any anti-diabetics other than the drugs of interest (drugs being compared) during the washout period. Sensitivity analysis will be conducted by excluding prevalent users of all antihyperglycemic drugs except metformin. Given IBRx or CompRx of interest are considered as the second line treatment for diabetes, we will conduct an analysis in which requires all eligible new users being on metformin during the washout period (12 months prior to the index date).

(4) The main study excludes patients with a diagnosis of retinopathy diseases and blindness. Given that non-retinopathy eye diseases may affect the probability of receiving eye examinations for a given patient, thus we plan a sensitivity analysis in which excludes patients with a diagnosis of any eye disease (ICD-0 codes: 360.xx-379.xx) before cohort entry and censors patients at the time of diagnosis of eye diseases during follow-up.

(5) We will perform sensitivity analyses with various lengths of grace period (e.g., 30 or 180 days)

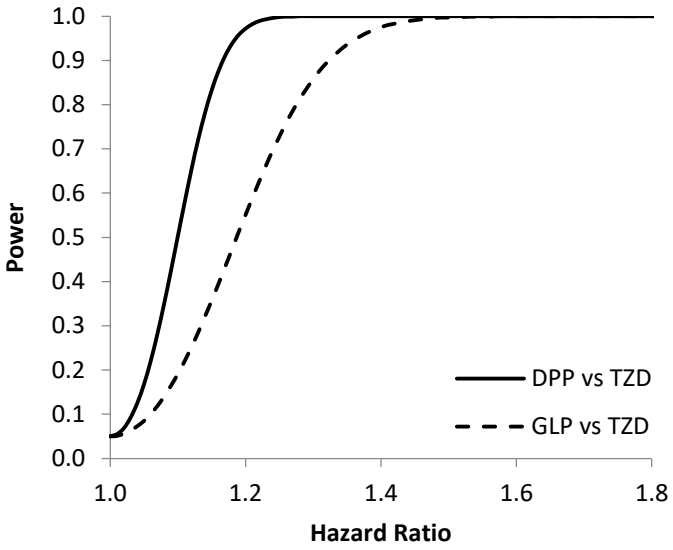
11. Power analysis:

We calculate the power of this study as a function of hazard ratio with a two-sided alpha of 0.05, given the conditions listed in Table below. With reaching 80% power, the hazard ratios of retinopathy are 1.15 comparing DPP-4i initiators with thiazolidinediones (TZD) initiators and 1.28 comparing GLP-1RA with thiazolidinediones (TZD) initiators under the assumption that the cumulative incidence of retinopathy is 2% over 2 years of follow-up.

Table. Parameter Values for Power Calculation

Parameter	Value or Range	
Cohorts	DPP-4i vs TZD	GLP-1RA vs TZD
α	0.05	0.05
% Loss to follow-up	0	0
N of IBRx	60,000	8,000
N of CompRx	30,000	30,000
Follow-up Time (years)	2	2
2-year Cumulative incidence of Retinopathy	3%	3%
Range for Hazard Ratio	1.0-2.0	1.0-2.0
Comparison Method	Log-Rank Test	Log-Rank Test

Figure. Power as a Function of Retinopathy Incidence



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Appendix A - New User Algorithm

Definitions/Conventions

Washout Period (WP) = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort

Grace Period (GP) = maximum length of time that a user can go after the last prescription date plus the days supply without a drug before being considered discontinued from drug use

Days Supply (DS) = assumed (or imputed) number of days supply to use as Days Supply when true value is unknown (usually 30 days)

W_i = Days since start of washout period prior to 1_{st} RX fill of i_{th} period of use for patient

G_j = Days from last day covered by the j_{th} RX fill to the $(j+1)_{th}$ RX fill date

Cohort Eligibility

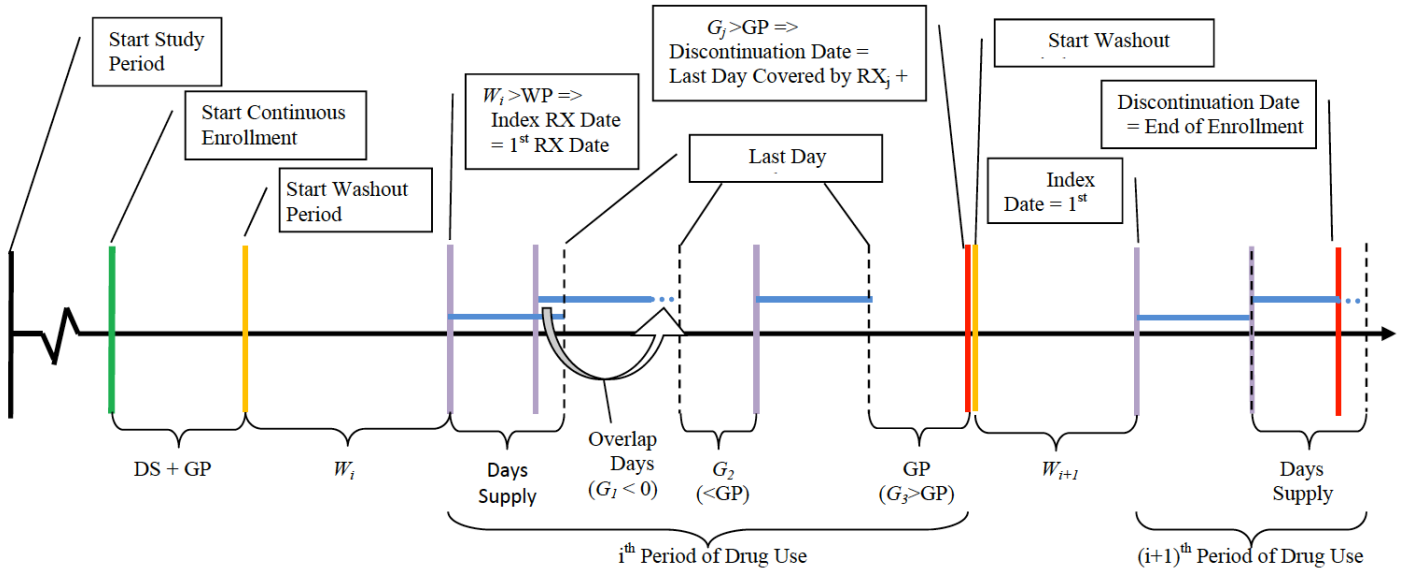
If $W_1 >$ WP then patient's period of drug use is eligible for the new user cohort.

If $W_i >$ WP and $i>1$ then patient's i_{th} period of drug use is eligible for new user cohort IFF the analysis allows for previous users to become new users.

Drug Discontinuation/Censor Date

If $G_j >$ GP then the patient is considered discontinued from drug use on the last day covered by the j_{th} RX fill + GP

If (End of Enrollment) – GP < (Last Day Covered by an RX Fill) then the patient is censored at End of Enrollment



Algorithm

1. Set (Last Day Covered) = (Start of Continuous Enrollment) + (Days Supply) + (Grace Period).

2. Set (Index Date) = (1st RX Fill Date following Start of Continuous Enrollment).

3. Let W = (Index Date) – (Last Day Covered). If W > (Washout Period) then flag the period of drug use as eligible for the new user cohort.

4. Let G = (RX Fill Date) – (Previous Last Day Covered). Sequentially cycle through the subsequent prescription claims for the patient, applying the appropriate step below, until (Discontinuation Date) is set:

a. If G > (Grace Period) then set (Discontinuation Date) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply) + (Grace Period).

b. If G <= (Grace Period) then set (Last Day Covered) = max(Previous Last Day Covered, RX Fill Date) + (Days Supply). If (Last Day Covered) + (Grace Period) > (End of Continuous Enrollment) and the patient has no additional RX claims with (RX Fill Date) <= (End of Continuous Enrollment), then set (Discontinuation Date) = (End of Continuous Enrollment). Otherwise, repeat Step 3 for the next prescription.

5. If the record was flagged for inclusion in the new user cohort in Step 3, output the record containing Index Date and Discontinuation Date3.

6. Set (Index Date) = (1st RX Fill Date following Discontinuation Date).

a. If the patient is continuously enrolled from (Discontinuation Date) to (Index Date), set (Last Day Covered) = (Discontinuation Date).

b. If the patient has a gap in enrollment between (Discontinuation Date) and (Index Date), then set (Last Day Covered) = (Start of Next Period of Continuous Enrollment) + (Days Supply) + (Grace Period) and set (Index Date) = (1st RX Fill Date following Start of Next Period Continuous Enrollment).

7. Repeat Steps 3-7 for the patient's remaining RX fills.

Notes:

- We declare that we have no knowledge, through advance exploratory analyses, of the likely ultimate findings of the study at the time that this protocol is submitted.

Appendix B - List of Drugs Related to Retinopathy

Drugs which possibly induce retinopathy (20) or macular edema (21) include:

1. Tamoxifen
2. Quinine
3. Chloroquine
4. Mefloquine
5. Hydroxychloroquine
6. Digoxin
7. Ethambutol
8. Allopurinol
9. Peginterferon Alfa 2a
10. Interferon Alfa 2b
11. Interferon Beta 1a
12. Isocarboxazid
13. Sildenafil
14. Isotretinoin
15. Vigabatrin
16. Fingolimod
17. Docetaxel
18. Niacin
19. Latanoprost (Ophthalmic)

Appendix C - List of codes for diagnostic workup

Type	Code	Procedure	Procedures Category
ICD9 Proc	V72.0	Eye & vision examination	medical eye exams
Proc CPT	92002	Intermediate eye exam, new patient	medical eye exams
Proc CPT	92004	Comprehensive eye exam, new patient	medical eye exams
Proc CPT	92005	Low vision examination	medical eye exams
Proc CPT	92012	Intermediate eye exam, established patient	medical eye exams
Proc CPT	92014	Comprehensive eye exam, established patient	medical eye exams
Proc CPT	92015	Describes refraction and any necessary prescription of lenses.	medical eye exams
Proc CPT	99201-99215	Evaluation and Management procedure codes, new and established patients (Refer to the CPT book for complete descriptions.)	medical eye exams
HCPCS	S0620	Routine ophthalmological examination including refraction; new patient	
HCPCS	S0621	Routine ophthalmological examination including refraction; established patient	
ICD-9 diagnosis	368.15	Other visual distortions and entoptic phenomena	Medical Emergency Diagnoses
ICD-9 diagnosis	369.9	Unspecified visual loss	Medical Emergency Diagnoses
ICD-9 diagnosis	379.21	Vitreous degeneration	Medical Emergency Diagnoses
ICD-9 diagnosis	379.23	Vitreous hemorrhage	Medical Emergency Diagnoses
ICD-9 diagnosis	379.24	Other vitreous opacities	Medical Emergency Diagnoses
ICD-9 diagnosis	930.0	Corneal foreign body	Medical Emergency Diagnoses
ICD-9 diagnosis	930.1	Foreign body in conjunctival sac	Medical Emergency Diagnoses