Incretin-based drugs and Pancreatic Cancer risk using Medicare data 2006-2010. Final Protocol, December 20, 2012

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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 antihyperglycemic 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 while oral DPP-4i drugs sitagliptin and saxagliptin were approved in 2006 and 2009, respectively.[5;6] Exenatide in its once weekly formulation and linagliptin were approved in 2011 and as a result will not be examined in this study.

An Adverse Event Reporting System (AERS) study suggested a ~3-fold increased reporting of pancreatic cancer (PC) in users of sitaglipitin or exenatide as compared to other diabetic medications and raised caution about potential long-term actions of these drugs to promote PC.[7] A claims-based study[8] in a privately insured population found a non-significant ~1.5-fold increased PC risk with cumulative exenatide use for 365+ days as of the preceding year. However, it is not clear if this study used 'initiators' of exenatide which is needed to prevent potential biases of prevalent user designs. Moreover since exenatide use was compared to 'no exenatide use', the comparator group is not clear.

IBRx in young rodents are associated with new islet formation from pancreatic ductal epithelium as well as anti-apoptotic effects in islet cells suggesting that the IBRx – PC association is biologically plausible.[9] Given the limitations of previous studies and lack of data from randomized controlled trials, further studies are warranted to assess the safety of incretin-based therapies.[10] This is particularly relevant given the high prevalence of DM and the potential for widespread use of IBRx for glucose management in DM.

Several studies assessing cancer risk after a new diabetes diagnosis have raised concerns about detection bias overestimating the association between diabetes and cancer.[11,12] Individuals newly diagnosed with diabetes may undergo increased diagnostic workup which may lead to earlier/increased discovery of cancer in this population compared to the non-diabetic population. The potential for detection bias also presents methodological challenges in studies assessing cancer risk with anti-diabetic drug therapies. Even though the treatments being compared are for the same indication (entire study population is diabetic), patients on one treatment may be subjected to increased diagnostic workup because of concerns about development of adverse events with that

treatment. For example, following the signal from the FDA AERS study, it is possible that diabetic patients starting on IBRx may be subject to increased screening/diagnostic procedures in the period just before and after the start of IBRx therapy which may lead to earlier/increased discovery of pancreatic cancer in the IBRx group relative to the CompRx group.

If we observe an increased incidence of pancreatic cancer with IBRx relative CompRx and also a differential increased incidence of diagnostic work-up in the IBRx group compared to the CompRx group, it is possible that detection bias exists which explains the increased incidence of pancreatic cancer with IBRx. Although differential diagnostic workup among IBRx patients may lead to earlier/increased discovery of pancreatic cancer, it is NOT expected to affect mortality due to pancreatic cancer. In other words, differential detection may bias the association between IBRx and PC, but the association between IBRx and PC mortality is expected to be unbiased by this form of length time bias. While plausible, there exists no data quantifying differential work-up and thus we will quantify the potential for detection bias when estimating the effect of IBRx on PC.

2. Objectives

Aim 1: To examine the effect of initiation of incretin-based therapies (IBRx) relative to other anti-diabetic therapies (CompRx) on the incidence of pancreatic cancer based on a new-user active comparator design. The comparisons to be made are listed in section 4.

Aim 2: Evaluate and quantify the use of diagnostic procedures (listed in Appendix B) that may lead to a preclinical diagnosis of pancreatic cancer among new users of IBRx and CompRx in the 6 month period before and after the start of drug therapy.

3. Study Design

A new user, active comparator cohort design will be used. New-user design helps to avoid the biases inherent in the prevalent user designs.[13] 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 PC risk. Even though diabetes is a risk factor for PC, such a design can therefore be used to examine the PC risk with IBRx (rather than with diabetes itself) adjusting for baseline PC risk.

4. Data source:

Medicare Part A, B and D claims data 2006-2010.
As of December 8 2012, only the data from 2006-09 is available. Data from 2010 is expected to be available in January 2013 and will be used in the analysis.

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 will be the index date. Drug use will be defined using Anatomical Therapeutic Chemical classification codes (ATC 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 + 180 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)	Thiazolidinediones (pioglitazone, rosiglitazone)
II	DPP-4i (Sitagliptin, Saxagliptin)	Sulfonylureas (glyburide, glipizide, glimepiride).
III	GLP-1ra (Exenatide, Liraglutide)	Long acting insulin (premixed, NPH, glargine, detemir)
IV	GLP-1ra (Exenatide, Liraglutide)	Thiazolidinediones (pioglitazone, rosiglitazone)
V	GLP-1ra (Exenatide, Liraglutide)	Sulfonylureas (glyburide, glipizide, glimepiride).
VI	GLP-1ra (Exenatide, Liraglutide)	Long acting insulin (premixed, NPH, glargine, detemir), Thiazolidinediones (pioglitazone, rosiglitazone), Sulfonylureas (glyburide, glipizide, glimepiride).

6. Study Population/Inclusion criteria:

- Medicare enrollees >65 years of age
- 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.
- Patients need to have at least 6 months of continuous Part D enrollment and at least 12 months of continuous enrollment in parts A and B before the index date.
- Since pharmacy data is available starting from January 1st 2007, the earliest index date will be July 1 2007 (to ensure that the patients have at least 6 months of baseline pharmacy data).

- Prevalent users of the drugs of interest in the 6 months prior to the index date will be excluded (wash-out 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.
- Patients will be required to fill a second prescription of the same drug class within (days-supply + 180 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 (PC) will be enumerated.
- Patients with a cancer diagnosis (except non-melanoma skin cancer) any time before the start of follow-up (cohort entry date) will be excluded.
- Patients who fulfill these inclusion criteria more than once will be enumerated and included as separate observations depending on their number.

7. Outcomes for Aim 1

Primary – Incident pancreatic cancer - Defined as at least 2 PC diagnoses (ICD-9-CM codes 157.xx) within 2 months. The diagnosis date will be the date of second PC diagnosis. Because the diagnostic work-up and therapy for other cancers may affect the diagnosis and incidence of pancreatic cancer we will censor patients with any other cancer (except non-melanoma skin cancer) for this outcome.

Secondary: Mortality due to pancreatic cancer. To reduce the potential for lead-time bias due to increased diagnostic work-up (see aim 2), we will assess the effects of treatments on pancreatic cancer mortality. To do so in the absence of cause of death data, we will assume that anyone dying within a year of the second PC diagnosis died of pancreatic cancer. Date of death will be determined from the BASF Medicare files. For this analysis (and in addition to the censoring for other cancers mentioned for the primary outcome) we will censor patients dying without a preceding incidence of pancreatic cancer (as defined above).

8. Follow-up and analysis:

Analysis for the primary outcome (incident pancreatic cancer): 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; end of enrollment; treatment discontinuation/switching/augmenting), whichever comes first.

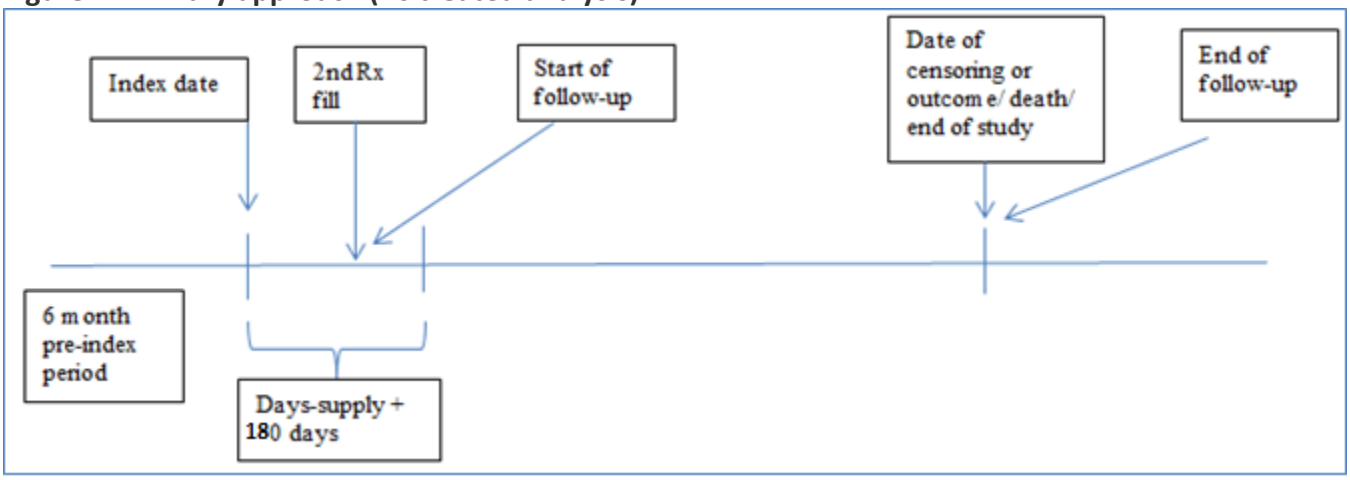
Treatment discontinuation will be defined as no new prescription of a drug from the same drug class within (days-supply + 180 days grace period) after the last prescription. Patients will be censored at days-supply + 180 days grace period.
Switching from the study drug will be defined as filling a prescription for a comparison drug without filling another prescription for the study drug within days-supply + 180 days 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 180 days grace period. Patients will be censored at the date of filling the comparison drug.

In addition, 'intention to treat' (ITT) analyses are also planned where we do not censor for augmenting, switching or stopping (i.e., counting all events until death or administrative censoring).

Several additional analyses will be performed as sensitivity analyses (listed in section 10 below).

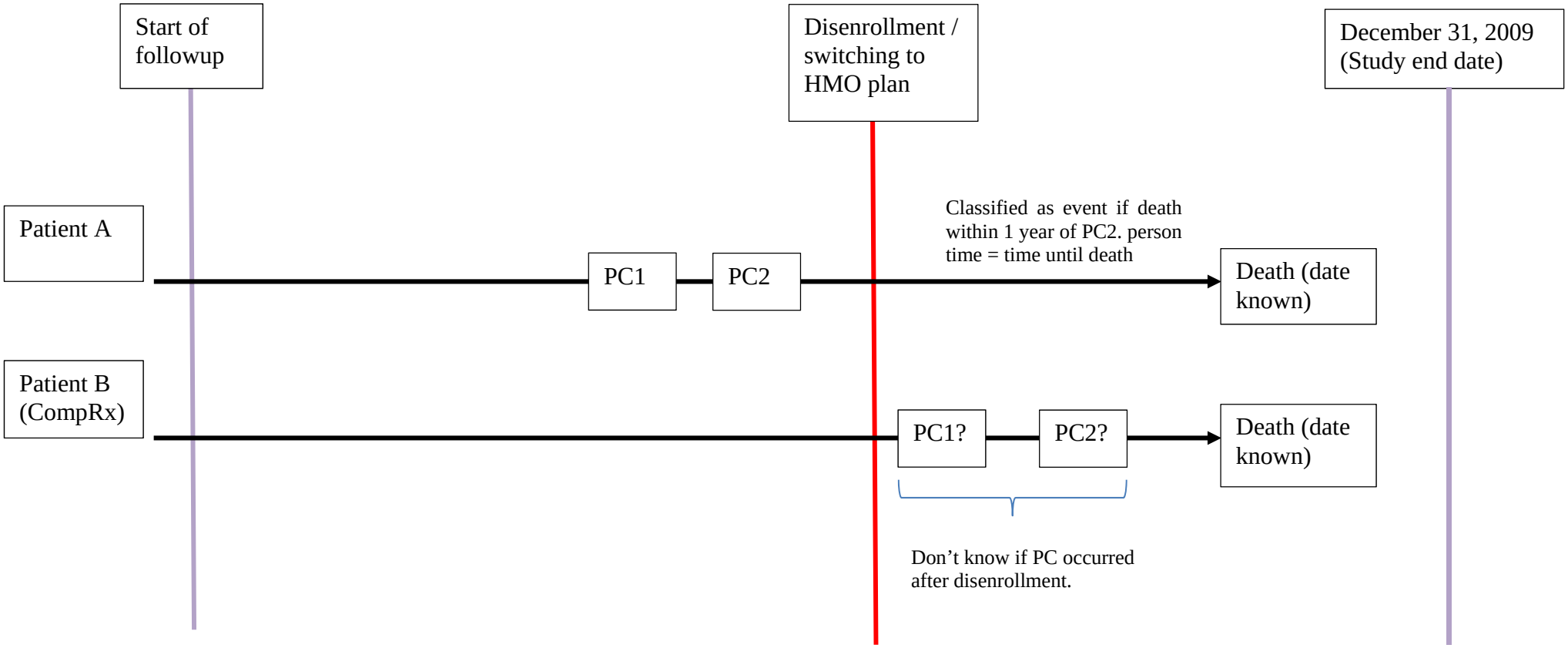
Figure 1: Primary approach (As treated analysis)



Analysis for the secondary outcome (pancreatic cancer mortality): For the analysis of PC mortality, 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 (death within a year of the second PC diagnosis) occurs or until the date of censoring (end of enrollment; end of the study period; death without 2 PC diagnoses in the prior year), whichever comes first.

While the date of death is known for every cohort member who actually died during the study period, we still need to consider censoring patients when they disenroll or switch to a HMO plan because we would not see a PC diagnosis after disenrollment. For example, as shown in figure 2, patient B will be censored according to the above algorithm when they disenroll or switch to a HMO plan. If we would ignore disenrollment, their death would be misclassified as a 'non-event'. The patient A disenrolls after 2 PC diagnoses and is not censored; with her death counted as an event and time until death as the person-time contributed. Comparing A and B may lead to biased estimates of hazard ratios. The magnitude of this bias may be small given that pancreatic cancer is rare and disenrollment rate from Medicare plans A and B is expected to be very low. Nevertheless, we will perform sensitivity analyses without censoring patient B at disenrollment or switch of plans based on the ITT approach.

Figure 2: Issues in the analysis of pancreatic cancer mortality



Additional analyses listed in section 10 will be performed as sensitivity analyses.

9. Covariates

Drug use will be measured in the 6 months up to (i.e., including) the index date and co-morbidity will be measured in the 12 months prior to the index date. The differential periods are chosen because of availability of parts A and B data prior to our first part D data (January 1, 2007).

Demographics: age, gender, race/ethnicity, available measures of socioeconomic status

Comorbidities: smoking status (COPD), congestive heart failure, renal insufficiency, diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, depression, inflammatory GI diseases, connective tissue diseases, infections (UTI and respiratory infections)

Co-Medications: number of drug classes used in the pre-index period

Health System Use: number of hospitalizations, days in hospital, number of physician encounters, number of ED visits, general utilization (flu vaccination, other health screenings), cancer screenings (mammography, endoscopy, PSA, pap smears)

Propensity score (PS) method will be used to adjust for potential confounding due to channeling between treatments. We will implement the PS using 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 in the weighted pseudo population. Any imbalance will be interpreted according to the potential of the imbalanced covariate to affect the risk for PC. 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. Sensitivity analyses

1. 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, 6-12, 12-24, 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, 24 months). This will be achieved by subtracting the corresponding days from the days of follow-up. Sensitivity analyses will also be conducted to account for carry-over effects (persistent effects

of the drug). To do so we will have additional censoring variables censoring follow-up time 3 months, 6 months, 12 months, and 24 months after the exposure defined censoring event as described 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 carry-over effects analyzed will be determined based on availability of (outcome) data for these analyses.

2. 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.
3. In the main study, patients with a diagnosis of any non-pancreatic cancer (except non-melanoma skin cancer) prior to the index date are excluded and patients with a diagnosis of any non-pancreatic cancer (except non-melanoma skin cancer) after the cohort entry date are censored since diagnostic-work-up or treatment of other cancers may affect the incidence of pancreatic cancer. Sensitivity analysis will be conducted by not excluding and/or censoring patients with cancers other than pancreatic cancer.
4. In the main study follow-up will start at the second prescription (cohort entry date). We will perform a sensitivity analysis starting follow-up at the first prescription (the index date).

11. Power analysis:

The following table presents the power and precision analysis estimated for different drug comparisons

Table 1: Power and precision analysis for different comparisons : based on estimated numbers from 2007 to 2010					
	GLP/TZD	**GLP/SU**	**GLP/LAI**	**DPP/TZD**	**DPP/SU**
Power calculations for Pancreatic Cancer					
Power to detect a relative risk of 3.0	74.00%	74.65%	91.59%	100%	100%
Power to detect a relative risk of 2.0	37.12%	38.30%	54.79%	99.36%	97.75%
Power calculations for death after Pancreatic Cancer diagnosis					
Power to detect a relative risk of 3.0	65.59%	62.30%	83.19%	100%	99.98%
Power to detect a relative risk of 2.0	31.76%	30.89%	44.85%	97.38%	90.39%
Precision analysis - Under the null (RR = 1), probability that the upper confidence limit will be less than a pre-specified value					
Outcome - Pancreatic Cancer (at least 2 PC diagnoses within 2 months, as treated analysis)					
probability that the upper confidence limit will be <3 under the null (RR = 1)	0.4048	0.4037	0.6626	0.9999	0.9994
probability that the upper confidence limit will be <2 under the null (RR = 1)	0.1907	0.1902	0.3232	0.956	0.9081
Outcome - Death anytime after Pancreatic Cancer diagnosis					
probability that the upper confidence limit will be <3 under the null (RR = 1)	0.3228	0.29	0.5158	0.9994	0.9875
probability that the upper confidence limit will be <2 under the null (RR = 1)	0.1552	0.1418	0.2425	0.909	0.7553

*As of Dec 8, 2012, only the data from 2006 – 2009 are available. For power and precision calculations, the number of new users and outcomes for 2010 were assumed to be the same as the number in 2009.
For the purposes of this table, the DPP group consists of only Sitagliptin new-users and the GLP group consists of Exenatide new-users.

12. Aim 2: Evaluate and quantify the use of diagnostic procedures (listed in Appendix B) that may lead to a preclinical diagnosis of pancreatic cancer among new users of IBRx and CompRx in the 6 month period before and after the start of drug therapy.

The study inclusion criteria for this analysis will be same as the criteria for aim 1 except that we will not require a second prescription of the same drug class. Patients filling only one prescription of IBRx and CompRx after a 6 month washout period will be included in the study. The index date will be the date of first prescription of IBRx or CompRx and follow-up will start at the index date.

Our aim is to quantify any differential in diagnostic workup:

1. Compare the cumulative incidence (incidence proportion) of diagnostic procedures/lab tests in the 6 months after drug initiation (index date) in the IBRx new-users with the corresponding incidence in CompRx new-users. This will be done using the primary analysis described below.
2. Compare the increase in cumulative incidence of diagnostic workup is in the 6 months post drug initiation relative to 6 months prior to initiation in IBRx with CompRx new-users. This will be done using the secondary analysis described below.

A. Primary analysis: Cumulative incidence post treatment initiation

In the primary analysis, cumulative incidence (incidence proportion) for each of the procedure categories (Appendix B column 4) and for all procedures together in the 6 months after the index date will be calculated.

To estimate the cumulative incidence e.g., for abdominal MRI in the 6 month post initiation for sitagliptin new-users we will use Kaplan-Meier plots and 1 – survival without an incident code for abdominal MRI in the 6 months after the index date. This method allows us to include everyone (i.e., allows for censoring).

For each of the comparisons in section 5, the cumulative incidence for each procedure and all procedures together for IBRx versus CompRx in the 6 months post-index period will be compared using a ratio of cumulative incidences (risk ratio) and a difference of cumulative incidences (risk difference).

Depending on the availability of data we will examine the monthly cumulative incidence of diagnostic work-up among the new users of IBRx and CompRx during 6 months before and after the index date. We will also examine the pattern of monthly risk ratios for diagnostic work-up with IBRx versus CompRx.

In addition to the unadjusted crude analysis described above, we will also conduct an analysis adjusted for the factors listed below. Drug use and diagnostic workup will be measured in the 6 months up to (i.e., including) the index date and co-morbidity will be measured in the 12 months prior to the index date.

- Diagnostic work-up in the 6 months before the index date
- Demographic factors (age, gender, race/ethnicity, region)

- Diabetes severity using measures available in the data (diabetic complications, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy)
- Other comorbidities (smoking status (COPD), congestive heart failure, renal insufficiency, depression, inflammatory GI diseases, connective tissue diseases, infections)
- Number of drug classes used prior to the index date
- Health System Use variables

B. Secondary analysis: Cumulative incidence pre and post treatment initiation

Cumulative incidences for each of the procedures and all procedures combined will be calculated for each drug or drug class of interest in the 6 months before and after the index date. Difference between the cumulative incidences post and pre drug initiation will be calculated for each drug as (cumulative incidence in the 6 months after the index date) – (cumulative incidence in the 6 months before the index date).

The change (most likely an increase) in cumulative incidence post-initiation for IBRx new-users versus CompRx new-users will be compared by taking a difference of the above differences.

C. Time to event analysis:

Because the main argument about earlier diagnosis of pancreatic cancer is about time to event rather than risk (cumulative incidence), we will also fit a time to event (Cox) model for the above defined outcomes over the entire follow-up period. Propensity score method as described above will be used to control confounding. Alternative methods to define cumulative incidence and risk periods will be considered based on the availability of data (following the primary and secondary analyses outlined above).

Sensitivity analysis:

1. The diagnostic work-up after drug initiation can be thought of as 'testing because of the drug'. Assuming that the drugs were actually used in the month before the index date, we will conduct a sensitivity analysis by counting the diagnostic procedures in that month as 'testing due to the drug'. That is, for the cumulative incidence analysis, the post-initiation diagnostic workup will include testing during 7 months (one month before and 6 months after the index date). For the time-to-event analysis, the follow-up will start a month before the index date.

2. It is possible that some 'new-users' of CompRx used IBRx before the start of washout period (as defined in the new-user algorithm) and discontinued IBRx because of adverse events. For such 'new-users' of CompRx, the diagnostic work-up before the initiation of CompRx may seem elevated (which is actually because of the IBRx therapy they were on). To increase the probability that CompRx initiators were previously not on IBRx therapy, the analyses A and C (cumulative incidence in the post initiation period and time-to-event analysis) will be conducted by EXCLUDING patients who had diagnostic workup in the period prior to initiation of therapy.

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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 1st 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

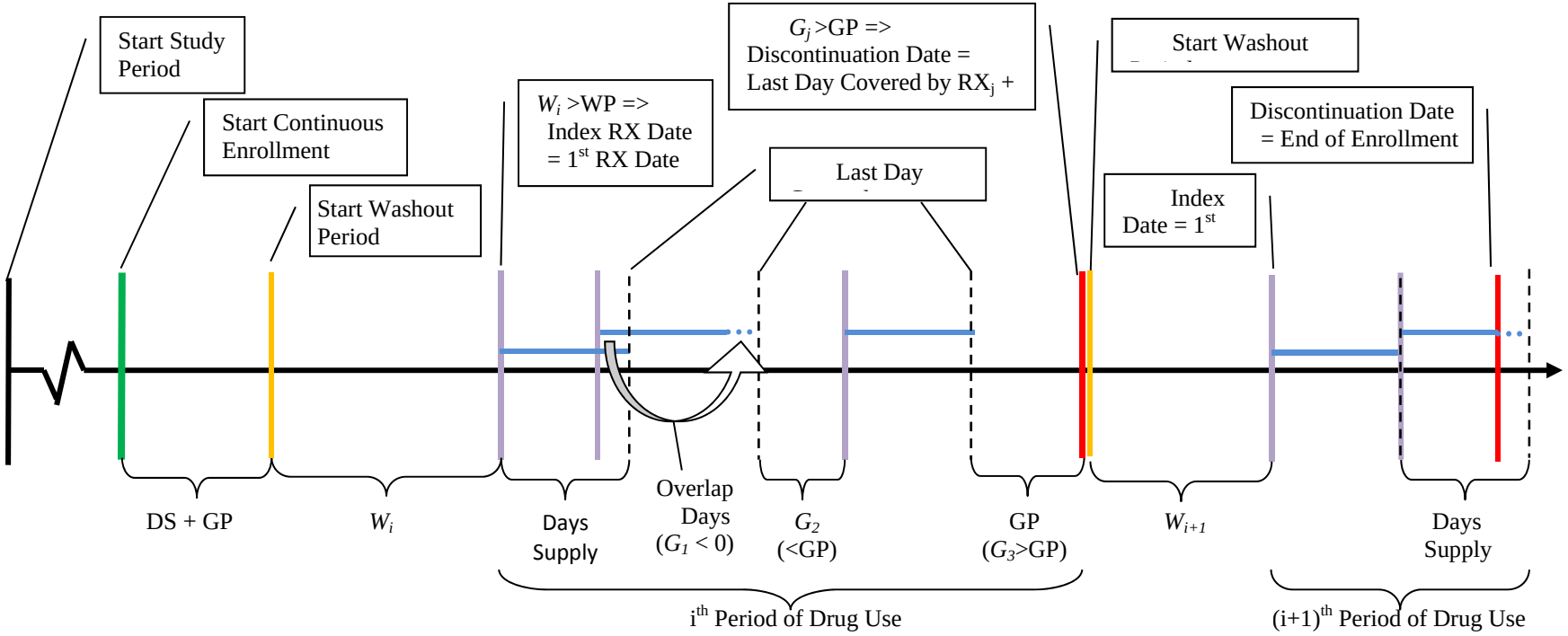
If W_1 > WP then patient's period of drug use is eligible for the new user cohort.

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(Pervious 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.

Appendix B - List of codes for diagnostic workup (aim 2)

Type	Code	Procedure	Procedure Categories
Proc ICD9	88.76	Diagnostic ultrasound of abdomen and retroperitoneum	endoscopic ultrasound
Proc CPT	43231	Esoph endoscopy w/US exam	
Proc CPT	43237	Endoscopic US exam, esoph	
Proc CPT	43259	Endoscopic ultrasound exam	
Proc CPT	76975	GI endoscopic ultrasound	
Proc CPT	48100	Biopsy of pancreas, open	Biopsy
Proc CPT	48102	Needle biopsy, pancreas	
Proc CPT	10021	FNA w/o image	
Proc CPT	10022	FNA w/image	
Proc ICD9	52.11	Closed [aspiration] [needle] [percutaneous] biopsy of pancreas	
Proc ICD9	52.12	Open biopsy of pancreas	
Proc ICD9	52.14	Closed [endoscopic] biopsy of pancreatic duct	
Proc CPT	74150	CT abdomen w/o dye	Abdominal CT scan
Proc CPT	74160	CT abdomen w/dye	
Proc CPT	74170	CT abdomen w/o & w/dye	
Proc CPT	74181	MRI abdomen w/o dye	Abdominal MRI
Proc CPT	74182	MRI abdomen w/dye	
Proc CPT	74183	MRI abdomen w/o & w/dye	
Proc CPT	76498	MRI procedure	
Proc CPT	74300	X-ray bile ducts/pancreas	X-ray
Proc CPT	74305	X-ray bile ducts/pancreas	
Proc CPT	74320	Contrast X-ray of bile ducts	
Proc CPT	74329	X-ray for pancreas endoscopy	
Proc CPT	74330	X-ray bile/panc endoscopy	
Proc CPT	43260	Endo cholangiopancreatograph	ERCP
Proc CPT	43261	Endo cholangiopancreatograph	
Proc CPT	43262	Endo cholangiopancreatograph	
Proc CPT	43263	Endo cholangiopancreatograph	
Proc CPT	43264	Endo cholangiopancreatograph	
Proc CPT	43265	Endo cholangiopancreatograph	
Proc CPT	43267	Endo cholangiopancreatograph	
Proc CPT	43268	Endo cholangiopancreatograph	
Proc CPT	43269	Endo cholangiopancreatograph	
Proc CPT	43271	Endo cholangiopancreatograph	
Proc CPT	43272	Endo cholangiopancreatograph	
Proc ICD9	51.1	Endoscopic retrograde cholangiopancreatography [ERCP]	
Proc ICD9	52.13	Endoscopic retrograde pancreatography [ERP]	ERP
Proc ICD9	51.82	Pancreatic sphincterotomy	Pancreatic sphincterotomy
Proc CPT	47560	Laparoscopy w/cholangio	Laparoscopy
Proc CPT	47561	Laparo w/cholangio/biopsy	

Appendix B - List of codes for diagnostic workup (aim 2)

Type	Code	Procedure	Procedure Categories
Proc CPT	80082	Pancreatic panel	Lab test 1
Proc CPT	82656	Pancreatic elastase, fecal	Lab test 2
Proc CPT	86301	Immunoassay, tumor, ca 19-9	Lab test 3
Proc CPT	82150	Assay of amylase	Lab test 4
Proc CPT	82156	Urine amylase	
Proc CPT	82378	carcinoembryonic antigen	Lab test 5
Proc CPT	83690	Assay of lipase	Lab test 6
Proc CPT	84488	Test feces for trypsin	Lab test 7
Proc CPT	84490	Assay of feces for trypsin	

Notes:

- As of Dec 8, 2012, only data from 2006-2009 is available and the 2010 data is expected to be available early January 2013. An abstract based on this protocol will be submitted to the ADA meeting based on the 2006-2009 data. The final presentation will have the results including 2010 data.
- 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.