Boehringer Ingelheim

Protocol for observational studies based on existing data

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BI Study Number:	1218.163
BI Investigational Product(s):	Linagliptin
Title:	Active surveillance research program for the assessment of the safety and the effectiveness of linagliptin
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PASS:	Yes Voluntarily initiated with the aim to better understand the comparative safety and effectiveness of oral hypoglycemic agents.
EU PAS register number:	To be completed
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Marketing authorization holder(s):	Boehringer Ingelheim GmbH
Joint PASS:	No
Research question and objectives:	This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other oral hypoglycemic medications, followed longitudinally for the occurrence of a variety of health outcomes. Objectives: 1) To conduct a multi-year surveillance program that establishes and periodically updates initiator cohorts of linagliptin, within-class comparators (saxagliptin, sitagliptin, alogliptin), and out-of-class comparators (glitazones, 2nd generation of sulfonylureas (SUs)), and longitudinally follow them for the incidence of a variety of health outcomes (e.g.cardiovascular, renal impairment).

	2) To conduct direct comparisons over time among hypoglycemic agents (linagliptin versus other DPP-4, glitazones 2nd generation of SUs) and quantify the association between hypoglycemic choice and the occurrence of specific outcomes of interest. The primary outcomes of interest will be the occurrence of a major cardiovascular event (defined as composite of coronary revascularization, acute coronary syndrome hospitalization, ischemic and hemorrhagic stroke) and the individual components of the composite cardiovascular outcome. Heart failure hospitalization, incident end-stage renal disease and acute renal failure will be considered secondary outcomes of interest.
Country(-ies) of study:	US
Author:	
Marketing authorisation holder(s):	
MAH contact person:	
EU-QPPV:	
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	Jul 03, 2014

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1. LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AES	Advanced Encryption Standard
AGI	Alpha-Glucosidase Inhibitors
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
ARF	Acute Renal Failure
ASCVD	Atherosclerotic Cardiovascular Disease
BI	Boehringer Ingelheim International, GmbH
CABG	Coronary Artery Bypass Graft
CHF	Congestive Heart Failure
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
CPT-4	Common Procedural Terminology, 4th Edition
Cr	Creatinine
DM	Diabetes Mellitus
DPP-4	Dipeptidyl Peptidase-4
dx	Diagnosis-Related Group
ECG	Electrocardiogram
EC-IC	Extracranial-Intracranial
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-stage Kidney Disease
ESRD	End-stage Renal Disease
FDA	United States Food and Drug Administration
FPG	Fasting Plasma Glucose
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HCPC	Healthcare Common Procedure Coding
HDL	High-density Lipoprotein
hdPS	High-dimensional Propensity Score
HIV	Human Immunodeficiency Virus
HIT	Heparin-Induced Thrombocytopenia
HONK	Hyperosmolar Hyperglycemic Nonketotic Syndrome
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision

IRB	Internal Review Board
ITT	Intention-to-Treat
LDL	Low-density Lipoprotein
LMWH	Low Molecular Weight Heparin
LOS	Length of Stay
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
NOS	Not Otherwise Specified
NPH	*Neutral Protamine Hagedorn*
NPV	Negative Predictive Value
OAD	Oral Antidiabetic
OTC	Over The Counter
Pap	Papanicolaou
PCI	Percutaneous Coronary Intervention
PCOS	Polycystic Ovary Syndrome
PPV	Positive Predictive Value
PS	Propensity Score
PSA	Prostate-Specific Antigen
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral Vascular Disease
RR	Relative Risk
SCr	Serum Creatinine
SD	Standard Deviation
s.e.	Standard Error
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TB	Terabytes
TZD	Thiazolidinedione
US	United States
VLDL	Very low-density lipoprotein

2. RESPONSIBLE PARTIES

3. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Trajenta			
Name of active ingredient: Linagliptin			
Protocol date: 03 Jul 2014	**Study number:** 1218.163	**Version/Revision: 1**	**Version/Revision date:**
Title of study:	Active surveillance research program for the assessment of the safety and the effectiveness of linagliptin		
Rationale and background:	Dipeptidyl peptidase-4 (DPP-4) inhibitors, including linagliptin, saxagliptin, alogliptin and sitagliptin, are a new class of oral hypoglycemic agents approved in the United States. They are indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Evidence to date suggests that these drugs offer advantages over older therapies in that they are weight-neutral, are associated with a minimal risk of hypoglycemia, and can be administered with once-daily dosing. Linagliptin offers a further advantage in that its dose does not need to be adjusted based on renal or hepatic function. While there do not appear to be contraindications (except for hypersensitivity to the active ingredient or any of the excipients) to the use of Linagliptin, the long-term safety and effectiveness have not been well characterized. Given the high prevalence of T2DM, it is important to understand the comparative safety and effectiveness of oral hypoglycemic agents. This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other oral hypoglycemic medications, followed longitudinally for the occurrence of a variety of health outcomes. The initial analyses will be based on data from May 2011 through June 2013 and will be sequentially updated every 6 months through December 2016.		
Research question and objectives:	This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other oral hypoglycemic medications, followed longitudinally for the occurrence of a variety of health outcomes. Objectives: 1. To conduct a multi-year surveillance program that establishes and periodically updates initiator cohorts of linagliptin, within-class comparators (saxagliptin, sitagliptin, alogliptin), and out-of-class comparators (glitazones, 2nd generation of sulfonylureas (SUs)), and longitudinally follow them for the incidence of a variety of health outcomes (i.e. cardiovascular, renal impairment).		

	2. To conduct direct comparisons over time among hypoglycemic agents (linagliptin versus other DPP-4 inhibitors, glitazones 2nd generation of SUs) and quantify the association between hypoglycemic choice and the occurrence of specific outcomes of interest. The primary outcomes of interest will be the occurrence of a major cardiovascular event (defined as composite of coronary revascularization, acute coronary syndrome hospitalization, ischemic and hemorrhagic stroke) and the individual components of the composite cardiovascular outcome. Heart failure hospitalization, incident end-stage renal disease and acute renal failure will be considered secondary outcomes of interest. We will use multiple comparators because there are several potential treatment alternatives to linagliptin for patients with T2DM. Although linagliptin is the only DPP-4 inhibitor that does not require dose adjustment for severe renal impairment, within-class comparators, i.e. other dipeptidyl peptidase-4 (DPP-4) inhibitors, are expected to have utilization patterns similar to linagliptin and to be prescribed to patients with similar clinical profile Out-of-class comparators, i.e. second-generation sulfonylureas and pioglitazone, will be considered in order to investigate between-class effects. 2nd generation sulfonylureas and glitazones are oral hypoglycemics and are not usually used as 1st-line therapy. Therefore, they may be more commonly used as an alternative to linagliptin than other treatment options such as glucagon-like peptide-1 (GLP-1) receptor agonists or metformin. SGLT2 inhibitors will not be included as comparators because the first agent in the class, canagliflozin, was not approved until March 2013. As such most SGLT2 inhibitors will be available for less than half the study period and the sample that will accumulate will most likely insufficient for powered analysis. Patients with prior use of a medication within the same class will be excluded from the primary analysis. We will also conduct a secondary analysis including DPP4 initiators with or without prior use of another DPP4, pioglitazone users with or without prior rosiglitazone use, and 2nd generation sulfonylurea use with or without prior sulfonylurea use.
Study design:	Observational cohort study
Population:	Patients ≥18 years old with a recorded diagnosis of type 2 diabetes mellitus (T2DM) who initiated linagliptin, sitagliptin, saxagliptin, alogliptin, glitazones, or 2nd generation sulfonylureas (Glipizide,Glimepiride) identified in US health insurance databases

Variables:	Pre-specified outcomes of interest include the following:
	• Primary outcome: Major adverse cardiovascular event
	  o Coronary revascularization (elective and non-elective procedure)
	  o Acute coronary syndrome (ACS) hospitalization
	  o Stroke (Ischemic and hemorrhagic stroke)
	• Individual components of the composite major adverse cardiovascular event listed above
	Secondary outcomes:
	• Heart failure hospitalization

	• Incident End-Stage Renal Disease (ESRD) • Acute renal failure (ARF) • ARF that requires dialysis
Data sources:	Two United States commercial health insurance databases: UnitedHealth 2006 through June 2013 and Marketscan 2006 through June 2013 both with 6-month updates through Dec 2016 Data include claims for prescriptions, inpatient and outpatient visits and procedures, and insurance plan enrollment information and demographics. Lab test results are available for a subset of the population.
Study size:	~ 30,000 linagliptin initiators, with other DPP-4, 2nd generation of SUs, Glitazones of ~30,000 each of the comparator groups
Data analysis:	For each comparison, study cohorts will be formed by propensity score matching within blocks of calendar time. This study will compare rates of outcomes among patients who initiate Linagliptin versus initiators of other DPP-4s, 2nd generation of SUs, glitazones. Analyses will account for different follow-up times and censoring. A total of seven interim analyses will be conducted starting from Jun 2014. The final analyses will be based on data from May 2011- Dec 2016 Patient characteristics will be based on all available information up to January 2006.

Milestones:	Year 1 Dec, 2012 Contract Apr, 2013 Draft Protocol Jun, 2014 Final Protocol Year 2 Oct, 2014 Interim Report Jan, 2015 Interim Report Year 3 Jun, 2015 Interim Report Dec, 2015 Interim Report Year 4 Jun, 2016 Interim Report Dec, 2016 Interim Report Year 5 Jun, 2017 Interim Report Year 6 Feb, 2018 Draft Final Report Apr, 2018 Final Report

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	**Planned Date**
Registration in the EU PAS register	30 June 2014
Start of data collection	1 July 2014
End of data collection	31 January 2018
Interim report 1	31 Oct2014
Interim report 2	31 January 2015
Interim report 3	30 June 2015
Interim report 4	31 December 2015
Interim report 5	30 June 2016
Interim report 6	31 December 2016
Interim report 7	30 June 2017
Draft final report	28 February 2018
Final report of study results:	31 April 2018

Planned dates for the following milestones:

Date	**Phase 4**		**Data Source**	
	Milestone	Month	United Claims and lab data are released every 6 months in Jan and Jul (6-month lag time)	MarketScan Claims data are released quarterly in Mar, Jun, Sept, and Dec (9-month lag time) *Lab data are released yearly in Dec (12-month lag time)*
	Year 1			
Dec, 2012	Contract	0		
Apr, 2013	Draft Protocol	4		
June, 2014	Final Protocol	18		
	Year 2			
Oct, 2014	Interim Report	22	Data through Jun 2013 (Update received in Jan 2014)	Claims through Jun 2013 (Update received in Mar 2014) *Labs through Dec 2012* *(Update received in Dec 2013)*

Jan, 2015	Interim Report	25	Data through Dec 2013 (Update received in Jul 2014)	Claims through Dec 2013 (Update received in Sept 2014) *Labs through Dec 2012* *(Update received in Dec 2013)*
	Year 3			
Jun, 2015	Interim Report	30	Data through Jun 2014 (Update received in Jan 2015)	Claims through Jun 2014 (Update received in Mar 2015) *Labs through Dec 2013* *(Update received in Dec 2014)*
Dec, 2015	Interim Report	36	Data through Dec 2014 (Update received in Jul 2015)	Claims through Dec 2014 (Update received in Sept 2015) *Labs through Dec 2013* *(Update received in Dec 2014)*
	Year 4			
Jun, 2016	Interim Report	42	Data through Jun 2015 (Update received in Jan 2016)	Claims through Jun 2015 (Update received in Mar 2016) *Labs through Dec 2014* *(Update received in Dec 2015)*
Dec, 2016	Interim Report	48	Data through Dec 2015 (Update received in Jul 2016)	Claims through Dec 2015 (Update received in Sept 2016) *Labs through Dec 2014* *(Update received in Dec 2015)*
	Year 5			
Jun, 2017	Interim Report	54	Data through Jun 2016 (Update received in Jan 2017)	Claims through Jun 2016 (Update received in Mar 2017) *Labs through Dec 2015* *(Update received in Dec 2016)*
	Year 6			
Feb, 2018	Draft Final Report	62	Data through Dec 2016 (Update received in Jul 2017)	Claims through Dec 2016 (Update received in Dec 2017) *Labs through Dec 2016* *(Update received in Dec 2017)*
Apr, 2018	Final Report	64	Data through Dec 2016 (Update received in Jul 2017)	

6. RATIONALE AND BACKGROUND

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including linagliptin, saxagliptin, alogliptin and sitagliptin, are a new class of oral hypoglycemic agents approved in the United States. They are indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Evidence to date suggests that these drugs offer advantages over older therapies in that they are weight-neutral, are associated with a minimal risk of hypoglycemia, and can be administered with once-daily dosing.[P12-05315] Linagliptin offers a further advantage in that its dose does not need to be adjusted based on renal or hepatic function.[P12-05992] While there do not appear to be contraindications (except for hypersensitivity to the active ingredient or any of the excipients) to the use of Linagliptin, the long-term safety and effectivness have not been well characterized.

Given the high prevalence of T2DM, it is important to understand the comparative safety and effectiveness of oral hypoglycemic agents.
This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts of patients initiating linagliptin, other DPP-4 inhibitors, and other oral hypoglycemic medications, followed longitudinally for the occurrence of a variety of health outcomes. The initial analyses will be based on data from May 2011 through June 2013and will be sequentially updated every 6 months through December 2016.

Table 1 Cohort-defining non-insulin hypoglycemic medications

Class	Drug	FDA approval date	Combination products
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Linagliptin	May 2, 2011	+ metformin (Jentadueto). approved Jan 30, 2012
	Sitagliptin	Oct 16, 2006	+ metformin (Janumet, Janumet XR), + simvastatin (Juvisync),
	Saxagliptin	July 31, 2009	+ metformin (Kombiglyze XR)
	Alogliptin	Jan 25, 2013	+ metformin (Kazano) + pioglitazone (Oseni)
Glitazones	Pioglitazone	Jul 15, 1999	+ metformin (ACTOplus met, ACTOplus met XR) + glimepiride (Duetact)
2nd Generation Sulfonylureas	Glipizide	May 8, 1984	+ metformin
	Glimepiride	Nov 30, 1995	+ rosiglitazone (Avandaryl) + pioglitazone (Duetact)
	Glyburide	May 1, 1984	+ metformin (Glucovance, generic)

7. RESEARCH QUESTION AND OBJECTIVES

This protocol is for a series of comparative effectiveness and safety analyses within periodically updated cohorts. The specific objectives of this surveillance program are:

- To conduct a multi-year research program that establishes and periodically updates initiator cohorts of linagliptin, within-class comparators (saxagliptin, sitagliptin, alogliptin), and out-of-class comparators (glitazones or second generation of SUs), describes patient characteristics over time, and longitudinally follows drug initiators for the incidence of a variety of health outcomes (i.e. cardiovascular outcomes, renal impairment).
- To conduct direct comparisons among hypoglycemic agents and quantify the association between hypoglycemic choice and the occurrence of both specific outcomes of interest and other outcomes potentially brought forward during the study period.

The primary outcomes of interest will be the occurrence of a major cardiovascular event (defined as composite of coronary revascularization, acute coronary syndrome hospitalization, ischemic and hemorrhagic stroke) and the individual components of the composite cardiovascular outcome. Heart failure hospitalization, incident end-stage renal disease and acute renal failure will be considered secondary outcomes of interest. There are no a priori hypotheses.

8. RESEARCH METHODS

Description of the research methods, including:

8.1 STUDY DESIGN

This study will involve a sequential new user cohort design (of Linagliptin and the other comparators).
This study design will allow the inclusion of additional subjects and follow-up time, as data become available, over the course of the study period.

8.2 SETTING

Initiators of linagliptin and other oral hypoglycemic medications from UnitedHealth Research Database and MarketScan source data between May 2011 and Jun 2013, with 6-month updates through December 2016.

The United Healthcare and Marketscan data were selected as data sources for several reasons. These commercial databases involve relatively short lag-times for inclusion of data so that they are more up-to-date than many alternatives (e.g. Medicare data) and they provide a fairly complete picture of interactions between patients and the healthcare system for a large cohort of patients. Further, there is the opportunity to go beyond the source data through linkages to laboratory data and electronic medical records.

Finally, the inclusion of two data sources will increase the size of the elderly population available for the study, since many patients over the age of 65 transition from commercial health insurers to Medicare and are thereby under-represented in commercial databases.

8.2.1 Subjects

From the UnitedHealth Research Database and MarketScan source data, we will identify patients with a recorded diagnosis of type 2 diabetes mellitus (T2DM) who initiated linagliptin, sitagliptin, saxagliptin, alogliptin, pioglitazone, or 2nd generation sulfonylureas between May 2011 and June 2013. The following inclusion and exclusion criteria were developed with the goal of obtaining a population that is broadly representative of patients with T2DM and within which valid comparisons can be made due to the selection of linagliptin users and users of other oral glucose medications that are used at similar stages of diabetes.

Inclusion criteria:

- Patients ≥18 years old
- Patients received a dispensing of linagliptin or a comparator hypoglycemic (see table 1) medication within the study timeframe AND had a diagnosis of T2DM (ICD-9 Dx code of 250.x0 or 250.x2) prior to drug initiation.[1]
  We are restricting to initiators with evidence of type T2DM in order to exclude

1 All available data prior to and including the index date will be used to identify the presence of a recorded T2DM and T1DM diagnoses

patients receiving non-insulin hypoglycemic agents for other indications (e.g., polycystic ovary syndrome, infertility, weight loss, etc.).

- The first dispensing is preceded by at least 6 months of continuous enrollment in the study database, defined as the routine maximum allowed bridge for administrative gaps of enrollment, i.e, <32 days enrollment gap using the enrollment and disenrollment dates.

'New users' definition: The study will focus on "new users", defined as patients with no dispensing of that particular medication in the prior 6 months. The patients will be additionally classified in:

- "Treatment-naive new users", defined as patients with no use of any hypoglycemic agent (including insulin) in the prior 6 months,
- "non-naive new users", defined as patients initiating a new hypoglycemic agent as a switch from or addition to a previous hypoglycemic medication, will also be identified and investigated in secondary analyses.

All patients initiating hypoglycemic drugs will be classified as initiators of a specific hypoglycemic drug or class on the basis of the first in time drug initiation within a time-block. Patients' follow-up will terminate at the end of their exposure time window, which will vary according to the specific outcome and analysis as specified in section 8.3. If the same patient re-initiates treatment later on, (s)he may re-enter the cohort at that time, but only in the case that the patient was not successfully matched during the time-block corresponding to his/her original drug initiation and meets all inclusion criteria at the time of the matching. Thus, patients will contribute only once to the balanced study cohort (Figure 1). Patients with prior within-class medication use during the preceding 6 months will be excluded from the primary analyses.

Exclusion criteria:

- Patients with missing or ambiguous age or sex information.
- Patients under the age of 18
- Patients with type 1 diabetes mellitus (T1DM) defined as at least 1 inpatient or outpatient ICD-9 Dx code of 250.x1 or 250.x3 prior to drug initiation1. Although the use of oral hypoglycemic drugs is a strong predictor for underlying T2DM [R12-3697], it was also decided to exclude the patients with prior recorded diagnosis of T1DM to further limit the chances of misclassification of the underlying disease.
- Secondary diabetes, and gestational diabetes in the 6 months prior to drug initiation
- History of cancer at any time prior to drug initiation
- End-stage renal disease (ESRD) in the 6 months prior to drug initiation
- HIV diagnosis or treatment at any time prior to drug initiation
- Organ transplant at any time prior to drug initiation

Table 2 Exclusion criteria: Definition of secondary diabetes, cancer history, ESRD, HIV, and organ transplant

Secondary diabetes	ICD-9 procedure: 249.xx Secondary diabetes 648.8x Gestational diabetes
History of cancer	MALIGNANT NEOPLASMS 140.xx-208.xx (except 173.xx, non-melanoma skin cancer) NEUROENDOCRINE TUMORS 209.xx BENIGN NEOPLASMS 210-229.xx CARCINOMA IN SITU 230-234.xx NEOPLASMS OF UNCERTAIN BEHAVIOR 235-238.xx NEOPLASMS OF UNSPECIFIED NATURE 239.xx
ESRD	A laboratory measurement of eGFR < 15ml/min/1.73m^2 OR DIALYSIS ICD-9 procedure: 39.95 hemodialysis 54.98 peritoneal dialysis 38.95 Venous catheterization for renal dialysis 39.27 Arteriovenostomy for renal dialysis 39.42 Revision of arteriovenous shunt for renal dialysis 39.43 Removal of arteriovenous shunt for renal dialysis ICD-9 diagnoses: V45.1 renal dialysis status V56.0 extracorporeal dialysis V56.8 peritoneal dialysis CPT4: 90935 HEMODIALYSIS PROC W/SINGLE PHYSICIAN EVALUATION 90937 HEMODIALYSIS, REPEATED EVAL, W/WO REVISION DIALYSIS PRESCRIPTION 90940 HEMODIALYSIS ACCESS FLOW STUDY, BY INDICATOR DILUTION METHOD, HOOK UP; MEASUREMENT & DISCONNECTION 90945 DIALYSIS, OTHER THAN HEMODIALYSIS, SINGLE PHYSICIAN EVAL 90947 DIALYSIS PROCEDURE, OTHER THAN HEMODIALYSIS, REPEATED PHYSICIAN EVAL 90989 DIALYSIS TRAINING, PATIENT, W/HELPER WHERE APPLICABLE, ANY MODE, COMPLETED COURSE 90993 DIALYSIS TRAINING, PATIENT, W/HELPER WHERE APPLICABLE, ANY MODE, COURSE INCOMPLETE, PER SESSION 99512 HOME VISIT, HEMODIALYSIS 99559 HOME INFUSION, PERITONEAL DIALYSIS, PER VISIT OR RENAL TRANSPLANT V42.0 Kidney transplant 55.6x Kidney transplant 996.81 Complication of transplanted kidney CPT4: 50360 RENAL ALLOTRANSPLANTATION, IMPLANTATION, GRAFT; W/O DONOR & RECIPIENT NEPHRECTOMY 50365 RENAL ALLOTRANSPLANTATION, IMPLANTATION, GRAFT; W/RECIPIENT NEPHRECTOMY 50380 RENAL AUTOTRANSPLANTATION, REIMPLANTATION, KIDNEY OR RENAL ICD9-defined ESRD 585.5 ESKD with no mention of dialysis 585.6 ESKD on dialysis

Table 2 (cont'd) Exclusion criteria: Definition of secondary diabetes, cancer history, ESRD, HIV, and organ transplant

HIV	042 Human immunodeficiency virus [HIV] disease 079.53 Human immunodeficiency virus, type 2 [HIV-2] V08 Asymptomatic human immunodeficiency virus [HIV] infection status OR filled prescription for HIV treatment: Abacavir Amprenavir Atazanavir Darunavir Delavirdine Didanosine Efavirenz Emtricitabine Enfuvirtide Etravirine Fosamprenavir Indinavir Lamivudine-Zidovudine Maraviroc Nelfinavir Nevirapine Raltegravir Rilpivirine Ritonavir Ritonavir-Lopinavir Saquinavir Stavudine Tipranavir Zalcitabine Zidovudine
Organ Transplant	ICD-9 diagnoses: V42.0 Kidney V42.1 Heart V42.6 Lung V42.7 Liver V42.8x Other specified organ or tissue V42.81 Bone marrow V42.83 Pancreas V42.84 Intestines V42.89 Other V42.9x Unspecified organ or tissue V58.44 Aftercare following organ transplant E878.0x Surgical operation with transplant of whole organ 996.8x Complications of transplanted organ ICD-9 procedures: 33.5x Lung transplant 33.6x Combined heart-lung transplantation 37.51 Heart transplantation 41.0x Bone marrow 46.97 Transplant of intestine 50.5x Liver transplant 52.8x Transplant of pancreas 55.6x Transplant of kidney

Table 2 (cont'd) Exclusion criteria: Definition of secondary diabetes, cancer history, ESRD, HIV, and organ transplant

	CPT4 codes 32851 LUNG TRANSPLANT, SINGLE; W/O CARDIOPULMONARY BYPASS 32852 LUNG TRANSPLANT, SINGLE; W/CARDIOPULMONARY BYPASS 32853 LUNG TRANSPLANT, DOUBLE (BILAT SEQUENTIAL/EN BLOC); W/O CARDIOPULMONARY BYPASS 32854 LUNG TRANSPLANT, DOUBLE (BILAT SEQUENTIAL/EN BLOC); W/CARDIOPULMONARY BYPASS 33935 HEART-LUNG TRANSPLANT W/RECIPIENT CARDIECTOMY-PNEUMONECTOMY 33945 HEART TRANSPLANT, W/WO RECIPIENT CARDIECTOMY 38240 BONE MARROW/BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION; ALLOGENIC 38241 BONE MARROW/BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION; AUTOLOGOUS 44135 INTESTINAL ALLOTRANSPLANTATION; FROM CADAVER DONOR 44136 INTESTINAL ALLOTRANSPLANTATION; FROM LIVING DONOR 47135 LIVER ALLOTRANSPLANTATION; ORTHOTOPIC, PARTIAL/WHOLE, FROM CADAVER/LIVING DONOR, ANY AGE 47136 LIVER ALLOTRANSPLANTATION; HETEROTOPIC, PARTIAL/WHOLE, FROM CADAVER/LIVING DONOR, ANY AGE 48554 TRANSPLANTATION, PANCREATIC ALLOGRAFT 48556 REMOVAL, TRANSPLANTED PANCREATIC ALLOGRAFT 50360 RENAL ALLOTRANSPLANTATION, IMPLANTATION, GRAFT; W/O DONOR & RECIPIENT NEPHRECTOMY 50365 RENAL ALLOTRANSPLANTATION, IMPLANTATION, GRAFT; W/RECIPIENT NEPHRECTOMY 50370 REMOVAL, TRANSPLANTED RENAL ALLOGRAFT 50380 RENAL AUTOTRANSPLANTATION, REIMPLANTATION, KIDNEY

8.2.2 Cohort formation

We will receive new data as they become available on a periodic basis (every 6 months) and we will update the study cohorts through Dec 2016. Initiators of linagliptin, and comparator drugs identified in each data cut, as previously described, will form sequential cohorts.
In each sequential cohort we will balance baseline covariates among patients initiating each drug by means of a multivariate confounder summary score (by matching on the exposure propensity score). In the primary as-treated analysis, patients' follow-up will end at treatment discontinuation, allowing a grace period, as specified in table 4. If the same patient re-initiates treatment later on after a treatment gap of ≥6 months, (s)he may re-enter the cohort at that time, but only in case the patient was not successfully matched during the time-block corresponding to his/her original drug initiation (Figure 1).

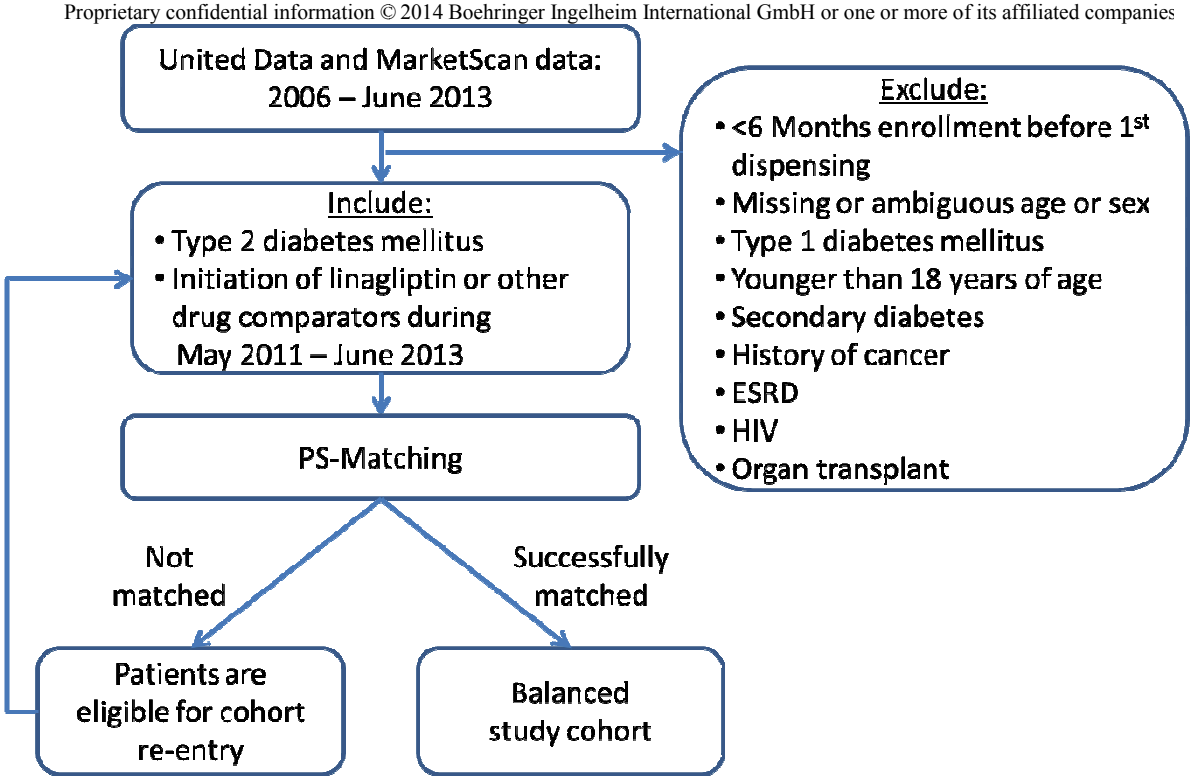

Figure 1 Patient Selection Flow Chart for initial time-block

8.3 VARIABLES

8.3.1 Exposure

- The primary contrast of interest is between "new users" of linagliptin and similar "new users" of 2nd generation of SU, pioglitazone, other DPP-4 inhibitors, with new use defined as patients with no dispensing of that particular medication in the prior 6 months. The primary analysis will be further restricted to patients with no use of a medication in the same class during the prior 6 months.
- In secondary analyses the initiation of linagliptin will be compared with the initiation of other agents among "treatment-naive new users", defined as patients with no use of any hypoglycemic agent (including insulin) in the prior 6 months, and "non-naive new users", defined as patients initiating a new hypoglycemic agent as a switch from or addition to a previous hypoglycemic medication. Patients filling linagliptin and each specific drug comparator on the same date will not be considered for that particular comparison, but is permitted for other comparisons.

  treatment initiation (Table 3). These analyses will be restricted to patients with no use of a medication in the same class during the prior 6 months.

Concomitant initiation or prevalent use of hypoglycemic medications that are not cohort-defining medications (i.e. hypoglycemic medications either initiated or continuously used on the day of linagliptin or comparator initiation) will be accounted for in the study analyses and used for balancing or stratification. This includes medications that are initiated as part of a

fixed-dose combination. A list of not cohort-defining hypoglycemic medications is provided in Annex 3 and will be updated over time as additional agents are approved.

Similarly, past therapy with hypoglycemic agents that are not cohort-defining medications (defined as any use in the 6-month period prior to linagliptin or comparator initiation with no prevalent use on the day of initiation of linagliptin or comparator) will be accounted for in the study analyses involving non-naive new users and used for balancing or stratification.

Operational definitions for study comparisons of interest and planned analyses are outlined in Table 3

Table 3 Study comparisons of interest and planned analyses

Comparison	Exposure	Comparator	Analyses[1]
Primary comparisons			
1	Linagliptin	Other DPP4 inhibitors (Saxagliptin or Sitagliptin or Alogliptin)	Overall By subgroups based on the status of treatment naive/non-naive new user By subgroups based on the presence[2] or non-presence of : Metformin Insulin
2	Linagliptin	Pioglitazone	
3	Linagliptin	2nd Generation Sulfonylureas	
Secondary comparisons			
4	Linagliptin monotherapy[3]	Comparator monotherapy[5]	Overall
5	Linagliptin + metformin (Dual therapy[4])	Comparator[5] + metformin (Dual therapy)	Overall
6	Linagliptin, allowing prior use of another DPP4	Comparator[5], allowing prior use of another within-class agent	Overall

[1] All the analyses will be balanced on the basis of past or concomitant use of other hypoglycemic medications (i.e., metformin, insulin, sulfonylureas, glitazones, GLP-1 receptor agonists, other DPP4 inhibitors, meglitinides, alpha-glucosidase inhibitors, SGLT2 inhibitors) through propensity score matching.

[2] Presence of metformin or insulin is defined as either past or concomitant therapy with these agents.

[3] Monotherapy is defined as no concomitant initiation or prevalent use of other hypoglycemic agents on the day of linagliptin or comparator initiation.

[4] Dual therapy is defined as concomitant initiation or prevalent use of metformin on the day of linagliptin or comparator initiation, and no concomitant initiation or prevalent use of other hypoglycemic agents.

[5] Linagliptin will be compared to each comparator (DPP4 inhibitors, pioglitazone, and 2nd generation sulfonylureas) separately.

We specify multiple comparators because there are multiple treatment alternatives to linagliptin for patients with T2DM.

Within-class comparators, i.e. other DPP-4 inhibitors. Although linagliptin is the only DPP-4 inhibitor that does not require dose adjustment for severe renal impairment, other DPP-4

inhibitors are expected to have utilization patterns more similar to linagliptin than out of class comparators and to be prescribed to patients with similar clinical profiles.

Out-of-class comparators, i.e. second-generation sulfonylureas and pioglitazone, will be considered in order to investigate between-class effects. 2nd generation sulfonylureas and thiazolidinediones are oral hypoglycemics and are not usually used as first-line therapy, so that they represent more similarly-used alternatives to linagliptin than other treatment options such as glucagon-like peptide-1 (GLP-1) receptor agonists or metformin. SGLT2 inhibitors will not be included as comparators because the first agent in the class, canagliflozin, was not approved until March 2013. As such most SGLT2 inhibitors will be available for less than half the study period and the sample that will accumulate will most likely be insufficient for powered analysis.

Study follow-up

The primary analyses will use an "as treated" approach (AT). Because of the considerable difference in the underlying biology of the outcomes considered in this research program, different definitions for the exposure risk window [R13-1120] will be explored for each outcome (Table 4). Separately for each outcome, follow-up will start the day after the initiation of linagliptin or a comparator and will end at one of the following (whichever comes first):

- Drug discontinuation (date of last dispensing + days supply + grace period). The grace period is a time period after exposure end during which observed outcomes are still attributed to the exposure. Grace period will vary according to the specific outcome.
- Drug augmentation or switching to a comparator
- A study outcome
- End of continuous enrollment, i.e. an enrollment gap of ≥32 days
- Death from any cause
- End of the observation period. According to the specific outcome, the observation period may use all the available data or end at a pre-specified date.

switching of exposure is handled by the AT approach.

To account for switching of exposure we will use a modified AT approach, with a latency period of 90 days. To address potential cumulative dose effects, we will conduct further analyses that stratify the AT and ITT analyses for duration of follow-up. Strata will be determined empirically, using 6 months blocks if feasible.

Table 4 Variations in exposure risk window definitions – AT approach

Outcome	Follow-up initiation	Follow-up initiation when a lag period is considered	Observation period	Grace period[1] (Main analyses)	Grace period (Sensitivity analyses)
Myocardial Infarction	Day 1	Day 31	Follow-up uses all the available data	90 days	30 days
Major cardiovascular event	Day 1	Day 31	Follow-up uses all the available data	90 days	30 days
Renal impairment	Day 1	Day 31	Follow-up uses all the available data	90 days	30 days

[1] The grace period is a time period after exposure end during which observed outcomes are still attributed to the exposure.

Secondary analyses will use an "intention-to-treat" (ITT) approach (first exposure carried forward). Separately for each outcome, follow-up will start the day after the initiation of linagliptin or a comparator and will end at one of the following (whichever comes first):

- A study outcome
- End of continuous enrollment
- Death from any cause
- End of the observation period. According to the specific outcome, the observation period may use all the available data or end at a pre-specified date.

Similarly to the AT approach, different definitions of the exposure risk window will be explored in the ITT analyses for each outcome (Table 5).

Table 5 Variations in exposure risk window definitions – ITT approach

Outcome	Follow-up initiation	Follow-up initiation when a lag period is considered	Observation period
Myocardial infarction	Day 1	Day 31	Follow-up uses all available data
Major cardiovascular event	Day 1	Day 31	Follow-up uses all available data
Renal impairment	Day 1	Day 31	Follow-up uses all available data

8.3.2 Outcomes

Pre-specified outcomes of interest include:

Primary outcome:

- Major adverse cardiovascular event as a composite of:
    - Coronary revascularization (elective and non-elective procedure)
    - Acute coronary syndrome (ACS) hospitalization (including acute MI)
    - Stroke (Ischemic and hemorrhagic stroke)
- Individual components of the composite major adverse cardiovascular event listed above (ischemic and hemorrhagic stroke, acute MI will be assessed separately)

Secondary outcomes:

- Heart failure hospitalization
- Incident End-Stage Renal Disease (ESRD)
- Acute renal failure (ARF)
- ARF that requires dialysis

Further outcomes:

- Any incident malignant neoplasms
- Site-specific incident malignant neoplasms grouped into categories used by the Surveillance, Epidemiology and End Results (SEER) program
- Glomerular Filtration Rate (GFR) event, among patients with laboratory test results
- Acute Pancreatitis
- Severe skin reactions
    - Erythema multiforme, Stevens-Johnson syndrome, or Toxic epidermal necrolysis
    - Bullous pemphigoid
- All cause mortality

Components of the pre-specified outcomes (e.g. coronary revascularization, ACS hospitalization) will be considered as "further outcomes."

Table 6 Outcome definitions

Outcome	Code(s)	Comments
Coronary revascularization	procedure for revascularization (PTCA, stenting, CABG surgery): PTCA: Inpatient CPT-4: 92973, 92982, 92984, 92995, 92996, 92920 – 92921, 92924 – 92925, 92937, 92938, 92941, 92943, 92944 OR – Inpatient ICD-9 procedure: 00.66, 36.01, 36.02, 36.03, 36.05, 36.09	[P10-01452]

Table 6 (cont'd) Outcome definitions

Outcome	Code(s)	Comments
	Stenting: Inpatient CPT-4: 92980, 92981, 92928 – 92929, 92933 - 92934 OR – Inpatient ICD-9 procedure: 36.06, 36.07 CABG: Inpatient CPT-4: 33510 – 33536, 33545, 33572 OR – Inpatient ICD-9 procedure: 36.1x, 36.2x Transmyocardial revascularization: Inpatient CPT-4: 33140, 33141 OR - Inpatient ICD-9 procedure: 36.31-36.34	
Myocardial infarction (MI)	Inpatient ICD-9 diagnosis: 410.X (acute myocardial infarction) excluding 410.x2, as the principal (primary) or the next (secondary) diagnosis	PPV 94% in Medicare claims data [R11-4316] PPV 88.4% in commercially-insured population [R11-4887]
Acute coronary syndrome (ACS)	Acute myocardial infarction Inpatient ICD-9 diagnosis: 410.X (acute myocardial infarction) excluding 410.x2, as the principal (primary) or the next (secondary) diagnosis OR Intermediate coronary syndrome and other acute and subacute forms of ischemic heart disease Inpatient ICD-9 diagnosis: 411.xx as primary or secondary	[P10-01452]
Ischemic stroke	Inpatient ICD-9 diagnosis: 433.x1, 434.x1 (pre-cerebral/cerebral artery occlusion)	PPV 95.5% in commercially-insured population [R11-4887]
Hemorrhagic stroke	Inpatient ICD-9 diagnosis: 430.x (SAH) or 431.x (ICH) (both as primary discharge diagnoses)	PPV 89% (80% if all discharge diagnoses) for ICH; PPV 94% (86% if all discharge diagnoses) for SAH [R13-4101]
Hospitalization with heart failure (HF)	Inpatient ICD-9 diagnosis (primary diagnosis): 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	Identification of current HF: Inpatient ICD-9 diagnosis (1st position): Sensitivity 33% Specificity 99% in Medicare claims data [R11-4334]

Table 6 (cont'd) Outcome definitions

Outcome	Code(s)	Comments
ESRD	eGFR < 15 ml/min/1.73m^2 OR Dialysis Inpatient or outpatient ICD-9 procedure: 39.95 hemodialysis 54.98 peritoneal dialysis Inpatient or outpatient ICD-9 diagnosis: V45.1 renal dialysis status V56.0 extracorporeal dialysis V56.1 Fitting and adjustment of extracorporeal dialysis catheter (Waikar) V56.2 Fitting and adjustment of peritoneal dialysis catheter (Waikar) V56.31 Encounter for adequacy testing for hemodialysis (Waikar) V56.32 Encounter for adequacy testing for peritoneal dialysis (Waikar) V56.8 peritoneal dialysis 585.6 ESKD on dialysis Inpatient or outpatient CPT4: 90935 HEMODIALYSIS PROC W/SINGLE PHYSICIAN EVALUATION 90937 HEMODIALYSIS, REPEATED EVAL, W/WO REVISION DIALYSIS PRESCRIPTION 90940 HEMODIALYSIS ACCESS FLOW STUDY, BY INDICATOR DILUTION METHOD, HOOK UP; MEASUREMENT & DISCONNECTION 90945 DIALYSIS, OTHER THAN HEMODIALYSIS, SINGLE PHYSICIAN EVAL 90947 DIALYSIS PROCEDURE, OTHER THAN HEMODIALYSIS, REPEATED PHYSICIAN EVAL 90989 DIALYSIS TRAINING, PATIENT, W/HELPER WHERE APPLICABLE, ANY MODE, COMPLETED COURSE 90993 DIALYSIS TRAINING, PATIENT, W/HELPER WHERE APPLICABLE, ANY MODE, COURSE INCOMPLETE, PER SESSION 99512 HOME VISIT, HEMODIALYSIS 99559 HOME INFUSION, PERITONEAL DIALYSIS, PER VISIT OR Renal transplant Inpatient or outpatient ICD-9 diagnosis: V42.0 Kidney transplant 55.6x Kidney transplant Inpatient or outpatient CPT4: 50360 RENAL ALLOTRANSPLANTATION,	[R12-3640]

Table 6 (cont'd) Outcome definitions

Outcome	**Code(s)**	**Comments**

Outcome	Code(s)	Comments
	IMPLANTATION, GRAFT; W/RECIPIENT NEPHRECTOMY 50380 RENAL AUTOTRANSPLANTATION, REIMPLANTATION, KIDNEY	
Acute renal failure (ARF)	Inpatient ICD-9 diagnosis: 584.5x ARF with lesion of tubular necrosis 584.6x ARF with lesion of renal cortical necrosis 584.7x ARF with lesion of renal medullary [papillary] necrosis 584.8x ARF with other specified pathological lesion in kidney 584.9x ARF, unspecified	Sensitivity 35% Specificity 98% PPV 48% NPV 96% [R14-1495]
Acute renal failure that requires dialysis (ARF-D)	Inpatient ICD-9 diagnosis: 584.5x ARF with lesion of tubular necrosis 584.6x ARF with lesion of renal cortical necrosis 584.7x ARF with lesion of renal medullary [papillary] necrosis 584.8x ARF with other specified pathological lesion in kidney 584.9x ARF, unspecified AND any of the following inpatient codes : 39.95 hemodialysis V45.1 renal dialysis status V56.0 extracorporeal dialysis V56.1 fitting and adjustment of dialysis catheter	Sensitivity 90% Specificity 94% PPV 94% NPV 90% [R14-1495]
GFR event	Persistent 25% decrease in GFR (~30 ml/min/1.73m^2)	[R12-3640]
All malignant neoplasms	Inpatient or outpatient ICD-9 diagnosis: 140.xx-172.xx, 174.xx-208.xx	[R14-1517]

Table 6 (cont'd) Outcome definitions

Outcome	Code(s)	Comments

Specific malignant neoplasms
• Breast
• Urinary Bladder
• Pancreas
• Oral and Pharynx
• Esophagus
• Stomach
• Colon & Rectum
  ○ Colon
  ○ Rectum
• Liver
• Larynx
• Lung & Bronchus
• Cervix Uteri
• Corpus Uteri
• Ovary
• Prostate
• Testis
• Kidney & Renal Pelvis
• Brain
• Thyroid
• Hodgkin Lymphoma
• Non-Hodgkin Lymphoma
• Myeloma
• All Leukemia
  ○ Acute Lymphatic
  ○ Chronic Lymphatic
  ○ Acute Myeloid
  ○ Chronic Myeloid
• Melanoma
	Inpatient or outpatient ICD-9 diagnosis:
	• 174.xx-175.xx
	• 188.xx
	• 157.xx
	• 140.xx -149.xx
	• 150.xx
	• 151.xx
	• 153.xx -154.xx
	  ○ 153.xx
	  ○ 154.xx
	• 155.xx
	• 161.xx
	• 162.xx -163.xx
	• 180.xx
	• 182.xx
	• 183.xx
	• 185.xx
	• 186.xx
	• 189.xx
	• 191.xx
	• 193.xx
	• 201.xx
	• 200.xx
	• 203.xx
	• 204.xx -208.xx
	  ○ 204.xx
	  ○ 204.1x
	  ○ 205.xx
	  ○ 205.1x
	• 172.xx
		[R14-1517]

Acute Pancreatitis	Inpatient ICD-9 diagnosis: 577.0x (as primary diagnosis)	Sensitivity 93% Specificity 72% [R14-1516] [R14-1501]

Table 6 (cont'd) Outcome definitions

Outcome	Code(s)	Comments
Erythema multiforme OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis	Inpatient ICD-9 diagnosis: 695.10 Erythema multiforme, unspecified Erythema iris Herpes iris 695.11 Erythema multiforme minor 695.12 Erythema multiforme major 695.13 Stevens-Johnson syndrome 695.14 SJS-TEN overlap syndrome 695.15 Toxic epidermal necrolysis, Lyell's syndrome 695.19 Other erythema multiforme	PPV 53-60% [R14-1494]
Bullous pemphigoid	Inpatient ICD-9 diagnosis: 694.5x	[P13-16208]

8.3.3 Covariates

Covariates describing demographics and healthcare characteristics will be assessed on the basis of enrollment information and claims over the 6 months (183 days) preceding (and including date of) dispensing.
All available data prior to and including the index date might be used to identify selected covariates (e.g. history of diabetes). Unless specified otherwise, covariates are based on 1 in- or outpatient diagnosis in any position, since we strive for high sensitivity for covariate definitions. A complete list is provided in Annex 3.

8.4 DATA SOURCES

The data source for this project will be a combination of claims data from United Healthcare, a large national commercial health insurer, and MarketScan, a research claims database from commercial employer-sponsored health plans from January 2006 through June 2013, with 6-month updates through Dec 2016. Because of a 6-month time lag before data become available, we will not have access to any information beyond June 2013 for the first interim report. Both data sources include meaningful numbers of older adults 65 years and older in Medicare Advantage plans, employer-sponsored plans covering seniors, and Medicare supplemental insurance plans, although it is important to note that elderly patients with Medicare Advantage might differ from the elderly patients with other types of Medicare coverage as they tend to be healthier and more likely to still be employed. These data sources readily allow for the identification of large numbers of exposed patients with a 6-month lag time from the occurrence of the service (medication dispensing) and availability of the claims for research. They are further suitable as a foundation for related projects that serve to describe additional features of the exposures, outcomes or covariates through sampled medical record review. Both data sources provide outpatient laboratory results data for about 20-30% of enrollees.

We have obtained the following preliminary estimates from the UnitedHealth and MarketScan databases regarding the number of patients initiating DPP4 inhibitors (new users) and meeting the main study selection criteria in the period May 2011 – December 2012.

Table 7 **UnitedHealth and MarketScan databases Pilot Data, New Users[1] of DPP-4 inhibitors with T2DM diagnosis[2], in the period May 2011 – December 2012***

DPP-4 Inhibitors	United Healthcare	MarketScan	Total
Linagliptin	2,877	5,608	8,485
Saxagliptin	8,258	20,501	28,759
Sitagliptin	19,616	50,397	70,013

*Note: the following exclusion criteria, which will be applied in the final cohort definition, were not applied in obtaining these counts: history of cancer, end-stage renal disease, HIV, organ transplant.

8.5 STUDY SIZE

The ability of this research program to detect a given risk increase depends on the incidence of the outcome as well as the number of cohort entrants and duration of follow-up. The table below provides estimates of the minimum relative rates that can be detected with 80% power for the major study outcomes under specific assumptions regarding their incidence in the comparator group (labeled "base rate") and the accrual of person-time. The base case incidence rates were derived from the literature. We conservatively assumed that the number of patients initiating linagliptin each month during 2013 - 2016 is equal to the average monthly number of initiators during the last half of 2012, that these patients are matched 1:1 to comparator patients, and that each patient contributes 6 months of follow-up time. Because of the large numbers of patients initiating comparator agents, we assumed that all linagliptin patients will be matched. The calculations assume an alpha level of 0.05 and a 2-sided test and are based on methods by Peterson and George. [R14-1502] For the purposes of this table, we have not applied an alpha spending function or any other alpha-adjustment to reflect multiple testing.

1New users are defined as patients with no dispensing of that particular medication in the prior 6 months.
2Initiators had recorded T2DM diagnosis prior to initiation of the index drug and no diagnosis of T1D

Table 8 Projected minimum detectable relative rates by reporting period with a power of 80%

		Interim report 1	Interim report 2	Interim report 3	Interim report 4	Interim report 5	Interim report 6	Interim report 7	Draft final report	Final report
Report Date		June, 2014	Dec, 2014	June, 2015	Dec, 2015	June, 2016	Dec, 2016	Jun, 2017	Feb, 2018	Apr, 2018
Data through		June, 2013	Dec, 2013	June, 2014	Dec, 2014	June, 2015	Dec, 2015	Jun, 2016	Dec, 2016	Dec, 2016
Cumulative person-years of observation		7,961	10,434	12,907	15,379	17,852	20,325	22,798	25,270	25,270
	Base rate, per 100 person-years:	Minimum detectable relative rate:								
Cardiovascular, scenario 1	0.4	1.8	1.7	1.6	1.6	1.5	1.5	1.5	1.4	1.4
Cardiovascular, scenario 2	3 [R04-2173] [R10-0459] [P14-05386] [P13-00007] [R13-3903] [R10-0519]	1.3	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Hospitalization for acute MI, scenario 1	0.4	1.8	1.7	1.6	1.6	1.5	1.5	1.5	1.4	1.4

Table 8 (cont'd) Projected minimum detectable relative rates by reporting period with a power of 80%

Hospitalization for acute MI, scenario 2	1.5	1.4	1.3	1.3	1.3	1.3	1.2	1.2	1.2	1.2
Renal impairment, scenario 1	0.09 [R04-2173]	3.0	2.7	2.5	2.3	2.2	2.1	2.1	2.0	2.0
Renal impairment, scenario 2	0.4 [R12-3640]	1.8	1.7	1.6	1.6	1.5	1.5	1.5	1.4	1.4

Table 8 (cont'd) Projected minimum detectable relative rates by reporting period with a power of 80%

		Interim report 1	Interim report 2	Interim report 3	Interim report 4	Interim report 5	Interim report 6	Interim report 7	Draft final report	Final report

* For each major study outcome, we provide two scenarios based on lower (Scenario 1) and higher (Scenario 2) base rates as derived from available literature. Because of the large numbers of patients initiating comparator agents, we assumed that all linagliptin patients will be matched. The calculations assume an alpha level of 0.05 and a 2-sided test and are based on methods by Peterson and George. [R14-1502] For the purposes of this table, we have not applied an alpha spending function to reflect multiple testing

8.6 DATA MANAGEMENT

The data will reside on a Linux-based computer cluster in Partners Healthcare's state-of-the-art computing facility located in a secure location in the Boston area. This facility houses clinical systems and electronic medical records for Partners hospitals, including Brigham and Women's and Massachusetts General Hospitals. Entry into the computer room requires passing through staffed building security, a successful palm scan, and then passing through staffed computer room security. All entries and exits are logged. We maintain 26 TB of redundant NetApp storage for maximal data integrity and high-speed data access. We also maintain 96 TB of database storage on a Netezza parallel supercomputer. The computers and data files are only accessible via a local area network, which is overseen by Partners Healthcare Information Security, who applies the same standards used for the hospital's electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility.

8.7 DATA ANALYSIS

The analyses will be based on data from May 2011- December 2016.
The first data cut will include data between May 2011 and June 2013.
We will receive new data as they become available on a periodic basis (every 6 months) and, at each data cut, we will update the original set of data, form sequential cohorts by propensity score (PS) matching within 6-month blocks of time, follow patients for each of the outcomes of interest in a prospective manner, and estimate measures of effect using person-time based analyses among patients who initiate linagliptin versus a comparator drug (Figure 2). Thus each analysis will include all patients initiating medication between May 2011 and the end of the data cut for that analysis.

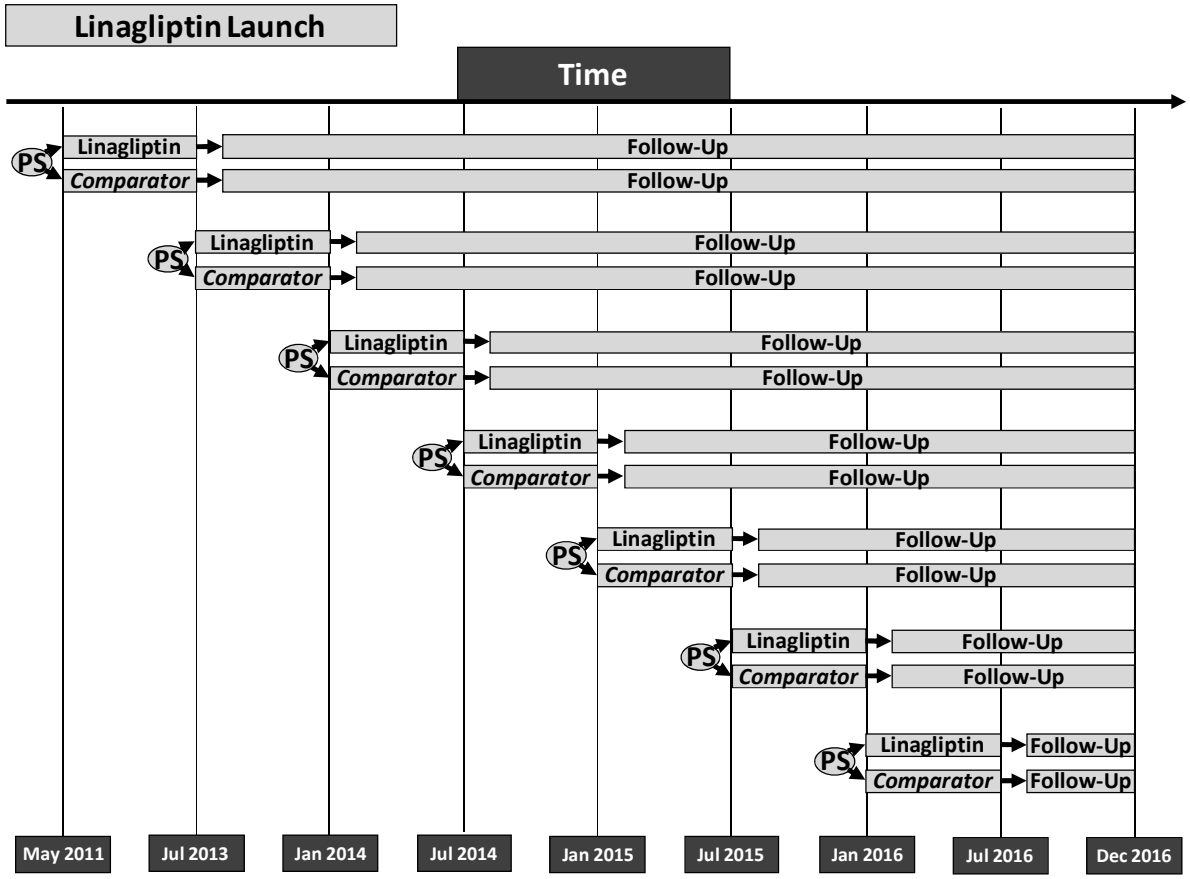

Figure 2 Sequential matched cohort study schematic

8.7.1 Main Analysis

We will compare distributions of socio-demographic, clinical and utilization characteristics among initiators of different hypoglycemic agents, and describe changes over time with respect to these features in a way that will illustrate the potential for change in channelling over time. We will calculate event rates during follow-up for each of the specified outcomes in each exposure group of interest.

Unadjusted and adjusted relative risks (hazard ratios) and rate differences will be estimated. In adjusted analyses, we will use propensity score (PS) matching to balance potential confounders.[R13-1120] [R12-1912] PS will be derived from predicted probabilities of treatment initiation estimated in logistic regression models, and will be progressively enriched by the information obtained through an ongoing drug uilization study (BI Study No. 1218.161) and a study assessing the impact of unmeasured confounding (BI Study No. 1218.162). The propensity score will be used to match linagliptin initiators to initiators of other drug comparators on a 1:1 fixed ratio basis using a nearest-neighbor algorithm. Individual covariates will be tabulated and compared across matched cohorts.

In addition, we will evaluate the balance across matched cohorts on the basis of empirical or established disease risk scores for selected study outcomes. [R13-0523]

We will plot Kaplan-Meier curves for event-free survival and 95% confidence intervals as a function of the duration of use of the index hypoglycemic agent after mutivariate PS matching.

In addition to using propensity scores developed on the basis of investigator-identified covariates, we will use high-dimensional propensity scores (hdPS) in confirmatory analyses. The hdPS algorithm evaluates thousands of diagnoses, procedures, and pharmacy claim codes to identify and prioritize those covariates that serve as proxies for unmeasured confounders. These empirically identified confounders are combined with investigator-identified covariates to improve confounding adjustment. HdPS approaches have been shown to improve validity in longitudinal claims data studies, particularly when combined with pre-specified covariates. [R13-0526] [R13-0528] [R13-0527] [R13-0525]

8.7.3 Bias

Various design and analysis methods will be implemented to reduce the potential for bias in the study.
We will employ new-user cohorts of linagliptin and comparator medications in order to address differences that might arise in the comparison of newer and older treatments, such as survivor bias and attrition of susceptibles.
The comparator cohorts will be formed based on medications with similar clinical use profiles to linagliptin to reduce confounding by indications.
We will employ propensity score matching of linagliptin and comparator cohorts in order to improve the balance of the cohorts with respect to numerous variables.

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1 The Cockroft-Gault formula cannot be used since information on body weight and race is not available in United Healthcare or Marketscan data [R96-0690]

We will use established algorithms for outcome identification and only outcomes expected to be ascertained well in insurance claims. The study assessing unmeasured confounding (BI Study No. 1218.162) will further inform the surveillance program regarding the potential for unmeasured confounding associated with the use of administrative claims databases, which have missing information on important confounders, such as body mass index, smoking, etc..

8.8 QUALITY CONTROL

All aspects of data analysis will be conducted according to standard procedures of the Division of Pharmacoepidemiology. Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst will review the program along with input and output data sets, and for select steps of the project will employ double programming techniques to reduce the potential for programming errors.

8.9 LIMITATIONS OF THE RESEARCH METHODS

As an observational study, there are inherent limitations with respect to potential for alternate explanations for any observed association.

The source claims data include limitations with respect to certainty of the capture of exposure, covariates, and outcomes. As a comprehensive insurance database, essentially all billable medical services will result in claims for reimbursement, so that the certainty of capture is tied to likelihood of a claim being submitted to the insurer.

Although duration of diabetes may represent a risk factor for study outcomes, this covariate will be incompletely captured since the patient history in the dataset is relatively short (at least 6 months, and an average of approximately 2 years), and a first claim within the database may not represent diabetes onset since the condition can be latent for some time and is typically not treated with hypoglycemic medications at its diagnosis.

There is potential for misclassification of dose based on healthcare utilization data, but the "days supply" field is expected to be fairly accurate.

New initiators are operationally defined as patients with no use in the prior 6 months. This does not ensure, however, that patients have never used the drug of interest; the possibility remains that these patients were treated at some prior time point before they enrolled in their insurance plan.
Medication use in United/MarketScan data - as in all administrative healthcare databases - is restricted to prescription drug medication. Consequently, the use of over-the-counter (OTC) medications (e.g., OTC aspirin) is not captured.
Although both data United Healthcare and MarketScan databases include meaningful numbers of older adults 65 years and older in Medicare Advantage plans, employer-sponsored plans covering seniors, and Medicare supplemental insurance plans, elderly with Medicare Advantage might differ from the elderly with other types of Medicare coverage as they tend to be healthier and more likely to still be employed.

8.10 OTHER ASPECTS

Any other aspect of the research method not covered by the previous sections.

9. PROTECTION OF HUMAN SUBJECTS

This study will be submitted to the Institutional Review Board (IRB) of the hospital.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable as this is a non-interventional study based on administrative data.
As stated in section VI.C.1.2.1. of GVP Module VI, for non-interventional study designs, which are based on secondary use of data, adverse reactions reporting is not required.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim and final reports will consist of a description of the methods, including patient selection and variable definitions along with tabular summaries of cohort characteristics, numbers of patients receiving each anticoagulant and associated follow-up time. Counts of outcomes and corresponding rates and measures of association will be presented. The tabular results will be followed by an interpretive summary along with a discussion of the findings and implications.

Manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences.

12. REFERENCES

Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow retrieval of the document.

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R10-0459	Habib ZA, Tzogias L, Havstad SL, et al. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. Pharmacoepidemiol Drug Saf 2009;18:437-47.
R10-0519	Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125-35.
R11-4316	Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99-104.
R11-4334	Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Medical care 2005;43:480-5.
R11-4887	Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596-603.
R12-1912	Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrica 1983:41-55.
R12-3640	Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int

	2012;81:698-706.
R12-3697	Lo-Ciganic W, Zgibor JC, Ruppert K, Arena VC, Stone RA. Identifying type 1 and type 2 diabetic cases using administrative data: a tree-structured model. J Diabetes Sci Technol 2011;5:486-93.
R13-0525	Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512-22.
R13-0526	Huybrechts KF, Rothman KJ, Silliman RA, Brookhart MA, Schneeweiss S. Risk of death and hospital admission for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011;183:E411-9.
R13-0527	Rassen JA, Schneeweiss S. Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:41-9.
R13-0528	Patorno E, Bohn RL, Wahl PM, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010;303:1401-9.
R13-1120	Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 2010;19:858-68.
R13-3903	Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. The New England journal of medicine 2013;369:1317-26.
R13-4101	Tirschwell DL, Longstreth WT, Jr. Validating administrative data in stroke research. Stroke 2002;33:2465-70.

R14-1495	Waikar SS, Wald R, Chertow GM, et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. J Am Soc Nephrol 2006;17:1688-94.
R14-1502	Peterson B, George SL. Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome [corrected]. Control Clin Trials 1993;14:511-22.
R96-0690	Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Active surveillance research program for the assessment of the safety and the effectiveness of linagliptin

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	16
1.1.2 End of data collection[2]	☒	☐	☐	16
1.1.3 Study progress report(s)	☒	☐	☐	16-17
1.1.4 Interim progress report(s)	☒	☐	☐	16-17
1.1.5 Registration in the EU PAS register	☒	☐	☐	16
1.1.6 Final report of study results.	☒	☐	☐	16-17

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	18, 19
2.1.2 The objective(s) of the study?	☒	☐	☐	19
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20-21
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	19

Comments:

There is no a priori hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	24,40-41
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29-35
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	41

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	20-21
4.2 Is the planned study population defined in terms of:	☒	☐	☐	20
4.2.1 Study time period?	☒	☐	☐	20-21
4.2.2 Age and sex?	☒	☐	☐	2
4.2.3 Country of origin?	☒	☐	☐	20-21
4.2.4 Disease/indication?	☒	☐	☐	22-24
4.2.5 Co-morbidity?	☒	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20-21

Comments:

The concept of seasonality is not relevant to diabetes, the condition under study.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	25-27
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	44
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	25-27
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	27-29
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	42

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	30-33
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	30-33

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	35,57-75
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	42-43

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	21,44

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	30-33
8.1.3 Covariates?	☐	☐	☐	57-75
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20,44
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	30-33,44
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	57-75,44
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	52-57
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30-33
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	20-21,55-6
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

No data linkages are planned.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	36-39

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	41
10.2 Is the choice of statistical techniques described?	☒	☐	☐	41-42
10.3 Are descriptive analyses included?	☒	☐	☐	41
10.4 Are stratified analyses included?	☒	☐	☐	42-43
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	41-42
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	42-43

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	43
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	40
11.3 Are methods of quality assurance described?	☒	☐	☐	44
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	44
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	48

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	43-44
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	43-44
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	37-39
12.3 Does the protocol address other limitations?	☒	☐	☐	44

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	46
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	40

Comments:

The study has been submitted to and approved by the Institutional Review Board of

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document	☒	☐	☐	15

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
future amendments and deviations?				

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	47
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	48

Comments:

Name of the main author of the protocol: _____

Date: 6/4/2014

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

ANNEX 3.1 OTHER HYPOGLYCEMIC AGENTS

The primary exposures of interest in this study are linagliptin, other DPP-4 inhibitors (saxagliptin or sitagliptin), pioglitazone, and 2nd generation sulfonylureas. In addition to these cohort-defining hypoglycemic agents, the following glucose-lowering drugs will be considered for the identification of monotherapy versus combination therapy, subgroup analyses, and characteristics balancing of exposure groups of interest. This table will be updated as additional hypoglycemic agents are approved.

Class	**Drug**	**FDA approval date**	**Combination products**
Sodium glucose co-transporter (SGLT2) inhibitors	Canagliflozin	March 29, 2013	N/A
	Dapagliflozin	Jan 8, 2014	N/A
Glitazones	Rosiglitazone	May 25, 1999	+ metformin (Avandamet) + glimepiride (Avandaryl)
Biguanides	Metformin	Mar 3, 1995	+ linagliptin + sitagliptin + saxagliptin + rosiglitazone + pioglitazone + glipizide + glyburide
1st Generation Sulfonylureas	Chlorpropamide	Prior to Jan 1, 1982	N/A
	Acetohexamide	1964	N/A
	Tolazamide	Jan 2, 1986	N/A
	Tolbutamide	Prior to Jan 1, 1982	N/A
Alpha-glucosidase inhibitors	Acarbose	Sep 6, 1995	N/A
	Miglitol	Dec 18, 1996	N/A
Meglitinides	Nateglinide	Dec 22, 2000	N/A
	Repaglinide	Dec 22, 1997	+ metformin (Prandimet)
Glucagon-like peptide-1 (GLP-1) receptor agonists	Exenatide	Apr 28, 2005	N/A
	Liraglutide	Jan 25, 2010	N/A
Injectable amylin analogues	Pramlintide	Mar 16, 2005	N/A

Class	Type	Drug
Insulin	Mixed insulin	insulin human isophane (NPH)/insulin human regular Insulin lispro/insulin lispro protamine insulin aspart/insulin aspart protamine
	Short-acting insulin	insulin human regular insulin human regular, buffered
	Rapid-acting insulin	insulin aspart, recombinant insulin glulisine insulin lispro, recombinant
	Intermediate-acting insulin	Insulin human isophane (NPH) Insulin human zinc
	Long-acting insulin	Insulin detemir Insulin glargine, recombinant Insulin human zinc, extended

* Use of these agents does not qualify subjects for cohort inclusion. However, use of these agents is relevant in defining the subgroup of treatment naive new users and in categorizing monotherapy versus combination therapy.

ANNEX 3.2 DEFINITIONS OF STUDY COVARIATES

Unless specified otherwise, covariates are based on 1 in- or outpatient diagnosis in any position, since we strive for high sensitivity for covariate definitions.

Covariate	Definition (unless otherwise noted, inpatient or outpatient dx, any position)
Number of patients	
Number naïve new users	
CHARACTERISTICS OF INITIATION	
Initiation as monotherapy	The drug of interest is initiated as monotherapy
Concomitant initiation of other specific hypoglycemic agents – Any agent	Concomitant initiation of other specific hypoglycemic agents on the day of initiation of the drug of interest. Concomitant initiation is defined as first use (no use in prior 6 months) on the same day Any agent is linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin
Concomitant initiation of linagliptin	
Concomitant initiation of sitagliptin	
Concomitant initiation of saxagliptin	
Concomitant initiation of metformin	
Concomitant initiation of sulfonylureas	
Concomitant initiation of glitazones	
Concomitant initiation of meglitinides	
Concomitant initiation of AGI	
Concomitant initiation of non-insulin injected agents (exenatide, liraglutide, albiglutide)	
SGLT2 inhibitors (Canagliflozin, dapagliflozin)	
Concomitant initiation of insulin – any formulation	Any formulation is Short-acting insulin, Rapid-acting insulin, Intermediate-acting insulin, Long-acting insulin, or Insulin mixtures
Concomitant initiation of short-acting insulin	Insulin human Regular
Concomitant initiation of rapid-acting insulin	Insulin lispro, Insulin aspart Insulin glulisine
Concomitant initiation of intermediate-acting insulin	Insulin human isophane (NPH) Insulin human zinc
Concomitant initiation of long-acting insulin	Insulin determir Insulin glargine Insulin human zinc, extended
Concomitant initiation of insulin mixtures	Insulin lispro protamine/insulin lispro Insulin aspart protamine/insulin aspart NPH/Regular
Initiation as component of dual therapy	The drug of interest is initiated in combination with 1 other drug only, i.e. only 2 medications are initiated on the same date among linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin)
Initiation as component of ≥3 therapies	The drug of interest is initiated in combination with 2 or more other drugs, i.e. only 3 or more medications are initiated on the same date among linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin)
Initiation as fixed-dose combination of two agents	The drug of interest is initiated as fixed-dose combination of two agents, regardless of the number of agents initiated on the same date
PRIOR USE OF OTHER HYPOGLYCEMIC AGENTS	
Previous use of other specific hypoglycemic agents – Any agent	Use of other specific hypoglycemic agents at any point during the 6 months preceding (and including date of) dispensing of the drug of interest Any agent is linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin
Previous use of linagliptin	
Previous use of sitagliptin	

… (List as above)	
Current use of other specific hypoglycemic agents – Any agent	Current use of other specific hypoglycemic agents on the day of initiation of the drug of interest (i.e., the agent has been initiated prior to and is continuously used on the day of initiation of the drug of interest) Any agent is linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin
Concomitant use of linagliptin	
Concomitant use of sitagliptin	
… (List as above)	
Past use of other specific hypoglycemic agents – Any agent	Any use in the 6-month period prior to the day of initiation of the drug of interest (i.e., the agent has been initiated prior to and is NOT continuously used on the day of initiation of the drug of interest) Any agent is linagliptin, sitagliptin, saxagliptin, metformin, sulfonylureas, glitazones, meglitinides, AGI, non-insulin injected agents, or insulin
Past use of linagliptin	
Past use of sitagliptin	
… (List as above)	
DEMOGRAPHICS	
Age	
Age category 18-35	
Age category 36-49	
Age category 50-64	
Age category 65-74	
Age category 75+	
Sex	Female, Male
Baseline year	
Comorbidity score, Charlson	
HEALTH CARE UTILIZATION	
Total N distinct non-insulin hypoglicemic agents prescribed	
Total N distinct pharmacological agents prescribed	
N physician visits	
Hospitalization (Y/N)	
N hospitalizations	
N hospital days	
Hospitalization in 30 days prior to treatment initiation	
Total N distinct ICD9 diagnoses at the 3rd digit level	
Number of laboratory tests ordered	
Number of hemoglobin A1C tests ordered	CPT4: 83036 (HEMOGLOBIN; GLYCOSYLATED (A1C)
Number of glucose tests ordered	82947 GLUCOSE; QUANTITATIVE, BLOOD (EXCEPT REAGENT STRIP) 82948 GLUCOSE; BLOOD, REAGENT STRIP 82962 GLUCOSE, BLOOD, GLUCOSE MONITORING DEVICE(S) CLEARED BY FDA SPECIFICALLY FOR HOME USE
Number of lipid tests ordered	V7791 - SCREENING FOR LIPOID DISORDERS 80061 - LIPID PROFILE 82465 - ASSAY CHOLEST SERUM/WHOLE BLD TTL 83718 - BLOOD LIPOPROTEIN ASSAY HDL 83719 - BLOOD LIPOPROTEIN ASSAY VLDL 83721 - BLOOD LIPOPROTEIN ASSAY LDL 84478 - ASSAY BLOOD TRIGLYCERIDES
Number of creatinine tests ordered	CPT4: 82565 CREATININE; BLOOD
Mammography	CPT: 76082 (COMPUTER AIDED DETECTION WITH FURTHER PHYSICIAN REVIEW FOR INTERPRETATION WITH OR WITHOUT DIGITIZATION OF FILM RADIOGRAPHIC IMAGES, DIAGNOSTIC MAMMOGRAPHY), 76083 (COMPUTER AIDED DETECTION WITH FURTHER PHYSICIAN REVIEW FOR INTERPRETATION WITH OR WITHOUT DIGITIZATION OF FILM RADIOGRAPHIC IMAGES, SCCREENING MAMMOGRAPHY), 76092 (SCREENING MAMMOGRAPHY, BILAT (2 VIEW FILM STUDY, EACH BREAST) HCPS: G0202 (SCREENING MAMMOGRAPHY, PRODUCING DIRECT DIGITAL IMAGE, BILATERAL, ALL VIEWS), G0203 (DIAGNOSTIC MAMMOGRAPHY. PRODUCING DIRECT DIGITAL IMAGE, BILATERAL, ALL VIEWS)
Pap test	HCPCS: Q0091 (SCREENING PAPANICOLAOU SMEAR; OBTAINING, PREPARING AND CONVEYANCE OF CERVICAL OR VAGINAL

	SMEAR TO LAB), P3000 (UP TO THREE SMEARS BY TECHNICIAN UNDER PHYSICIAN SUPERVISION), P3001 (UP TO THREE SMEARS REQUIRING INTERPRETATION BY PHYSICIAN), G0123 (SCREENING CYTOPATHOLOGY, CERVICAL OR VAGINAL, ANY REPORTING SYSTEM, COLLECTED IN PRESERVING FLUID, AUTOMATED THIN LAYER PREP, BY CYTOTECHNOLOGIST), G0124 (SCREENING CYTOPATHOLOGY, CERVICAL OR VAGINAL, REQUIRING PHYSICIAN INTERPRETATION), G0141 (SCREENING CYTOPATHOLOGY, SMEARS, CERVICAL OR VAGINAL, PERFORMED BY AUTOMATED SYSTEM, WITH MANUAL RESCREENING, REQUIRING INTERPRETATION BY PHYSICIAN) , G0143 (MANUAL SCREENING, AND RESCREENING BY CYTOTECHNOLOGIST UNDER PHYSICIAN SUPERVISION), G0144 (SCREENING BY AUTOMATED SYSTEM UNDER PHYSICIAN SUPERVISION), G0145 (SCREENING BY AUTOMATED SYSTEM AND MANUAL RESCREENING UNDER PHYSICIAN SUPERVISION), G0147 (SCREENING CYTOPATHOLOGY SMEARS, CERVICAL OR VAGINAL, PERFORMED BY AUTOMATED SYSTEM UNDER PHYSICIAN SUPERVISION), G0148 (SCREENING CYTOPATHOLOGY SMEARS, CERVICAL OR VAGINAL, PERFORMED BY AUTOMATED SYSTEM WITH MANUAL RESCREENING), 88141 – 88158 (CYTOPATHOLOGY, CERVICAL OR VAGINAL (ANY REPORTING SYSTEM), REQUIRING INTERPRETATION BY PHYSICIAN; CYTOPATHOLOGY, CERVICAL OR VAGINAL (ANY REPORTING SYSTEM), COLLECTED IN PRESERVATIVE FLUID, AUTOMATED THIN LAYER PREPARATION; MANUAL SCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, CERVICAL OR VAGINAL, (ANY REPORTING SYSTE) COLLECTED IN PRESERVATIVE FLUID, AUTOMATED THING LAYER PREPARATION, WITH MANUAL SCREENING AND RESCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY SMEARS, CERVICAL OR VAGINAL, SCREENING BY SUTOMATED SYSTEM UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY SMEARS, CERVICAL OR VAGINAL, SCREENING BY AUTOMATED SYSTEM WITH MANUAL RESCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, MANUAL SCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY; SLIDES, CERVICAL OR VAGINAL, WITH MANUAL SCREENING AND COMPUTER ASSISTED RESCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, WITH MANUAL SCREENING AND COMPUTER ASSISTED RESCREENING USING CELL SELECTION AND REVIEW UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, DEFINITIVE HORMONAL EVALUATION (EG, MATURATION INDEX, KARYOPTKNOTIC INDEX, ESTROGENIC INDEX)), 88164 – 88167 (CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, BETHESDA SYSTEM, MANUAL SCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, THE BETHESDA SYSTEM, WITH MANUAL SCREENING AND RESCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, THE BETHESDA SYSTEM, WITH MANUAL SCREENING AND COMPUTER ASSISTED RESCREENING UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, SLIDES, CERVICAL OR VAGINAL, THE BETHESDA SYSTEM, WITH MANUAL SCREENING AND COMPUTER ASSISTED RESCREENING USING CELL SELECTION AND REVIEW UNDER PHYSICIAN SUPERVISION), 88174 – 88175 (CYTOPATHOLOGY, CERVICAL OR VAGINAL, ANY REPORTING SYSTEM, COLLECTED IN PRESERVATIVE FLUID, AUTOMATED THIN LAYER PREPARATION, SCREENING BY AUTOMATED SYSTEM, UNDER PHYSICIAN SUPERVISION; CYTOPATHOLOGY, CERVICAL OR VAGINAL, ANY REPORTING SYSTEM, COLLECTED IN PRESERVATIVE FLUID, AUTOMATED THIN LAYER PREPARATION, WITH SCREENING BY AUTOMATED SYSTEM AND MANUAL RESCREENING OR REVIEW, UNDER PHYSICIAN SUPERVISION)
PSA test	HCPCS: G0103 (PROSTATE CANCER SCREENING; PROSTATE SPECIFIC ANTIGEN TEST (PSA)) CPT: 84153, 84152 – 84154 (PROSTATE SPECIFIC ANTIGEN (PSA): COMPLEXED (DIRECT MEASUREMENT) or TOTAL or FREE)
Colonoscopy	45.23 (COLONOSCOPY) HCPCS: G0105 (COLORECTAL CANCER SCREENING;

	COLONOSCOPY ON INDIVIDUAL AT HIGH RISK), G0121 (COLORECTAL CANCER SCREENING; COLONOSCOPY ON INDIVIDUAL NOT MEETING CRITERIA FOR HIGH RISK) CPT: 45378-45392 (COLONSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, DIAGNOSTIC, WITH OR WITHOUT COLLECTION OF SPECIMENS BY BRUSHING OR WASHING, WITH OR WITHOUT COLON DECOMPRESSION; COLONSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH REMOVAL OF FOREIGN BODY; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH BIOPSY, SINGLE OR MULTIPLE; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH DIRECTED SUBMUCOSAL INJECTIONS, ANY SUBSTANCE; COLONOSCOPY FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH CONTROL OF BLEEDING; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIX FLEXURE, WITH ABLATION OF TUMORS POLYPS OR OTHER LESIONS NOT AMEABLE TO REMOVAL BY HOT BIOPSY FORCEPS, BIPOLAR CAUTERY OR SNARE TECHNIQUE; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH REMOVAL OF TUMORS POLYPS OR OTHER LESIONS BY HOT BIOPSY FORCEPS OR BIPOLAR CAUTERY; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH REMOCAL OF TUMORS POLYPS OR OTHER LESIONS BY SNARE TECHNIQUE; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH DILATION BY BALLOON, ONE OR MORE STRUCTURES; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH TRANSECNDOSCOPIC STENT PLACEMENT INCLDUING PREDILATION; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH ENDOSCOPIC ULTRASOUND EXAMINATION; COLONOSCOPY, FLEXIBLE, PROXIMAL TO SPLENIC FLEXURE, WITH TRANSENDOSCOPIC ULTRASOUND GUIDED INTRAMURAL OR TRANSMURAL FINE NEEDLE ASPIRATION/BIOPSY)
Fecal occult blood test	HCPCS: G0107 (COLORECTAL CANCER SCREENING; *FECAL-OCCULT* BLOOD TEST, 1-3 SIMULTANEOUS DETERMINATIONS) G0328 (COLORECTAL CANCER SCREENING; FECAL OCCULT BLOOD TEST, IMMUNOASSAY, 1-3 SIMULTANEOUS) CPT: 82270 (BLOOD, OCCULT, BY PEROXIDASE ACTIVITY (EG, GUAIAC), QUALITATIVE; FECES, CONSECUTIVE COLLECTED SPECIMENS WITH SINGLE DETERMINATION), 82274 (BLOOD, OCCULT, BY FECAL HEMOGLOBIN DETERMINATION BY IMMUNOASSAY, QUALITATIVE, FECES, 1-3 SIMULTANEOUS DETERMINATIONS)
Flu shot	CPT: 90655 – 90660 (INFLUENZA VIRUS VACCINE, SPLIT VIRUS, PRESERVATIVE FREE, WHEN ADMINISTERED TO CHILDREN 6-35 MONTHS OF AGE, FOR INTRAMUSCULAR USE; INFLUENZA VIRUS VACCINE, SPLIT VIRUS, PRESERVATIVE FREE, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS AND OLDER, FOR INTRAMUSCULAR USE; INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO CHILDREN 6-35 MONTHS OF AGE, FOR INTRAMUSCULAR USE; INFLUENZA VIRUS VACCINE, SPLIT VIRUS, WHEN ADMINISTERED TO INDIVIDUALS 3 YEARS OF AGE AND OLDER, FOR INTRAMUSCULAR USE; INFLUENZA VIRUS VACCINE, WHOLE VIRUS, IM/JET INJECTION USE; INFLUENZA VIRUS VACCINE, LIVE, FOR INTRANASAL USE), 90724 (INFLUENZA VIRUS VACCINE) HCPCS: G0008 (ADMINISTRATION OF INFLUENZA VIRUS VACCINE) ICD-9 diagnosis: V04.8 (NEED FOR PROPHYLACTIC VACCINATION AND INOCULATION AGAINST OTHER VIRAL DISEASES), V04.81 (NEED FOR PROPHYLACTIC VACCINATION AND INOCULATION AGAINST INFLUENZA), V06.6 (NEED FOR PROPHYLACTIC VACCINATION AND INOCULATION AGAINST STREPTOCOCCUS PNEUMONIAE AND INFLUENZA)
Pneumococcal vaccine	90669 (PNEUMOCOCCAL CONJUGATE VACCINE, 7 VALENT, FOR INTRAMUSCULAR USE), 90670 (PNEUMOCOCCAL CONJUGATE VACCINE, 13 VALENT, FOR INTRAMUSCULAR USE), 90732 (PNEUMOCOCCAL POLYSACCHARIDE VACCINE, 23-VALENT, ADULT/IMMUNOSUPPRESSED PATIENT DOSAGE, SUBQ/IM USE) G0009 (ADMINISTRATION OF PNEUMOCOCCAL POLYSACCHARIDE VACCINE) V03.82 (NEED FOR PROPHYLACTIC VACCINATION AND INOCULATION AGAINST STREPTOCOCCUS PNEUMONIAE)

BMD testing	CPT: 76070 (CT BONE MINERAL DENSITY STUDY, 1+ SITES; AXIAL SKELETON), 76075 (DEXA, BONE DENSITY STUDY, 1+ SITES; AXIAL SKELETON), 76076 (DEXA, BONE DENSITY STUDY, 1+ SITES ;APPENDICULAR SKELETON), 76977 (US BONE DENSITY MEASUREMENT & INTERPRETATION, PERIPHERAL SITE(S), ANY METHOD)
Number of electrocardiograms	ICD-9 procedure code: 89.51 (RHYTHM ELECTROCARDIOGRAM), 89.52 (ELECTROCARDIOGRAM) CPT4: 93000 (ELECTROCARDIOGRAM, ROUTINE ECG WITH AT LEAST 12 LEADS; WITH INTERPRETATION AND REPORT), 93005 (ELECTROCARDIOGRAM, ROUTINE ECG WITH AT LEAST 12 LEADS; TRACING ONLY, WITHOUT INTERPRETATION AND REPORT), 93010 (ELECTROCARDIOGRAM, ROUTINE ECG WITH AT LEAST 12 LEADS; INTERPRETATION, AND REPORT ONLY)
Long-term (current) use of insulin	V58.67
Use of glucose test strips	CPT: 82948 (GLUCOSE; BLOOD, REAGENT STRIP)
LABORATORY TESTS	
HbA1c (%)	
Creatinine (mg/dl)	
eGFR (ml/min per 1.73 m^2)	
Total cholesterol (mg/dl)	
HDL level (mg/dl)	
LDL level (mg/dl)	
Triglyceride level (mg/dl)	
COMORBIDITIES AT BASELINE	
Diabetes during pregnancy	648.0x
PCOS	256.4x
Female Infertility	628.x
Precocious puberty	259.1
Hyperglycemia	**790.29**
Diabetic ketoacidosis	**250.1x**
Hyperosmolar hyperglycemic nonketotic syndrome (HONK)	250.2x
Diabetes with coma	**250.3x, excluding 250.30 (DIABETES WITH OTHER COMA)**
Hypoglycemic coma	**251.0 (HYPOGLYCEMIC COMA), 250.30 (DIABETES WITH OTHER COMA)**
Hypoglycemia	**251.1 (**OTHER SPECIFIED HYPOGLYCEMIA**), 251.20 (**HYPOGLYCEMIA UNSPECIFIED**), 962.30 (**POISONING BY INSULINS AND ANTIDIABETIC AGENTS**), 775.60 (**NEONATAL HYPOGLYCEMIA) **Also, 250.8x (**DIABETES WITH OTHER SPECIFIED MANIFESTATIONS) **as long as none of the following codes are co-diagnoses: 259.8 (**OTHER SPECIFIED ENDOCRINE DISORDERS**), 272.7 (**LIPIDOSES**), 681.xx (**CELLULITIS AND ABSCESS OF FINGER AND TOE**), 682.xx (**OTHER CELLULITIS AND ABSCESS**), 686.9x (**UNSPECIFIED LOCAL INFECTION OF SKIN AND SUBCUTANEOUS TISSUE**), 707.xx (**CHRONIC ULCER OF SKIN**), 709.3 (**DEGENERATIVE SKIN DISORDERS**), 730.0-730.2 (**OSTEOMYELITIS PERIOSTITIS AND OTHER INFECTIONS INVOLVING BONE; CHRONIC OSTEOMYELITIS; UNSPECIFIED OSTEOMYELITIS**), 731.8 (**OTHER BONE INVOLVEMENT IN DISEASES CLASSIFIED ELSEWHERE)
Diabetic retinopathy	362.01-362.07 (DIABETIC RETINOPATHY: BACKGROUND, PROLIFERATIVE, NONPROLIFERATIVE, MILD NONPROLIFERATIVE, MODERATE NONPROLIFERATIVE, SEVERE; DIABETIC MACULAR EDEMA)
Diabetic nephropathy NOS	**583.81**
Opthalmology visit	ICD-9 procedure code: 14.11 (DIAGNOSTIC ASPIRATION OF VITREOUS), 14.19 (OTHER DIAGNOSTIC PROCEDURES ON RETINA, CHOROID, VITREOUS, AND POSTERIOR CHAMBER), 14.21-14.29 (DESTRUCTION OF CHOIORETINAL LESION BY DIATHERMY, BY CRYOTHERAPY, BY XENON ARC PHOTOCOAGULATION, BY LASER PHOTOCOLAGULATION, BY UNSPECIFIED COAGULATION, BY RADIATION THERAPY, BY IMPLANTATION OF RADIATION SOURCE, BY OTHER), 14.31-14.35 (REPAIR OF RETINAL TEAR BY IATHERMY, BY CRYOTHERAPY, BY XENON ARC PHOTOCOAGULATION, BY LASER PHOTOCOAGULATION, BY PHOTOCOAGULATION OF UNSPECIFIED TYPE), 14.39 (OTHER REPAIR OF RETINAL TEAR), 14.41 (SCLERAL BUCKLING WITH IMPLANT), 14.49 (OTHER SCLERAL BUCKLING), 14.51-14.55 (REPAIR OF RETINAL DETACHMENT WITH DIATHERMY, WITH CRYOTHERAPY, WITH XENON ARC PHOTOCOAGULATION, WITH LASER PHOTOCOAGULATION), 14.59 (OTHER), 14.9 (OTHER

	OPERATIONS OF RETINA, CHOROID, AND POSTERIOR CHAMBER), 95.02-95.04 (COMPREHENSIVE EYE EXAMINATION, OPTHAMALOGIC WORK-UP, EYE EXAM UNDER ANESTHESIA), 95.11 (FUNDUS PHOTOGRAPHY), 95.12 (FLUORESCEIN ANGIOGRAPHY OR ANGIOSCOPY OF EYE), 95.16 (P32 AND OTHER TRACER STUDIES OF EYE) CPT-4 code: 67028 (INTRAVITREAL INJECTION OF A PHARMACOLOGIC AGENT (SEPARATE PROCEDURE), 67038-67040 (VITRECTOMY, MECHANICAL, PARS PLANA APPROACH; WITH ENDOLASER PANRETINAL PHOTOCOAGULATION), 67101 (REPAIR OF RETINAL DETACHMENT, 1 OR MORE SESSIONS; CRYOTHERAPY OR DIATHERMY, WITH OR WITHOUT DRAINAGE OF SUBRETINAL FLUID), 67105 (REPAIR OF RETINAL DETACHMENT, 1 OR MORE SESSIONS; PHOTOCOAGULATION, WITH OR WITHOUT DRAINAGE OF SUBRETINAL FLUID), 67107 (REPAIR OF RETINAL DETACHMENT; SCLERAL BUCKLING (SUCH AS LAMELLAR SCLERAL, DISSECTION, IMBRICATION OR ENCIRCLING PROCEDURE) 67108 (REPAIR OF RETINAL DETACHMENT; WITH VITRECTOMY, ANY METHOD, WITH OR WITHOUT AIR OR GAS TAMPONADE, FOCAL ENDOLASER PHOTOCOAGULATION), 67110 (REPAIR OF RETINAL DETACHMENT; BY INJECTION OF AIR OR OTHER GAS (EG, PNEUMATIC RETINOPEXY), 67112 (REPAIR OF RETINAL DETACHMENT; BY SCLERAL BUCKLING OR VITRECTOMY, ON PATIENT HAVING PREVIOUS IPSILATERAL RETINAL DETACHMENT REPAIRS), 67141 (PROPHYLAXIS OF RETINAL DETACHMENT (EG, RETINAL BREAK, LATTICE DEGENERATION) WITHOUT DRAINAGE, 1 OR MORE SESSIONS; CRYOTHERAPY), 67145 (PROPHYLAXIS OF RETINAL DETACHMENT (EG, RETINAL BREAK, LATTICE DEGENERATION) WITHOUT DRAINAGE, 1 OR MORE SESSIONS; PHOTOCOAGULATION), 67208 (DESTRUCTION OF LOCALIZED LESION OF RETINA (EG, MACULAR EDEMA, TUMORS), 1 OR MORE SESSIONS; CRYOTHERAPY, DIATHERMY), 67210 (DESTRUCTION OF LOCALIZED LESION OF RETINA (EG, MACULAR EDEMA, TUMORS), 1 OR MORE SESSIONS; PHOTOCOAGULATION), 67218 (DESTRUCTION OF LOCALIZED LESION OF RETINA (EG, MACULAR EDEMA, TUMORS), 1, OR MORE SESSIONS; RADIATION BY IMPLANTATION OF SOURCE), 67227 (DESTRUCTION OF EXTENSIVE OR PROGRESSIVE RETINOPATHY (EG, DIABETIC RETINOPATHY), 1 OR MORE SESSIONS, CRYOTHERAPY, DIATHERMY), 67228 (TREATMENT OF EXTENSIVE OR PROGRESSIVE RETINOPATHY, 1 OR MORE SESSIONS; (EG, DIABETIC RETINOPATHY), PHOTOCOAGULATION), 92002 (OPHTHALMOLOGICAL SERVICES: MEDICAL EXAMINATION AND EVALUATION WITH INITIATION OF DIAGNOSTIC AND TREATMENT PROGRAM; INTERMEDIATE), 92004 (OPHTHALMOLOGICAL SERVICES: MEDICAL EXAMINATION AND EVALUATION WITH INITIATION OF DIAGNOSTIC AND TREATMENT PROGRAM; COMPREHENSIVE), 92012 (OPHTHALMOLOGICAL SERVICES: MEDICAL EXAMINATION AND EVALUATION, WITH INITIATION OR CONTINUATION OF DIAGNOSTIC AND TREATMENT PROGRAM), 92014 (OPHTHALMOLOGICAL SERVICES: MEDICAL EXAMINATION AND EVALUATION, WITH INITIATION OR CONTINUATION OF DIAGNOSTIC AND TREATMENT PROGRAM), 92018 (OPHTHALMOLOGICAL EXAMINATION AND EVALUATION, UNDER GENERAL ANESTHESIA, WITH OR WITHOUT MANIPULATION OF GLOBE FOR PASSIVE RANGE OF MOTION), 92019 (OPHTHALMOLOGICAL EXAMINATION AND EVALUATION, UNDER GENERAL ANESTHESIA, WITH OR WITHOUT MANIPULATION OF GLOBE FOR PASSIVE RANGE OF MOTION), 92225 (OPHTHALMOSCOPY, EXTENDED, WITH RETINAL DRAWING (EG, FOR RETINAL DETACHMENT, MELANOMA), WITH INTERPRETATION AND REPORT), 92226 (OPHTHALMOSCOPY, EXTENDED, WITH RETINAL DRAWING (EG, FOR RETINAL DETACHMENT, MELANOMA), WITH INTERPRETATION AND REPORT), 92230 (FLUORESCEIN ANGIOSCOPY WITH INTERPRETATION AND REPORT), 92235 (FLUORESCEIN ANGIOGRAPHY (INCLUDES MULTIFRAME IMAGING) WITH INTERPRETATION AND REPORT), 92240 (INDOCYANINE-GREEN ANGIOGRAPHY (INCLUDES MULTIFRAME IMAGING) WITH), 92250 (FUNDUS PHOTOGRAPHY WITH INTERPRETATION AND REPORT),

	92260 (OPHTHALMODYNAMOMETRY), V72.0 (EXAMINATION OF EYES AND VISION) HCPCS: S0620 (ROUTINE OPHTHALMOLOGICAL EXAMINATION INCLUDING REFRACTION; NEW PATIENT), S0621 (ROUTINE OPHTHALMOLOGICAL EXAMINATION INCLUDING REFRACTION; ESTABLISHED PATIENT), S0625 (RETINAL TELESCREENING BY DIGITAL IMAGING OF MULTIPLE DIFFERENT FUND US AREAS TO SCREEN FOR VISION-THREATENING CONDITIONS, INCLUDING IMAGING, INTERPRETATION AND REPORT), S3000 (DIABETIC INDICATOR; RETINAL EYE EXAM, DILATED, BILATERAL)
Diabetes with ophthalmic manifestations	250.5x
Glaucoma	365.xx
Cataract	366.xx, 743.30-743.34 (CONGENITAL CATARACT: CAPSULAR AND SUBCAPSULAR, CORTICAL AND ZONULAR, NUCLEAR, TOTAL AND SUBTOTAL)
Retinal detachment, vitreous hemorrhage, vitrectomy	ICD-9-CM Diagnosis 361.9x, 379.23 ICD-9-CM procedure 14.7x (OPERATIONS ON VITREOUS)
Pyelonephritis/infections of kidney	590.xx
Diabetic neuropathy	250.6 (DIABETES WITH NEUROLOGICAL MANIFESTATIONS), 357.2 (POLYNEUROPATHY IN DIABETES)
Mononeuropathy or polyneuropathy	354.xx (MONONEURITIS OF UPPER LIMB AND MONONEURITIS MULTIPLEX) 355.xx (MONONEURITIS OF LOWER LIMB AND UNSPECIFIED SITE) 356.xx HEREDITARY AND IDIOPATHIC PERIPHERAL NEUROPATHY) 357.xx (INFLAMMATORY AND TOXIC NEUROPATHY)
Peripheral autonomic neuropathy	337.1x
Gastroparesis	**536.3**
Peripheral vascular disease or PVD surgery	1 inpatient or 2 outpatient claims with any of the following codes: ICD9 diagnosis: 440.20 - 440.24 (ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES, ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES WITH INTERMITTENT CLAUDICATION, ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES WITH REST PAIN, ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES WITH ULCERATION, ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES WITH GANGRENE), 440.29 – 440.32 (OTHER ATHEROSCLEROSIS OF NATIVE ARTERIES OF THE EXTREMITIES, ATHEROSCLEROSIS OF BYPASS GRAFT OF THE EXTREMITIES, ATHEROSCLEROSIS OF AUTOLOGOUS VEIN BYPASS GRAFT OF THE EXTREMITIES, ATHEROSCLEROSIS OF NONAUTOLOGOUS BIOLOGICAL BYPASS GRAFT OF THE EXTREMITIES), 440.3 (ATHEROSCLEROSIS OF BYPASS GRAFT OF THE EXTREMITIES), 443.9 (PERIPHERAL VASCULAR DISEASE UNSPECIFIED) ICD9 procedure: 38.08 (INCISION OF VESSELS, LOWER LIMB ARTERIES), 38.09 (INCISION OF VESSELS, LOWER LIMB VEINS), 38.18 (ENDARTERECTOMY, LOWER LIMB ARTERIES), 38.48 (RESECTION OF VESSEL WITH REPLACEMENT, LOWER LIMB ARTERIES), 38.49 (RESECTION OF VESSEL WITH REPLACEMENT, LOWER LIMB VEINS), 39.25 (AORTA-ILIAC-FEMORAL BYPASS), 39.5 (OTHER REPAIR OF VESSELS), 39.9 (OTHER OPERATIONS ON VESSELS), 84.10 - 84.17 (AMPUTATION OF LOWER LIMB, AMPUTATION OF TOE, AMPUTATION THROUGH FOOT, DISARTICULATION OF ANKLE, AMPUTATION OF ANKLE THROUGH MALLEOLI OF TIBIA AND FIBULA, OTHER AMPUTATION BELOW KNEE, DISARTICULATION OF KNEE, AMPUTATION ABOVE KNEE) HCPCs: 35256 (REPAIR BLOOD VESSEL WITH VEIN GRAFT; LOWER EXTREMITY), 35286 (REPAIR BLOOD VESSEL WITH GRAFT OTHER THAN VEIN; LOWER EXTREMITY), 35351 (THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; ILIAC), 35355 (THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; ILIOFEMORAL), 35361 (THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; COMBINED AORTOILIAC), 35363 (THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; COMBINED AORTOILIOFEMORAL), 35371

	(THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; COMMON FEMORAL), 35372 (THROMBOENDARTERECTOMY, INCLUDING PATCH GRAFT, IF PERFORMED; DEEP (PROFUNDA) FEMORAL), 35381 (THROMBOENDARTERECTOMY, W/WO PATCH GRAFT; FEMORAL/POPLITEAL/TIBIOPERONEAL), 35454 (TRANSLUMINAL BALLOON ANGIOPLASTY, OPEN; ILIAC), 35456 (TRANSLUMINAL BALLOON ANGIOPLASTY, OPEN; FEMORAL-POPLITEAL), 35459 (TRANSLUMINAL BALLOON ANGIOPLASTY, OPEN; TIBIOPERONEAL TRUNK & BRANCHES), 35470 (TRANSLUMINAL BALLOON ANGIOPLASTY, PERCUTANEOUS; TIBIOPERONEAL TRUNK/BRANCHES, EACH VESSEL), 35473 (TRANSLUMINAL BALLOON ANGIOPLASTY, PERCUTANEOUS; ILIAC), 35474 (TRANSLUMINAL BALLOON ANGIOPLASTY, PERCUTANEOUS; FEMORAL-POPLITEAL), 35482 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, OPEN; ILIAC), 35483 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, OPEN; FEMORAL-POPLITEAL), 35485 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, OPEN; TIBIOPERONEAL TRUNK & BRANCHES), 35492 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, PERCUTANEOUS; ILIAC), 35493 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, PERCUTANEOUS; FEMORAL-POPLITEAL), 35495 (TRANSLUMINAL PERIPHERAL ATHERECTOMY, PERCUTANEOUS; TIBIOPERONEAL TRUNK & BRANCHES), 35521 (BYPASS GRAFT, WITH VEIN; AXILLARY-FEMORAL), 35533 (BYPASS GRAFT, WITH VEIN; AXILLARY-FEMORAL-FEMORAL), 35541 (BYPASS GRAFT, W/VEIN; AORTOILIAC/BI-ILIAC), 35546 (BYPASS GRAFT, W/VEIN; AORTOFEMORAL/BIFEMORAL), 35548 (BYPASS GRAFT, W/VEIN; AORTOILIOFEMORAL, UNILAT), 35549 (BYPASS GRAFT, W/VEIN; AORTOILIOFEMORAL, BILAT), 35551 (BYPASS GRAFT, W/VEIN; AORTOFEMORAL-POPLITEAL), 35556 (BYPASS GRAFT, WITH VEIN; FEMORAL-POPLITEAL), 35558 (BYPASS GRAFT, WITH VEIN; FEMORAL-FEMORAL), 35563 (BYPASS GRAFT, WITH VEIN; ILIOILIAC), 35565 (BYPASS GRAFT, WITH VEIN; ILIOFEMORAL), 35566 (BYPASS GRAFT, WITH VEIN; FEMORAL-ANTERIOR TIBIAL, POSTERIOR TIBIAL, PERONEAL ARTERY OR OTHER DISTAL VESSELS), 35571 (BYPASS GRAFT, WITH VEIN; POPLITEAL-TIBIAL, -PERONEAL ARTERY OR OTHER DISTAL VESSELS), 35621 (BYPASS GRAFT, WITH OTHER THAN VEIN; AXILLARY-FEMORAL), 35623 (BYPASS GRAFT, WITH OTHER THAN VEIN; AXILLARY-POPLITEAL OR –TIBIAL), 35641 (BYPASS GRAFT, W/OTHER THAN VEIN; AORTOILIAC/BI-ILIAC), 35646 (BYPASS GRAFT, WITH OTHER THAN VEIN; AORTOBIFEMORAL), 35647 (BYPASS GRAFT, WITH OTHER THAN VEIN; AORTOFEMORAL),35650 (BYPASS GRAFT, WITH OTHER THAN VEIN; AXILLARY-AXILLARY), 35651 (BYPASS GRAFT, W/OTHER THAN VEIN; AORTOFEMORAL-POPLITEAL), 35654 (BYPASS GRAFT, WITH OTHER THAN VEIN; AXILLARY-FEMORAL-FEMORAL), 35656 (BYPASS GRAFT, WITH OTHER THAN VEIN; FEMORAL-POPLITEAL), 35661 (BYPASS GRAFT, WITH OTHER THAN VEIN; FEMORAL-FEMORAL), 35663 (BYPASS GRAFT, WITH OTHER THAN VEIN; ILIOILIAC), 35666 (BYPASS GRAFT, WITH OTHER THAN VEIN; FEMORAL-ANTERIOR TIBIAL, POSTERIOR TIBIAL, OR PERONEAL ARTERY), 35671 (BYPASS GRAFT, WITH OTHER THAN VEIN; POPLITEAL-TIBIAL OR -PERONEAL ARTERY), 27590 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL), 27591 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; IMMEDIATE FITTING TECHNIQUE INCLUDING FIRST CAST), 27592 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; OPEN, CIRCULAR (GUILLOTINE)), 27594 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; SECONDARY CLOSURE OR SCAR REVISION), 27596 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; RE-AMPUTATION), 27880 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA), 27881 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; WITH IMMEDIATE FITTING TECHNIQUE INCLUDING APPLICATION OF FIRST CAST), 27882 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; OPEN, CIRCULAR (GUILLOTINE)), 27884 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; SECONDARY CLOSURE OR SCAR REVISION), 27886 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; RE-AMPUTATION), 27888 (AMPUTATION, ANKLE, THROUGH MALLEOLI OF TIBIA AND FIBULA (EG, SYME, PIROGOFF TYPE PROCEDURES), WITH PLASTIC CLOSURE AND RESECTION OF NERVES)
Deep vein thrombosis and venous embolism	451.1 (PHLEBITIS AND THROMBOPHLEBITIS OF DEEP VEINS OF

	LOWER EXTREMITIES), 451.2 (PHLEBITIS AND THROMBOPHLEBITIS OF LOWER EXTREMITIES UNSPECIFIED), 451.81 (PHLEBITIS AND THROMBOPHLEBITIS OF ILIAC VEIN), 451.9 (PHLEBITIS AND THROMBOPHLEBITIS OF UNSPECIFIED SITE), 453.1 (THROMBOPHLEBITIS MIGRANS), 453.2 (EMBOLISM AND THROMBOSIS OF INFERIOR VENA CAVA), 453.8 (ACUTE VENOUS EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS), 453.9 (EMBOLISM AND THROMBOSIS OF UNSPECIFIED SITE), 415.1x (pulmonary embolism)
Diabetes with peripheral circulatory disorders	250.7 Diabetes with peripheral circulatory disorders
Coronary atherosclerosis	414.0x
Atherosclerosis	ICD-9 440.9 (arteriosclerosis) ICD-9 429.2 (ASCVD)
Aortic aneurysm and dissection	441.xx
Other aneurysm of artery of lower extremity	442.3
Atherosclerosis of extremity with ulceration	**440.23**
Peripheral vascular disease	443.9
Arterial embolism and thrombosis of lower extremity	444.22
Peripheral angiopathy	443.81
Gangrene	785.4x
Diabetic foot	**707.1x (ulcer of lower limbs)**
Amputation	**ICD-9 diagnosis: V49.7x – lower limb amputation status, V52.1 – artificial leg** **ICD-9 procedure: 84.1x (amputation of lower limb)** CPT: 26910 (AMPUTATION, METACARPAL, WITH FINGER OR THUMB (RAY AMPUTATION), SINGLE, WITH OR WITHOUT INTEROSSEOUS TRANSFER), 27290 (INTERPELVIABDOMINAL AMPUTATION (HINDQUARTER AMPUTATION), 27295 (DISARTICULATION OF HIP), 27590 – 27598 (AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; IMMEDIATE FITTING TECHNIQUE; AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; OPEN, CIRCULAR (GUILLOTINE); AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; SECONDARY CLOSURE OR SCAR REVISION; AMPUTATION, THIGH, THROUGH FEMUR, ANY LEVEL; RE-AMPUTATION; DISARTICULATION AT KNEE), 27880-27889 (AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; WITH IMMEDIATE FITTING TECHNIQUE INCLUDING APPLICATION OF FIRST CAST; AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; OPEN, CIRCULAR (GUILLOTINE); AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; SECONDARY CLOSURE OR SCAR REVISION; AMPUTATION, LEG, THROUGH TIBIA AND FIBULA; RE-AMPUTATION; AMPUTATION, ANKLE, THROUGH MALLEOLI OF TIBIA AND FIBULA (EG, SYME, PIROGOFF TYPE PROCEDURES), WITH PLASTIC CLOSURE AND RESECTION OF NERVES; ANKLE DISARTICULATION), 28800 (AMPUTATION, FOOT; MIDTARSAL (EG, CHOPART TYPE PROCEDURE)), 28805 (AMPUTATION, FOOT; TRANSMETATARSAL), 28810 (AMPUTATION, METATARSAL, WITH TOE, SINGLE), 28820 (AMPUTATION, TOE; METATARSOPHALANGEAL JOINT), 28825 (AMPUTATION, TOE; INTERPHALANGEAL JOINT) (CPT-4 codes): 26910 (AMPUTATION, METACARPAL, WITH FINGER OR THUMB (RAY AMPUTATION), SINGLE, WITH OR WITHOUT INTEROSSEOUS TRANSFER)
Osteomyelitis	**730.xx**
Osteoporosis	733.0x or the use of bisphosphonates (see below for definition), calcitonin, raloxifene, or teriparatide
Skin infections	**680.xx-686.xx (**CARBUNCLE AND FURUNCLE, CELLULITIS AND ABSCESS OF FINGER AND TOE, CELLULITIS AND ABSCESS OF FINGER AND TOE, ACUTE LYMPHADENITIS, IMPETIGO, PILONIDAL CYST, OTHER LOCAL INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE, UNSPECIFIED LOCAL INFECTION OF SKIN AND SUBCUTANEOUS TISSUE)
Skin ulcer	**682.xx**
Chronic ulcer of skin	**707.xx**
Diabetes with other specified manifestations	250.8x

Diabetes with unspecified complication	250.9x
Diabetic bone changes	731.8x
Erectile dysfunction	607.84
Nutrition counseling	CPT-4 code: 97802 – 97804 (MEDICAL NUTRITION THERAPY; INITIAL ASSESSMENT AND INTERVENTION, INDIVIDUAL, FACE-TO-FACE WITH THE PATIENT, EACH 15 MINUTES; MEDICAL NUTRITION THERAPY; RE-ASSESSMENT AND INTERVENTION, INDIVIDUAL, MEDICAL NUTRITION THERAPY; RE-ASSESSMENT AND INTERVENTION, INDIVIDUAL; MEDICAL NUTRITION THERAPY; GROUP (2 OR MORE INDIVIDUAL(S)), EACH 30 MINUTES) S9470 (NUTRITIONAL COUNSELING, DIETITIAN VISIT) G0270 – G0271 (MEDICAL NUTRITION THERAPY; REASSESSMENT AND SUBSEQUENT INTERVENTION(S) FOLLOWING SECOND REFERRAL IN SAME YEAR FOR CHANGE IN DIAGNOSIS, MEDICAL CONDITION OR TREATMENT REGIMEN (INCLUDING ADDITIONAL HOURS NEEDED FOR RENAL DISEASE), INDIVIDUAL, FACE TO FACE WITH THE PATIENT, EACH 15 MINUTES - OR - GROUP (2 OR MORE INDIVIDUALS), EACH 30 MINUTES)
Diabetes education	CPT-4: 98960 – 98960 (EDUCATION AND TRAINING FOR PATIENT SELF-MANAGEMENT BY A QUALIFIED, NONPHYSICIAN HEALTH CARE PROFESSIONAL USING A STANDARDIZED CURRICULUM) G0108 – G0109 (DIABETES OUTPATIENT SELF-MANAGEMENT TRAINING SERVICES, INDIVIDUAL, PER 30 MINUTES; DIABETES OUTPATIENT SELF-MANAGEMENT TRAINING SERVICES, GROUP SESSION (2 OR MORE), PER 30 MINUTES)
Podiatry	**CPT-4:** **11055 (**PARING OR CUTTING OF BENIGN HYPERKERATOTIC LESION (EG, CORN OR CALLUS); SINGLE LESION**), 11056 (2 TO 4 LESIONS), 11057 (MORE THAN 4 LESIONS), 11719 (**TRIMMING OF NONDYSTROPHIC NAILS, ANY NUMBER**), G0127 (**TRIMMING OF DYSTROPHIC NAILS, ANY NUMBER**), 11720 – 11721 (**DEBRIDEMENT OF NAIL(S) BY ANY METHOD(S); 1 TO 5; 6 OR MORE) G0245 (INITIAL PHYSICIAN EVALUATION AND MANAGEMENT OF A DIABETIC PATIENT WITH DIABETIC SENSORY NEUROPATHY RESULTING IN A LOSS OF PROTECTIVE SENSATION (LOPS) WHICH MUST INCLUDE: (1) THE DIAGNOSIS OF LOPS, (2) A PATIENT HISTORY, (3) A PHYSICAL EXAMINATION THAT CONSISTS OF AT LEAST THE FOLLOWING ELEMENTS: (A) VISUAL INSPECTION OF THE FOREFOOT, HINDFOOT AND TOE WEB SPACES, (B)EVALUATION OF A PROTECTIVE SENSATION, (C) EVALUATION OF FOOT STRUCTURE AND BIOMECHANICS, (D) EVALUATION OF VASCULAR STATUS AND SKIN INTEGRITY, AND (E) EVALUATION AND RECOMMENDATION OF FOOTWEAR AND (4) PATIENT EDUCATION), G0246 (FOLLOW-UP EVALUATION)
Urinary tract infection	**599.0x**
Renal Dysfunction	Acute renal disease (see below) Chronic renal disease (see below) Diabetic nephropathy (see below) Hypertensive nephropathy (see below) Miscellaneous Renal Insufficiency (see below) or ICD-9 procedure: 39.95 hemodialysis 54.98 peritoneal dialysis V56.0 extracorporeal dialysis V56.8 peritoneal dialysis CPT-4: 90935 – 90993 (hemodialysis, miscellaneous dialysis procedures, see code appendix), 99512 (home visit for hemodialysis), 99559 (home infusion, peritoneal dialysis, per visit)
Acute Renal Disease	580.0 (ACUTE GLOMERULONEPHRITIS), 580.4 (ACUTE GLOMERULONEPHRITIS WITH LESION OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS), 580.8 (WITH OTHER SPECIFIED PATHOLOGICAL LESION INKIDNEY), 580.9 (WITH UNSPECIFIED PATHOLOGICAL LESION IN KIDNEY), 581.0 (NEPHROTIC SYNDROME WITH LESION OF MEMBRANOUS GLOMERULONEPHRITIS), 581.1 (WITH LESION OF MEMBRANOUS

	GLOMERULONEPHRITIS), 581.2 (NEPHROTIC SYNDROME WITH LESION OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS), 581.3 (NEPHROTIC SYNDROME WITH LESION OF MINIMAL CHANGE GLOMERULONEPHRITIS), 581.8 (NEPHROTIC SYNDROME WITH OTHER SPECIFIED PATHOLOGICAL LESION IN KIDNEY), 581.9 (NEPHROTIC SYNDROME WITH UNSPECIFIED PATHOLOGICAL LESION IN KIDNEY), 584.6 (ACUTE KIDNEY FAILURE WITH LESION OF RENAL CORTICAL NECROSIS), 584.7 (ACUTE KIDNEY FAILURE WITH LESION OF RENAL MEDULLARY [PAPILLARY] NECROSIS), 584.8 (ACUTE KIDNEY FAILURE WITH OTHER SPECIFIED PATHOLOGICAL LESION IN KIDNEY), 584.9 (ACUTE KIDNEY FAILURE, UNSPECIFIED)
Chronic Renal Insufficiency	582.x (CHRONIC GLOMERULONEPHRITIS), 583.x (NEPHRITIS AND NEPHROPATHY NOT SPECIFIED AS ACUTE OR CHRONIC), 585.x (CHRONIC KIDNEY DISEASE (CKD)), 586.x (RENAL FAILURE UNSPECIFIED), 587.x (RENAL SCLEROSIS UNSPECIFIED)
Diabetic Nephropathy	250.4 (DIABETES WITH RENAL MANIFESTATIONS), 250.41 (DIABETES MELLITUS WITH RENAL MANIFESTATIONS TYPE I NOT STATED AS UNCONTROLLED), 250.42 (DIABETES MELLITUS WITH RENAL MANIFESTATIONS TYPE II OR UNSPECIFIED TYPE UNCONTROLLED), 250.43 (DIABETES MELLITUS WITH RENAL MANIFESTATIONS TYPE I UNCONTROLLED)
Hypertensive Nephropathy	403.xx (HYPERTENSIVE CHRONIC KIDNEY DISEASE), 404.xx (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE)
Miscellaneous Renal Insufficiency	274.10 (GOUTY NEPHROPATHY), 440.1 (ATHEROSCLEROSIS OF RENAL ARTERY), 442.1 (ANEURYSM OF RENAL ARTERY), 453.3 (EMBOLISM AND THROMBOSIS OF RENAL VEIN), 581.xx (NEPHROTIC SYNDROME), 593.xx (OTHER DISORDERS OF KIDNEY AND URETER), 753.0 (CONGENITAL ANOMALIES OF URINARY SYSTEM), 753.3 (OTHER SPECIFIED ANOMALIES OF KIDNEY), 866.00 (INJURY TO KIDNEY), 866.01 (HEMATOMA OF KIDNEY WITHOUT RUPTURE OF CAPSULE WITHOUT OPEN WOUND INTO CAVITY), 866.1 (INJURY TO KIDNEY WITH OPEN WOUND INTO CAVITY)
Prior chronic liver disease and cirrhosis	571.xx
Prior other liver disease	ICD-9 diagnosis: 070.xx viral hepatitis 570.xx acute and subacute necrosis of liver 572.xx liver abscess and sequalae of chronic liver disease 573.xx other disorders of liver 456.0x – 456.2x esophageal varices 155.0x primary cancer of liver 155.1x cancer of intrahepatic bile ducts 155.2x cancer of liver not specified as primary or secondary 576.8x cholestasis 782.4x Jaundice 789.5x Ascites ICD-9 procedure codes: 39.1x intra-abdominal venous shunt 42.91 ligation of esophageal varices
Porphyria	277.1x (DISORDERS OF PORPHYRIN METABOLISM)
Hypertension	1 inpatient or 2 outpatient claims with any of ICD-9 codes : 401.xx-405.xx (ESSENTIAL HYPERTENSION; HYPERTENSIVE HEART DISEASE; HYPERTENSIVE CHRONIC KIDNEY DISEASE; HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE; SECONDARY HYPERTENSION)
Hyperlipidemia	272.xx [hospital discharge, any position or 2 outpatient visits]
Congestive heart failure	1 inpatient or 2 outpatient claims with any of ICD-9 codes : 428.xx (HEART FAILURE), 398.91 (RHEUMATIC HEART FAILURE (CONGESTIVE)), 402.01 (MALIGNANT HYPERTENSIVE HEART DISEASE WITH HEART FAILURE), 402.11 (BENIGN HYPERTENSIVE HEART DISEASE WITH HEART FAILURE), 402.91 (UNSPECIFIED HYPERTENSIVE HEART DISEASE WITH HEART FAILURE), 404.01 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, MALIGNANT, WITH HEART FAILURE AND WITH CHRONIC KIDNEY DISEASE STAGE I THROUGH STAGE IV, OR UNSPECIFIED), 404.11 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, BENIGN, WITH HEART FAILURE OR AND WITH CHRONIC KIDNEY DISEASE STAGE I THROUGH STAGE IV, OR UNSPECIFIED), 404.91 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, UNSPECIFIED, WITH HEART FAILURE AND WITH CHRONIC KIDNEY DISEASE STAGE I THROUGH STAGE IV,

	OR UNSPECIFIED), 404.03 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, MALIGNANT, WITH HEART FAILURE AND WITH CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL DISEASE), 404.13 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, BENIGN, WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL DISEASE), 404.93 (HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE, UNSPECIFIED, WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL DISEASE)
Edema	782.3x
Acute MI	410.xx
Old MI	412.xx
Unstable angina	411.xx
Stable angina	413.xx
Other chronic ischemic heart disease	414.xx (except for 414.0x, coronary atherosclerosis)
CABG	36.1x (BYPASS ANASTOMOSIS FOR HEART REVASCULARIZATION), 36.2x (HEART REVASCULARIZATION BY ARTERIAL IMPLANT) CPT4: 33510 – 33536 (CORONARY ARTERY BYPASS, VEIN ONLY; SINGLE/2/3/4/5/6 (OR MORE) CORONARY VENOUS GRAFT; CORONARY ARTERY BYPASS, USING VENOUS GRAFT(S) AND ARTERIAL GRAFT(S) SINGLE/2/3/4/5/6 (OR MORE) VEIN GRAFT; REOPERATION, CORONARY ARTERY BYPASS PROCEDURE OR VALVE PROCEDURE, MORE THAN 1 MONTH AFTER ORIGINAL OPERATION; CORONARY ARTERY BYPASS, USING ARTERIAL GRAFT(S); SINGLE/2/3/4 (OR MORE) ARTERIAL GRAFT), 33545 (REPAIR OF POST-INFARCTIONVENTRICULAR SEPTAL DEFECT WITH OR WITHOUT MYOCARDIAL RESECTION), 33572 (CORONARY ENDARTERECTOMY, OPEN, ANY METHOD, OF LEFT ANTERIOR DESCENDING, CIRCUMFLEX, OR RIGHT CORONARY ARTERY)
Transmyocardial revascularization	36.31 (OPEN CHEST TRANSMYOCARDIAL REVASCULARIZATION), 36.32 (Other transmyocardial revascularization), 36.33 (Endoscopic transmyocardial revascularization), 36.34 Percutaneous transmyocardial revascularization CPT-4: 33140 (TRANSMYOCARDIAL LASER REVASCULARIZATION, BY THORACOTOMY), 33141(TRANSMYOCARDIAL LASER REVASCULARIZATION, BY THORACOTOMY, PERFORMED AT THE TIME OF OTHER OPEN CARDIAC PROCEDURES)
PTCA or atherectomy	00.66 (EXCISION OF LINGUAL THYROID), 36.01 (SINGLE VESSEL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY [PTCA] OR CORONARY ATHERECTOMY WITH MENTION OF THROMBOLYTIC AGENT), 36.02 (SINGLE VESSEL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY [PTCA] OR CORONARY ATHERECTOMY WITHOUT MENTION OF THROMBOLYTIC AGENT) , 36.03 (OPEN CHEST CORONARY ARTERY ANGIOPLASTY), 36.05 (MULTIPLE VESSEL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY [PTCA] OR CORONARY ATHERECTOMY PERFORMED DURING THE SAME OPERATION, WITH OR WITHOUT MENTION OF THROMBOLYTIC AGENT), 36.09 (OTHER REMOVAL OF CORONARY ARTERY OBSTRUCTION) CPT4: 92973 (PERCUTANEOUS TRANSLUMINAL CORONARY THROMBECTOMY (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE), 92982 (PERCUTANEOUS TRANSLUMINAL CORONARY BALLOON ANGIOPLASTY; SINGLE VESSEL), 92984 (PERCUTANEOUS TRANSLUMINAL CORONARY BALLOON ANGIOPLASTY; EACH ADDITIONAL VESSEL), 92995 (PERCUTANEOUS TRANSLUMINAL CORONARY ATHERECTOMY, BY MECHANICAL OR OTHER METHOD, WITH OR WITHOUT BALLOON ANGIOPLASTY; SINGLE VESSEL), 92996 (EACH ADDITIONAL VESSEL), 92920 – 92921, 92924 – 92925, 92937, 92938, 92941, 92943, 92944
Stent	36.06 (bare metal) 36.07 (drug-eluting) CPT4: 92980, 92981, 92928 – 92929, 92933 - 92934
CABG or PTCA or atherectomy or Stent	See above for definition

History of PTCA	V45.82
History of CABG	V45.81
History of PTCA or History of CABG	See above for definition
Injection/infusion of thrombolytic agent (Alteplase, Anistreplase, Reteplase, Streptokinase, Tenecteplase, Tissue plasminogen activator, Urokinase)	99.10
Rheumatic/aortic/mitral valve disease	394.xx (DISEASES OF MITRAL VALVE), 395.xx (DISEASES OF AORTIC VALVE), 396.xx (DISEASES OF MITRAL AND AORTIC VALVES), 424.0x (MITRAL VALVE DISORDERS), 424.1x (AORTIC VALVE DISORDERS)
Other cardiovascular disorders	390.xx-393.xx, 397.xx, 398.xx, 420.xx-424.xx (except for 424.0x, 424.1x), 425.xx, 441.xx-447.xx (except for 443.9x, 745.xx-747.xx)
Cardiac dysrhythmia	427.xx, exclude 427.5 (cardiac arrest)
Atrial fibrillation or flutter	427.3x
Ventricular fibrillation or flutter	427.4x
Other dysrythmias	427.0x (PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA), 427.1x (PAROXYSMAL VENTRICULAR TACHYCARDIA), 427.2x (PAROXYSMAL TACHYCARDIA UNSPECIFIED), 427.6x (PREMATURE BEATS), 427.8x (OTHER SPECIFIED CARDIAC DYSRHYTHMIAS), 427.9x (CARDIAC DYSRHYTHMIA UNSPECIFIED), 785.0x (TACHYCARDIA UNSPECIFIED)
Cardiac conduction disorders	426.xx
History of sudden cardiac arrest	V12.53
Ischemic stroke	433.x1 (OCCLUSION AND STENOSIS CAROTID ARTERIES), 434.x1 (CEREBRAL EMBOLISM), 436.xx (ACUTE BUT ILL-DEFINED CEREBROVASCULAR DISEASE), 437.1x (OTHER GENERALIZED ISCHEMIC CEREBROVASCULAR DISEASE), 437.9x (UNSPECIFIED CEREBROVASCULAR DISEASE)
Late effects of cerebrovascular disease	438.xx
TIA	435.xx
Personal history of stroke	V12.54
Hemorrhagic stroke	430.xx (SUBARACHNOID HEMORRHAGE), 431.xx (INTRACEREBRAL HEMORRHAGE), 432.xx (OTHER AND UNSPECIFIED INTRACRANIAL HEMORRHAGE)
COPD	491.xx (CHRONIC BRONCHITIS), 492.xx (EMPHYSEMA), 496.xx (CHRONIC AIRWAY OBSTRUCTION NOT ELSEWHERE CLASSIFIED), 493.2x (chronic obstructive asthma)
Asthma	493.xx (excluding 493.2x)
Obstructive sleep apnea	327.23
Oxygen	V46.2x
Pneumonia	480.xx – 486.xx, 487.0x, 507.xx
Polyuria, Nocturia	**788.4**
Polydipsia	**783.5**
Acidosis	**276.2,** diabetic acidosis (249.1, 250.1)
Asthenia/fatigue	**780.79**
Syncope and collapse	**780.2**
Abdominal pain	**789.0x**
Nausea and/or vomiting	**787.0x**
Diarrhea	**787.91**
Pancreatitis	**577.0 (**DISEASES OF PANCREAS**), 577.1 (**CHRONIC PANCREATITIS)
Hyperthyroidism	**242.1x (**TOXIC UNINODULAR GOITER**), 242.3x (**TOXIC NODULAR GOITER UNSPECIFIED TYPE**), 242.9x (**THYROTOXICOSIS WITHOUT MENTION OF GOITER OR OTHER CAUSE)
Hypothyroidism	**243 (**CONGENITAL HYPOTHYROIDISM**), 244.x (**ACQUIRED HYPOTHYROIDISM)
Other disorders of thyroid gland	**240.xx – 246.xx, excluding hyperthyroidism and hypothyroidism (**SIMPLE AND UNSPECIFIED GOITER; NONTOXIC NODULAR GOITER; THYROIDITIS; OTHER DISORDERS OF THYROID)
Osteoarthritis	715.xx
Rheumatoid arthritis	714.xx
Other arthritis, arthropathies and musculoskeletal pain	710.xx−713.xx, 716.xx −719.xx, 725.xx−729.xx
Fractures	733.1x (PATHOLOGIC FRACTURE), 800.xx-829.xx (FRACTURE OF VAULT OF SKULL; FRACTURE OF BASE OF SKULL; FRACTURE OF FACE BONES; OTHER AND UNQUALIFIED SKULL FRACTURES; MULTIPLE FRACTURES INVOLVING SKULL OR FACE WITH OTHER BONES; FRACTURE OF VERTEBRAL COLUMN WITHOUT MENTION OF SPINAL CORD INJURY; FRACTURE OF VERTEBRAL COLUMN WITH SPINAL CORD INJURY; FRACTURE OF RIB(S) STERNUM LARYNX AND TRACHEA; FRACTURE OF PELVIS; ILL-DEFINED FRACTURES OF BONES OF TRUNK; FRACTURE OF CLAVICLE; FRACTURE OF SCAPULA; FRACTURE OF HUMERUS; FRACTURE

	OF RADIUS AND ULNA; FRACTURE OF CARPAL BONE(S); FRACTURE OF METACARPAL BONE(S); FRACTURE OF ONE OR MORE PHALANGES OF HAND; MULTIPLE FRACTURES OF HAND BONES; ILL-DEFINED FRACTURES OF UPPER LIMB; MULTIPLE FRACTURES INVOLVING BOTH UPPER LIMBS AND UPPER LIMB WITH RIB(S) AND STERNUM; FRACTURE OF NECK OF FEMUR; FRACTURE OF OTHER AND UNSPECIFIED PARTS OF FEMUR; FRACTURE OF PATELLA; FRACTURE OF TIBIA AND FIBULA; FRACTURE OF ANKLE; FRACTURE OF ONE OR MORE TARSAL AND METATARSAL BONES; FRACTURE OF ONE OR MORE PHALANGES OF FOOT; OTHER MULTIPLE AND ILL-DEFINED FRACTURES OF LOWER LIMB; MULTIPLE FRACTURES INVOLVING BOTH LOWER LIMBS LOWER WITH UPPER LIMB AND LOWER LIMB(S) WITH RIB(S) AND STERNUM; FRACTURE OF UNSPECIFIED BONES)
Falls	E885 (ACCIDENTAL FALL ON SAME LEVEL FROM SLIPPING TRIPPING OR STUMBLING), E885.9x (ACCIDENTAL FALL FROM OTHER SLIPPING TRIPPING OR STUMBLING), E888.xx (OTHER AND UNSPECIFIED FALL)
Anemia	**285.21 (ANEMIA IN CHRONIC KIDNEY DISEASE), 281.x (OTHER DEFICIENCY ANEMIAS)**
Folate/vit-12 deficiency or vitamin B12 deficiency anemia	**281.2 (FOLATE DEFICIENCY ANEMIA), 281.3 (**OTHER SPECIFIED MEGALOBLASTIC ANEMIAS NOT ELSEWHERE CLASSIFIED)
Haemostatic disorders	**269.0x, 286.7x Vitamin K deficiency** **286.0x-2x Hemophilia** **286.3x Congenital afibrinogenemia** **286.4x Von Willebrand disease** **286.5x Hemorrhagic disorder due to intrinsic circulating anticoagulants** **286.6x Disseminated intravascular coagulation** **286.9x Other and unspecified coagulation defects** **287.1x Platelet defects** **287.3x idiopathic thrombocytopenia** **287.4x Secondary thrombocytopenia** **287.5x Thrombocytopenia unspecified** **289.81 Protein S deficiency, protein C deficiency** **289.82 Secondary hypercoagulable state** **289.84 Heparin-induced thrombocytopenia (HIT)** **208.xx Leukemia**
Convulsions or seizures NOS	**345.xx (**EPILEPSY**), 780.39 (OTHER CONVULSIONS)**
Parkinson's disease	332.xx, 333.0x
Depression	293.83 (MOOD DISORDER IN CONDITIONS CLASSIFIED ELSEWHERE), 296.2x (MAJOR DEPRESSIVE DISORDER SINGLE EPISODE), 296.3x (MAJOR DEPRESSIVE DISORDER RECURRENT EPISODE), 296.90 (OTHER AND UNSPECIFIED EPISODIC MOOD DISORDER), 298.0x (DEPRESSIVE TYPE PSYCHOSIS), 300.4x (DYSTHYMIC DISORDER), 309.0x (ADJUSTMENT REACTION WITH ADJUSTMENT DISORDER WITH DEPRESSED MOOD), 309.1x (ADJUSTMENT REACTION WITH PROLONGED DEPRESSIVE REACTION), 309.28 (ADJUSTMENT DISORDER WITH MIXED ANXIETY AND DEPRESSED MOOD), 311 (DEPRESSIVE DISORDER NOT ELSEWHERE CLASSIFIED)
Bipolar disorder	296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x, 296.99
Anxiety disorders	293.84, 300.0x, 300.2x, 300.3x, 309.24, 308.0x, 309.81
Sleep disorder	307.4x, 327.0x, 327.2x 780.5x, 347.xx
Dementia	290.xx, 294.xx, 330.xx, 331.xx
Delirium	290.11, 290.3x, 290.41, 291.0x, 292.81, 293.xx, 348.3x, 349.82
Psychosis	290.8x, 290.9x, 295.xx, 297.xx, 298.xx, 299.xx, 780.1x
LIFE STYLE FACTORS	
Alcohol abuse or dependence	291.xx (ALCOHOL-INDUCED MENTAL DISORDERS), 303.xx (ALCOHOL DEPENDENCE SYNDROME)
Drug abuse or dependence	292.xx (DRUG-INDUCED MENTAL DISORDERS), 304.xx (DRUG DEPENDENCE), 305.xx (NONDEPENDENT ABUSE OF DRUGS) (excluding 305.1x (NONDEPENDENT TOBACCO USE DISORDER))
Smoking	V15.82 (PERSONAL HISTORY OF TOBACCO USE), 305.1x (NONDEPENDENT TOBACCO USE DISORDER), prescription of varenicline tartrate or nicotine replacement therapy
Obesity	278.00 (OVERWEIGHT, OBESITY AND OTHER HYPERALIMENTATION), 278.01 (MORBID OBESITY), V85.3x, V85.4x
Overweight	278.02

Abnormal weight gain	783.1
MEDICATIONS	
ACE inhibitor	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
ARB	Azilsartan, candesartan, eprostartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta blocker	Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol, pindolol, nadolol, nebivolol, sotalol, timolol
Thiazides	Bendroflumethiazide Benzthiazide Chlorothiazide Chlorthalidone Cyclothiazide Hydrochlorothiazide Hydroflumethiazide Indapamide Methyclothiazide Metolazone Polythiazide Quinethazone Trichlormethiazide
Loop diuretics	furosemide, bumetanide, torsemide, ethacrynic acid
Other diuretics	Amiloride, eplerenone, spironolactone, triamterene
Other antihypertensives	Doxazosin, eplerenone, prazosin, terazosin, clonidine, guanabenz, guanadrel, guanethidine, guanfacine, hydralazine, methyldopa, metyrosine, reserpine, minoxidil
Calcium channel blockers	Diltiazem Mibefradil Verapamil Amlodipine Clevidipine Bepridil Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine Amlodipine–atorvastatin
Nitrates	Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, ranolazine
Aliskiren	Aliskiren
Digoxin	Digoxin
Antiarrhythmics	Amiodarone, dronedarone, flecainide, ibutilide, procainamide, propafenone, quinidine disopyramide, dofetilide, mexiletine, moricizine, tocainide
Statins	Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, lovastatin–niacin, ezetimibe–simvastatin, pravastatin- aspirin, pitavastatin.
Other lipid-lowering drugs	Niacin Nicotinic acid Niacinamide Fenofibrate Gemfibrozil Cholestyramine Colesevelam Colestipol Ezetimibe alone
Colesevelam	Colesevelam
Bromocriptine	Bromocriptine
Pramlintide	Pramlintide
Oral anticoagulants	Warfarin, dabigatran, rivaroxaban, apixaban
Heparin and other LMWH	Heparin, dalteparin, enoxaparin, tinzaparin
Other anticoagulants	argatroban, bivalirudin, eptifibatide, fondaparinux, lepirudin, tirofiban
Aspirin	Aspirin alone
Antiplatelet	Clopidogrel, prasugrel, ticlopidine, aspirin–dipyridamole, dipyridamole alone, cilostazol, ticagrelor
Oral corticosteroids	Cortisone hydrocortisone prednisone prednisolone methylprednisolone

	triamcinolone dexamethasone, bethamethasone
Nonselective nonsteroidal anti-inflammatory drugs	diclofenac etodolac flurbiprofen ketorolac ibuprofen indomethacin meloxicam naproxen piroxicam sulindac
Selective COX-2 inhibitors	Celecoxib Rofecoxib valdecoxib
Bisphosphonates	Alendronate, risedronate, ibandronate or etidronate, zoledronic acid, pamidronic acid
DMARDs	Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide, Cyclosporine, Azathioprine, Cyclophosphamide, d-penicillamine Gold Sodium Thiomalate, Auranofin, Solganol, Myochrysine, Adalimumab, Etanercept, Infliximab, Certolizumab, Golimumab, Abatacept, Rituximab, Tocilizumab, Anakinra
Opiates	Codeine Fentanyl Hydrocodone Hydromorphone Meperidine Morphine Oxycodone Propoxyphene Oxymorphone Tramadol
Antidepressants	Paroxetine Citalopram Escitalopram Fluoxetine Fluvoxamine Sertraline Venlafaxine Desvenlafaxine Levomilnacipran Duloxetine Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline Trimipramine Bupropion Mirtazapine Nefazodone Trazodone Phenelzine Isocarboxazid Tranylcypropine Vilazodone, Vortioxetine
Antipsychotics	clozapine risperidone olanzapine quetiapine aripiprazole ziprasidone acetophenazine chlorpromazine fluphenazine mesoridazine perphenazine promazine thioridazine trifluoperazine trifluprom azine chlorprothixene haloperidol loxapine molindone pimozide thiothixene asenapine iloperidone lurasidone paliperidone pimozide propiomazine trifluprom azine
Anticonvulsants	carbamazepine, divalproex, eslicarbazepine, ethotoin, ethosuximide, ezogabine, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, methsuximide, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid, vigabatrin, zonisamide
Lithium	lithium carbonate lithium citrate
Benzodiazepines	Alprazolam Chlordiazepoxide Clonazepam Clorazepate Diazepam Estazolam Flurazepam Halazepam Lorazepam Midazolam Oxazepam Prazepam Quazepam Temazepam

	Triazolam
Other anxiolytics/hypnotics	Eszopiclone Zaleplon Zolpidem Chloral hydrate Diphenhydramine Doxylamine Ethclorvynol Glutethimide Methaqualone buspirone hydroxyzine meprobamate
Agents for dementia	Ergoloid donepezil rivastigmine galantamine memantine tacrine
Antiparkinson agents	Benztropine biperiden procyclidine trihexyphenidyl tolcapone amantadine levodopa pergolide pramixepole ropinirole rotigotine carbidopa/levodopa rasagiline selegiline carbidopa

ANNEX 3.3 GENERAL CONSIDERATIONS FOR DIABETES MELLITUS TYPE 2 THERAPY

Insulin secretagogues, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-IV inhibitors, and insulin are approved for monotherapy of type 2 DM.
Unless contraindicated, metformin is generally recommended as initial therapy because of its efficacy, known side-effect profile, and relatively low cost. Metformin has also the advantage that it promotes mild weight loss, lowers insulin levels, and improves the lipid profile slightly. However, due to the paucity of long-term comparative effectiveness trials available, uniform recommendations on the best agent to be combined with metformin cannot be made. Advantages and disadvantages of specific drugs for each patient should be considered.

Treatment algorithm for diabetes mellitus type 2 treatment

1st Use Agents	**2nd Use Agents** **If HbA1c > 7% after 2-3 months**	**3rd Use agents** **If HbA1c > 7% after 2-3 months**
Metformin (added at, or soon after, diagnosis) If metformin is contraindicated[1]: - sulfonylureas (Cheap, generally well-tolerated)/meglitinides (considered in place of a sulfonylurea in patients with irregular meal schedules or with late postprandial hypoglycemia while on sulfonylurea agents) - TZDs (No hypoglycemia) - DPP-4 inhibitors (No weight gain, no hypoglycemia) - GLP-1 receptor agonists where weight loss is seen as an essential aspect of therapy - AGIs, colesevelam, bromocriptine, where available in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain and hypoglycaemia should play a major role in this drug selection If markedly symptomatic patient and/or elevated blood glucose levels (FPG >11.1–13.9 mmol/L or 200–250 mg/dL) or HbA1C (>9.0%): - Insulin with or without additional agents (starting with basal/intermediate insulin[2] (insulin glargine, insulin detemir, or NPH insulin))	- sulfonylureas/meglitinides - TZDs - DPP-4 inhibitors - GLP-1 receptor agonists - AGIs, colesevelam, bromocriptine (can be added but their modest glycemic effects and side effect profiles make them less attractive candidates) No good evidence supports one combination therapy over another. If markedly symptomatic patient and/or elevated blood glucose levels or HbA1C (>9%): - basal insulin If already on basal insulin, intensification of insulin regimen with: - addition of pre-meal rapid-acting insulin analogue - twice daily pre-mixed insulin (fixed combination of an intermediate insulin with regular insulin or a rapid analogue)	Some studies have shown advantages of adding a third non-insulin agent (sulfonylureas/meglitinides, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists) to a two-drug combination that is not yet or no longer achieving the glycemic target. However at this juncture, the most robust response will usually be with insulin, especially with elevated HbA1C (>9%). Metformin is often continued when basal insulin is added (less weight gain when the two are used together). Sulfonylureas/meglitinides should be avoided once more complex insulin regimens than basal insulin are used. TZDs should be reduced in dose (or stopped) to avoid edema and excessive weight gain (in certain individuals with large insulin requirements from severe insulin resistance, these insulin sensitizers may be very helpful in lowering HbA1c and minimising the required insulin dose).

Treatment algorithm for diabetes mellitus type 2 treatment (con't)

		Combination of basal insulin with GLP-1 receptor agonists may be helpful in some patients.

[1] Metformin is contraindicated in patients at risk of lactic acidosis such as those with significant renal dysfunction (e.g., serum creatinine values >1.5 mg/dL [males] and >1.4 mg/dL [females]) or alcoholism. Metformin should be used with caution for patients with conditions that predispose them to risk of hypoxia (congestive heart failure, chronic obstructive pulmonary disease or obstructive sleep apnea), liver dysfunction, and age > 80 years (because of the decline in renal function).

[2] At any stage insulin therapy can be augmented with human amylin analogs (pramlintide)

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ANNEX 3.4 EXAMPLE STUDY SHELL TABLES

Table A1 Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Number of patients						
Number naïve new users						
CHARACTERISTICS OF INITIATION						
Initiation as monotherapy						
Concomitant initiation of other specific hypoglycemic agents – Any agent						
Concomitant initiation of linagliptin						
Concomitant initiation of sitagliptin						
Concomitant initiation of saxagliptin						
Concomitant initiation of metformin						
Concomitant initiation of sulfonylureas						
Concomitant initiation of glitazones						
Concomitant initiation of meglitinides						
Concomitant initiation of AGI						
Concomitant initiation of non-insulin injected agents (exenatide, liraglutide, albiglutide)						
SGLT2 inhibitors (Canagliflozin, dapagliflozin)						
Concomitant initiation of insulin – any formulation						
Concomitant initiation of short-acting insulin						
Concomitant initiation of rapid-acting insulin						
Concomitant initiation of intermediate-acting insulin						
Concomitant initiation of long-acting insulin						
Concomitant initiation of insulin mixtures						
Initiation as component of dual therapy						
Initiation as component of ≥3 therapies						
Initiation as fixed-dose combination of two agents						
PRIOR USE OF OTHER HYPOGLYCEMIC AGENTS						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Previous use of other specific hypoglycemic agents – Any agent						
Previous use of linagliptin						
Previous use of sitagliptin						
… (List as above)						
Current use of other specific hypoglycemic agents – Any agent						
Concomitant use of linagliptin						
Concomitant use of sitagliptin						
… (List as above)						
Past use of other specific hypoglycemic agents – Any agent						
Past use of linagliptin						
Past use of sitagliptin						
… (List as above)						
DEMOGRAPHICS						
Age (Mean, SD)						
Age category 18-35						
Age category 36-49						
Age category 50-64						
Age category 65-74						
Age category 75+						
Sex						
Baseline year						
Comorbidity score, Charlson						
HEALTH CARE UTILIZATION						
Total N distinct non-insulin hypoglicemic agents prescribed in past 180 days						
Total N distinct pharmacological agents prescribed in past 180 days						
N physician visits						
Hospitalization (Y/N)						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
N hospitalizations						
N hospital days						
Hospitalization in 30 days prior to treatment initiation						
Total N distinct ICD9 diagnoses at the 3rd digit level						
Number of laboratory tests ordered						
Number of hemoglobin A1C tests ordered						
Number of glucose tests ordered						
Number of lipid tests ordered						
Number of creatinine tests ordered						
Mammography						
Pap test						
PSA test						
Colonoscopy						
Fecal occult blood test						
Flu shot						
Pneumococcal vaccine						
BMD testing						
Number of electrocardiograms						
Long-term (current) use of insulin						
Use of glucose test strips						
LABORATORY TESTS						
HbA1c (%)						
Creatinine (mg/dl)						
eGFR (ml/min per 1.73 m2)						
Total cholesterol (mg/dl)						
HDL level (mg/dl)						
LDL level (mg/dl)						
Triglyceride level (mg/dl)						
COMORBIDITIES AT BASELINE						
Diabetes during pregnancy						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
PCOS						
Female Infertility						
Precocious puberty						
Hyperglycemia						
Diabetic ketoacidosis						
Hyperosmolar hyperglycemic nonketotic syndrome (HONK)						
Diabetes with coma						
Hypoglycemic coma						
Hypoglycemia						
Diabetic retinopathy						
Diabetic nephropathy NOS						
Opthalmology visit						
Diabetes with ophthalmic manifestations						
Cataract						
Glaucoma						
Retinal detachment, vitreous hemorrhage, vitrectomy						
Pyelonephritis/infections of kidney						
Diabetic neuropathy						
Mononeuropathy or polyneuropathy						
Peripheral autonomic neuropathy						
Gastroparesis						
Peripheral vascular disease or PVD surgery						
Deep vein thrombosis and venous embolism						
Diabetes with peripheral circulatory disorders						
Coronary atherosclerosis						
Atherosclerosis						
Aortic aneurysm and dissection						
Other aneurysm of artery of lower extremity						
Atherosclerosis of extremity with ulceration						
Peripheral vascular disease						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Arterial embolism and thrombosis of lower extremity						
Peripheral angiopathy						
Gangrene						
Diabetic foot						
Amputation						
Osteomyelitis						
Osteoporosis						
Skin infections						
Skin ulcer						
Chronic ulcer of skin						
Diabetes with other specified manifestations						
Diabetes with unspecified complication						
Diabetic bone changes						
Erectile dysfunction						
Nutrition counseling						
Diabetes education						
Podiatry						
Urinary tract infection						
Renal Dysfunction						
Acute Renal Disease						
Chronic Renal Insufficiency						
Diabetic Nephropathy						
Hypertensive Nephropathy						
Miscellaneous Renal Insufficiency						
Prior chronic liver disease and cirrhosis						
Prior other liver disease						
Porphiria						
Hypertension						
Hyperlipidemia						
Congestive heart failure						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Edema						
Acute MI						
Old MI						
Unstable angina						
Stable angina						
Other chronic ischemic heart disease						
CABG						
Transmyocardial revascularization						
PTCA or atherectomy						
Stent						
CABG or PTCA or atherectomy or Stent						
History of PTCA						
History of CABG						
Injection/infusion of thrombolytic agent (Alteplase, Anistreplase, Reteplase, Streptokinase, Tenecteplase, Tissue plasminogen activator, Urokinase)						
Rheumatic/aortic/mitral valve disease						
Other cardiovascular disorders						
Cardiac dysrhythmia						
Atrial fibrillation or flutter						
Ventricular fibrillation or flutter						
Other dysrythmias						
Cardiac conduction disorders						
History of sudden cardiac arrest						
Ischemic stroke						
Late effects of cerebrovascular disease						
TIA						
Personal history of stroke						
Hemorrhagic stroke						
COPD						
Asthma						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Obstructive sleep apnea						
Oxygen						
Pneumonia						
Polyuria, Nocturia						
Polydipsia						
Acidosis						
Asthenia/fatigue						
Syncope and collapse						
Abdominal pain						
Nausea and/or vomiting						
Diarrhea						
Pancreatitis						
Hyperthyroidism						
Hypothyroidism						
Other disorders of thyroid gland						
Osteoarthritis						
Rheumatoid arthritis						
Other arthritis, arthropathies and musculoskeletal pain						
Fractures						
Falls						
Anemia						
Folate/vit-12 deficiency or vitamin B12 deficiency anemia						
Haemostatic disorders						
Convulsions or seizures NOS						
Depression						
Bipolar disorder						
Anxiety disorders						
Sleep disorder						
Dementia						
Delirium						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Psychosis						
LIFE STYLE FACTORS						
Alcohol abuse or dependence						
Drug abuse or dependence						
Smoking						
Obesity						
Overweight						
Abnormal weight gain						
MEDICATIONS						
ACE inhibitor						
ARB						
Beta blocker						
Thiazides						
Loop diuretics						
Other diuretics						
Other antihypertensives						
Calcium channel blockers						
Nitrates						
Aliskiren						
Digoxin						
Antiarrhythmics						
Statins						
Other lipid-lowering drugs						
Colesevelam						
Bromocriptine						
Pramlintide						
Oral anticoagulants						
Heparin and other LMWH						
Other anticoagulants						
Aspirin						

Table A1 (cont'd) Characteristics of Diabetes Therapy Users

	Diabetes Therapy Users					
Characteristic	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin	Pioglitazone	2nd Generation Sulfonylureas
Antiplatelet						
Oral corticosteroids						
Nonselective nonsteroidal anti-inflammatory drugs						
Selective COX-2 inhibitors						
Bisphosphonates						
DMARDs						
Opiates						
Antidepressants						
Antipsychotics						
Anticonvulsants						
Lithium						
Benzodiazepines						
Other anxiolytics/hypnotics						
Agents for dementia						
Antiparkinson agents						

This table will be tabulated for the population overall and stratified by new user/naive new user/non-naive new user.

Table A2 Follow-up and outcomes among matched cohorts

Group	Size	Follow-up (P-Y)	Outcome events	Incidence Rate	HR	95% CI
Linagliptin	N					
Comparator	N					

This table will be repeated for each of the outcomes

Table A3 Follow-up and distribution of reasons for discontinuation

Group	Size	Follow-up (years)			Reasons for discontinuation (N, %)				
		Mean	Median	Max	Discontinue	Switch	Event	Disenrollment	Death
Linagliptin	N								
Comparator	N								

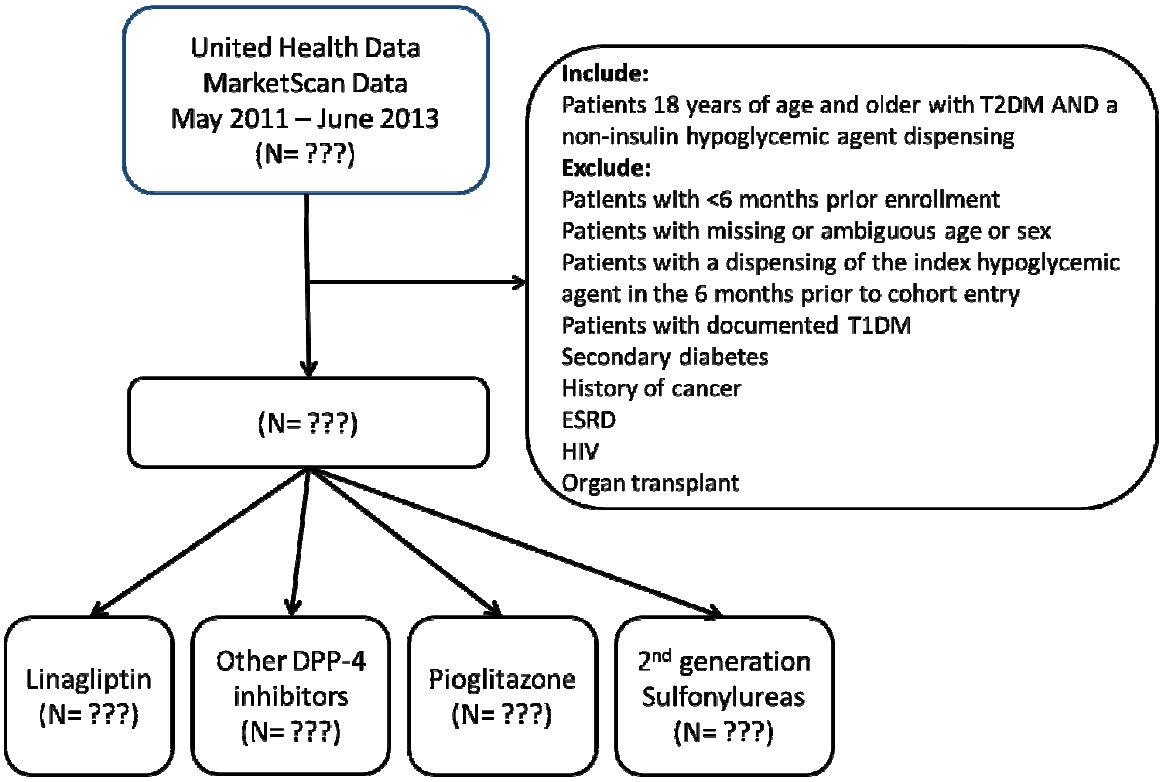
This table will be repeated for each of the outcomes.

Table A4 Stratifications

Subgroup	Group	Size	Follow-up (P-Y)	Outcome events	Incidence Rate	HR	95% CI
Age 18-35							
	Linagliptin	N					
	Comparator	N					
Age 36-49							
	Linagliptin	N					
	Comparator	N					
Age 50-64							
	Linagliptin	N					
	Comparator	N					
Age 65-74							
	Linagliptin	N					
	Comparator	N					
Age 75+							
	Linagliptin	N					
	Comparator	N					

This table will extend to encompass all of the stratification variables and will be repeated for each of the outcomes.

ANNEX 3.5 EXAMPLE STUDY FIGURES



T2DM Type 1 diabetes mellitus
T1DM: Type 1 diabetes mellitus
DPP-4: Dipeptidyl peptidase-4

Figure A1 **Patient Selection Flow Diagram (CONSORT Style)**

Separate figures to be created for each of the study outcomes.

Figure A2 Survival curves (time to event)

The actual figures will be displayed in the study report.

Separate figures to be created for each of the stratification variables, and for each of the study outcomes.

Figure A3 Survival curves (time to event) within subgroup strata

The actual figures will be displayed in the study report.

APPROVAL / SIGNATURE PAGE

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