**CNODES**

**Technical Analytical Protocol:**

**Phase I**

**The use of incretin-based drugs and the risk of acute pancreatitis, pancreatic cancer, and congestive heart failure in patients with type 2 diabetes**

**Version 1.6**

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Table of Contents

[I. Document Control 3](#_Toc402955318)

[II. Objectives & hypotheses 3](#_Toc402955319)

[III. Study design for all study objectives 4](#_Toc402955320)

[IV. Base-cohort for all study objectives 4](#_Toc402955321)

[V. Study cohort for acute pancreatitis 8](#_Toc402955322)

[VI. Baseline covariates for acute pancreatitis 12](#_Toc402955323)

[VII. Study cohort for pancreatic cancer 17](#_Toc402955324)

[VIII. Baseline covariates for pancreatic cancer 19](#_Toc402955325)

[IX. Study cohort for congestive heart failure 23](#_Toc402955326)

[X. Baseline covariates for CHF 26](#_Toc402955327)

[XI. APPENDIX I: Site-specific protocol deviations 34](#_Toc402955328)

[XII. APPENDIX II: Amendments 35](#_Toc402955329)

[XIII. APPENDIX III: Questions & Answers 38](#_Toc402955330)

# Document Control

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Author(s)** | **Type of Change** |
| 1.0 | July 2, 2014 | LA, KBF | Initial version of Analytical Protocol Phase I (cohort, outcome, and covariate definitions) |
| 1.1 | July 14, 2014 | MD | Revisions and additions to Analytical Protocol Phase I |
| 1.2 | August 11, 2014 | LA, KBF | Revisions after inclusion of comments from CNODES liaisons and analysts |
| 1.3 | August 12, 2014 | LA, MD | Small correction regarding timing of the HIV/HAART exclusion for acute pancreatitis and congestive heart failure study cohorts. Refer to Appendix II. |
| 1.4 | August 19, 2014 | LA, KBF, MD | Miscellaneous amendments and clarifications. Refer to Appendices II and III. |
| 1.5 | September 11, 2014 | LA, KBF, LS | Miscellaneous amendments and clarifications. Refer to Appendices II and III. Revised Excel Workbook. |
| 1.6 | November 5, 2014 | LA, KBF, LS | Added expanded utilization table (1987 to 2014) as well as number of excluded pancreatic cancer cases in revised Excel Workbook. Modified pancreatic cancer event definition. Altered the tables to match the new excel workbook. |

**Note:** Text in **red** fontin the analytical protocol refers to Excel worksheets that should be completed. See file **“CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx”** located in Dropbox.

**Note:** Amendments in the analytical protocol are indicated in **blue** font. See Appendix II: Amendments for specific details.

# Objectives & hypotheses

1. **Objectives**
2. To determine whether the use of incretin-based drugs (alone or in combination with other anti-diabetic drugs), compared to oral hypoglycemic agent (OHA) combinations, is associated with an increased risk of acute pancreatitis.
3. To determine whether the use of incretin-based drugs (alone or in combination with other anti-diabetic drugs), compared to sulfonylureas drugs (alone or in combination with other anti-diabetic drugs), is associated with an increased risk of pancreatic cancer.
4. To determine whether the use of incretin-based drugs (alone or in combination with other anti-diabetic drugs), compared to OHA combinations, is associated with an increased risk of congestive heart failure (CHF).
5. **Hypotheses**
6. The use of incretin-based drugs is associated with an increased risk of acute pancreatitis, compared to OHA combinations.
7. The use of incretin-based drugs is associated with an increased risk of pancreatic cancer, compared to sulfonylureas.
8. The use of incretin-based drugs is associated with an increased risk of CHF, compared to OHA combinations.

# Study design for all study objectives

Three separate retrospective cohort studies will be conducted, each corresponding to one of the study objectives. For each of these studies, nested case-control analyses will be conducted within each of the seven participating CNODES sites (Alberta, Manitoba, Saskatchewan, Ontario, Quebec, US MarketScan or British Columbia, and UK Clinical Practice Research Datalink [CPRD]).

# Base-cohort for all study objectives

A common base-cohort will be used for all three study objectives. It will consist of all patients newly-treated with non-insulin anti-diabetic agents.

**Note:** While the analytical protocol provides ATC codes to define medications, the corresponding list of DINs can be found in Dropbox.

**Note:** The ICD-9 codes at some sites are limited to 3 digits for outpatient (physician) billing codes. In such cases, it is permissible to use only 3 digits to apply exclusion criteria and define covariates (**unless otherwise specified**). However, this must be noted in the site-specific protocol deviations (Appendix I).

1. **Base-cohort construction**

**Identification of potentially eligible patients**

Identify all patients with a first-ever prescription of a non-insulin anti-diabetic medication (WHO ATC code A10B), including biguanides (A10BA), sulfonylureas (A10BB or A10BC), thiazolidinediones (A10BG), DPP-4 inhibitors (A10BH), GLP-1 analogs (A10BX04, A10BX07), alpha-glucosidase inhibitors (A10BF), and meglitinides (A10BX02, A10BX03) from the earliest availability of data to the last date of availability of data at your site.

Patients with first-ever prescriptions of two or more of the above drug classes [either two separate prescriptions from different classes or a combination pill (A10BD)] at the same date will be defined as combination users. See Dropbox for the non-insulin anti-diabetic medication DIN list.

**Exclusion criteria**

The following **sequential** exclusions will be performed:

1. Exclude patients <18 years (or the minimum age for which medication data are available in your site + 1 year) at the time of the first non-insulin anti-diabetic prescription
2. Exclude patients with less than 365 days of continuous coverage in the database before the first non-insulin prescription (**Note:** This step will exclude all patients who received their first prescription in the first year of data availability, as well as all those with less than 365 days of continuous coverage during the period thereafter)
3. Exclude patients with inconsistent dates, i.e., those where the first-ever prescription date is equal or later than the earliest of the following events:
   1. Date of death (from any cause)
   2. Date of emigration from your province
   3. Date of first loss of continuous health plan or drug plan enrolment (or date no longer registered in the general practice for CPRD)
   4. Entry into a long-term care facility
   5. End of the study period (June 30, 2014, or the last date of data availability at your site)
4. Exclude patients with insulin prescriptions (ATC code A10A) ever before (look back as far as your data allows) and including the date of the first non-insulin prescription. See Insulin medication DIN list (excel file: incretin\_DIN\_list.xlsx).
5. Exclude women diagnosed with polycystic ovarian syndrome (ICD 9 code 256.4; ICD 10 code E28.2) ever before (look back as far as your data allows) and including the date of the first non-insulin prescription in any of the available databases at your site (such as physician and hospital data)
6. Exclude women diagnosed with gestational diabetes (ICD 9 code 648.8; ICD 10 code O24.4) in the 365 days before and including the date of the first non-insulin prescription in any of the available databases at your site (such as physician and hospital data)
7. **Descriptive analyses for the base-cohort**

**Please enter information in the following worksheets of Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx”:**

* Flowchart 1: Base-cohort
* Description base-cohort (Table 1)
  + If you choose, a program template (incretins\_template\_table1.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code or modify the variable names with the program to match your variable names). If your site does not contain some categories (i.e., if your data only have 66+ year olds), we still want those categories in the table (just leave them blank) (the template is set up to account for this).

**Note:** Please rename your Excel workbooks to include your site initials after the name to facilitate identification.

* Utilization\_base-cohort (Table 2)
  + If a combination product (ATC A10BD) is prescribed, be sure to count as 1 prescription in each appropriate category of anti-diabetic medication.
    - A10BD01, A10BD02: metformin and sulfonylurea
    - A10BD03, A10BD05: metformin and thiazolidinedione
    - A10BD04, A10BD06: sulfonylurea and thiazolidinedione
    - A10BD07, A10BD08, A10BD10, A10BD11, A10BD13: metformin and DPP-4
    - A10BD09, A10BD12: thiazolidinedione and DPP-4
    - A10BD14, A10BD15: metformin and other
  + Use all anti-diabetic prescriptions from the base cohort entry date (first non-insulin anti-diabetic prescription date) until the earliest of:
    - Date of death (from any cause)
    - Date of emigration from your province
    - Date of first loss of continuous health plan or drug plan enrolment (or date no longer registered in the general practice for CPRD)
    - Entry into a long-term care facility
    - End of the study period (June 30, 2014, or the last date of data availability at each site)
  + Total number of patients: a patient is counted once in every quarter that they are in for at least 1 day between the base cohort entry date (first non-insulin anti-diabetic prescription date) and end of follow-up date (defined above)
  + Total number of person-days: Person-days will be the person-time contributed by all individuals present at some point in each quarter. This will include patients already present at the beginning of the quarter, as well as patients entering at some point during the quarter. The person-time contribution of each patient will be limited to the time they spent in each quarter (which can range from 1 to 90 days).
  + If you choose, a program template (incretins\_template\_table2.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names).
* Incretin\_distrib\_base-cohort **(Table 4)**

Number of patients prescribed incretin-based drugs **(Table 4)**

* + If you choose, a program template (incretins\_template\_table3.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names).
* Utilization base cohort 1987 worksheet in Excel Workbook **CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx**

**(Table 3)**

# Study cohort for acute pancreatitis

1. **Study cohort assembly**

Using the base-cohort defined above, we will identify a study cohort of all patients who initiated a new anti-diabetic drug class after incretin-based drugs entered the market in each respective CNODES site up until June 30, 2014 or the last availability of data at your site.

The following **sequential** exclusions will be performed:

1. Exclude from the base-cohort all patients who died or left the cohort before the year (starting January 1st) the first incretin-based drug entered the market in your jurisdiction
2. Exclude patients who never added-on, switched to, or initiated a new anti-diabetic drug class (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogs, alpha-glucosidase inhibitors, meglitinides, insulin) after incretin-based drugs entered the market in your jurisdiction up until June 30, 2014 (or the latest available date at your site)
3. **Study cohort entry** will be defined by the date of dispensation (or prescription date in the CPRD) for the new anti-diabetic drug class (i.e., the first anti-diabetic drug class to which the patient was initiated, switched to or added on to their existing anti-diabetic therapy after incretin-based drugs entered the market)

**Note:** Please be sure that this is a new anti-diabetic drug class that was never prescribed to the patient before incretin-based drugs entered the market in your jurisdiction. It is not just one that is different from the first-ever non-insulin prescription (the base cohort entry drug).

**Example 1:** Suppose a patient entered the base-cohort with metformin, and then later added on a sulfonylurea. Study cohort entry date would be the date of the prescription for the sulfonylurea, only if that sulfonylurea was prescribed for the first time after when incretin-based drugs entered the market.

**Metformin** 🡪 **Sulfonylurea**

Base-cohort entry Study cohort entry

Jan 2000 Feb 2007

**Example 2:** It is possible for patients to add-on or switch to a number of anti-diabetic drugs between base-cohort entry and the year the first incretin-based drug entered the market in your jurisdiction. Once again, study cohort entry will be date of the anti-diabetic drug class prescribed for the first time after when incretin-based drugs entered the market.

**Metformin + sulfonylurea** 🡪 **Thiazolidinedione** 🡪 **DPP-4 inhibitor**

Base-cohort entry Switch Study cohort entry

Apr 1995 Mar 2001 Jun 2008

**Example 3:** It is possible for patients to enter the base cohort and study cohort simultaneously if the first non-insulin anti-diabetic drug occurs during or after the year the first incretin-based drug entered the market in your jurisdiction.

**Metformin** 🡪 **Metformin**

Base-cohort entry Study cohort entry

Apr 2009 Apr 2009

1. Exclude patients with a previous diagnosis of pancreatic cancer (ICD 9 code 157.0-157.9; ICD 10 code C25.x), those who underwent pancreatectomy (ICD 9 procedure codes 52.5x-52.7x; for CCI and CCP codes, please see file “Pancreatectomy CCP & CII codes (August 11, 2014).xlsx in Dropbox), congenital defects of the pancreas (ICD 9 code 751.7; ICD 10 codes Q45.0-Q45.3), cystic fibrosis (ICD 9 code 277.x; ICD 10 code E84.x), lupus (ICD 9 code 695.4; ICD 10 code M32), or previous bariatric surgery (ICD 9 procedure codes 43.3x, 43.8, 44.68, 44.95, V45.86**\***; ICD 10 code Z98.84; CCI code 1.NF.78.xx; CCP code 56.93), all measured at any time prior and including the date of study cohort entry

**Note:** The ICD-9 code V45.86 should only be used for exclusion by sites with at least 4 digits.

1. Exclude patients with HIV (ICD 9 code 042; ICD 10 code B20.x-B24.x) or prescriptions for HAART (ATC codes J05AE03, J05AF01, J05AF04, J05AF05, J05AF06, J05AF07, J05AF09, J05AG01, J05AG03, J05AG05, J05AR01-J05AR11, J05AX11) ever before and including the date of study cohort entry. See HAART medication DIN list (excel file: incretin\_DIN\_list.xlsx).
2. Exclude patients hospitalized for acute pancreatitis (ICD-9 code: 577.0; ICD-10 codes: K85.0, K85.1, K85.2, K85.3, K85.8, and K85.9 in the primary [or most responsible] or secondary position, including post-admission diagnoses)\* in the 30 days immediately before and including the date of study cohort entry

\* Hospital Abstracts User’s Manual (HAUM) Diagnosis Types to include are:

‘M’ (most responsible)

‘P’ (primary)

‘C’ (condition arising in hospital)

‘A’ (admitting)

‘U’ – ‘Z’ (service transfer diagnosis code type)

\* Discharge Abstract Database (DAD) Diagnosis Types to include are:

‘M’ (most responsible)

‘2’ (post-admit comorbidity)

‘5’ (admitting)

‘W’ – ‘Y’ (service transfer diagnosis code type)

**Complete the Flowchart 2 for acute pancreatitis located in the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx”**

1. **End of follow-up**

Follow-up will be from study cohort entry until the earliest of the following events:

1. A hospitalization for acute pancreatitis during follow-up (ICD-9 code: 577.0; ICD-10 codes: K85.0, K85.1, K85.2, K85.3, K85.8, and K85.9 in the primary [or most responsible] or secondary position, including post-admission diagnoses)\*.

\* Hospital Abstracts User’s Manual (HAUM) Diagnosis Types to include are:

‘M’ (most responsible)

‘P’ (primary)

‘C’ (condition arising in hospital)

‘A’ (admitting)

‘U’ – ‘Z’ (service transfer diagnosis code type)

\* Discharge Abstract Database (DAD) Diagnosis Types to include are:

‘M’ (most responsible)

‘2’ (post-admit comorbidity)

‘5’ (admitting)

‘W’ – ‘Y’ (service transfer diagnosis code type)

1. Date of death (from any cause)
2. Date of emigration from your province
3. Date of first loss of continuous health plan or drug plan enrolment (or date no longer registered in the general practice for CPRD or HES linkable)
4. Entry into a long-term care facility
5. End of the study period (June 30, 2014, or the last date of data availability at each site)
6. Date of a new diagnosis of HIV (ICD 9 code 042; ICD 10 code B20.x-B24.x)
7. Date of a new prescription for HAART (ATC codes J05AE03, J05AF01, J05AF04, J05AF05, J05AF06, J05AF07, J05AF09, J05AG01, J05AG03, J05AG05, J05AR01-J05AR11, J05AX11)

**Note:** The minimum duration of follow-up for all patients is 1 day. Consequently, when calculating follow-up time for the acute pancreatitis analysis, use ((Cohort exit date) – (Cohort entry date) + 1).

1. **Rate of the outcome in study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* Acute pancreatitis rate **(Tables 5 and 6)**
  + If you choose, a program template (incretins\_template\_tables4\_and\_5.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names).

# Baseline covariates for acute pancreatitis

1. **Table of the baseline covariates**

**Note:** Please use all data sources at your disposal to define the covariates below; these include physician and hospitalization data sources.

**Note:** ICD-9 codes **bolded** with an **\*** should only be used with data that include at least 4 digits. If physician billing is only available up to 3 digits, please restrict the covariate definition to hospitalization data (that contain at least 4 digits) for these codes. Three digit data can be used for the other components of such definitions.

| **Covariate** | **ICD-9 code** | **ICD-10 code** | **ATC code** | **Variable coding** | **Comment** |
| --- | --- | --- | --- | --- | --- |
| Age | - | - | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 18-25  2: 26-35  3: 36-45  4: 46-55  5: 56-65  6: 66-75  7: 76+ | Measured at study cohort entry |
| Calendar year | - | - | - | 2006…  2014 | Measured at study cohort entry |
| Duration of treated diabetes (years) | - | - | A10 | Continuous | (Date of cohort entry –date of first non-insulin prescription)/365.25 days |
| Sex | - | - | - | 1: M  0: F | - |
| Body mass index (kg/m2) | - | - | - | 1: <25  2: 25-29  3: ≥30  9: Missing | Last measure before study cohort entry (where available) |
| Hemoglobin A1c (%) | - | - | - | 1: ≤7  2: 8  3: >8  9: Missing | Last measure before study cohort entry (where available) |
| Excessive alcohol use | 291.x  303x  **571.0-571.3\*** **535.3\*** | F10x  K70x K29.2 G31.2 G62.1 G72.1 I42.6 E24.4 K85.2 K86.0 Z50.2 Z71.4 | - | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Smoking status | - | - | - | 1: Yes  0: No  9: Missing | Last measure before study cohort entry (where available) |
| Statins | - | - | C10AA, C10BA, C10BX | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Fibrates | - | - | C10AB, C10BA03  C10BA04 | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| ACE inhibitors | - | - | C09A  C09B | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Loop or thiazide diuretics | - | - | C03CA01-CO0CA04  C03CC01  C03CX01  C03CD01  C03AA01-CO3AA09  C03AA13  C03AB01-C03AB09  C03AH01  C03AH02  C03AX01 | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Oral Contraceptives  /Hormone Replacement Therapy | - | - | G03AA01-G03AA16  G03AB01- G03AB08  G03CA01  G03CA03  G03CA04  G03CA06  G03CA07  G03CA09  G03CA53  G03CA57 | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Vaproic acid | - | - | N03AG01 | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Gallstones | 574.x  **575.0\***  **575.1\*** | K80  K81 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Cancer  (other than non-melanoma skin cancer) | 140-172 174-209 | C00-C43 C45-C97 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Acute or chronic pancreatitis | **577.0\***  **577.1\*** | K85.0 K85.1 K85.2 K85.3 K85.8 K85.9  K86.0  K86.1 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Neuropathy | **357.2\*** | E11.4x  E13.4x  E14.4x  G59.0  G63.2 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Renal disease | 403.x  404.x  585.x  586.x  588.x  **250.4\*** | E11.2  E13.2  E14.2  I12.x  I13.x  N08.x  N18.x  N19.X | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Retinal disorders | 362.x | E11.3x  H36.0 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Peripheral arterial or vascular disease | **440.2\***  **440.8\***  **440.9\***  **557.1\***  **443.9\***  **444.2\*** | I70.0  I70.2  I70.8  I70.9  I73.1  I73.8  I73.9  K55.1 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Number of hospitalization episodes of care | - | -  - | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before the date of study cohort entry |
| Number of unique non-anti-diabetic medications | - | - | Not A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before and excluding the date of study cohort entry; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |
| Pre-study cohort entry anti-diabetic medications | - | - | A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | From date of first non-insulin prescription to study cohort entry (excluding study cohort entry date) ; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |

1. **Description of the study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* Description acute pancreatitis **(Table 7)**
  + If you choose, a program template (incretins\_template\_table6.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names). If your site does not contain some categories (i.e. if your data only have 66+ year olds or do not have the BMI, hemoglobin, and smoking status variables), we still want those categories in the table (just leave them blank) (the template is set up to account for this).

# Study cohort for pancreatic cancer

1. **Study cohort assembly**

Using the base-cohort defined above, we will identify a study cohort of all patients who initiated a new anti-diabetic after incretin-based drugs entered the market in each respective CNODES site up until June 30, 2014, or the latest date of availability at your site. The following **sequential** exclusions will be performed:

1. Exclude from the base-cohort all patients who died or left the cohort before the year (January 1st) the first incretin-based drug entered the market in your jurisdiction
2. Exclude patients who never added-on, switched to, or initiated a new anti-diabetic drug (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogs, alpha-glucosidase inhibitors, meglitinides, insulin) after incretin-based drugs entered the market in each respective CNODES site up until June 30, 2014, or the latest date of data availability at your site
3. **Study cohort entry** will be defined by the date of dispensation (or prescription date in the CPRD) for the new anti-diabetic drug (i.e., the first anti-diabetic drug to which the patient switched to or added on to their existing anti-diabetic therapy after incretins entered the market)
4. Exclude patients with a previous diagnosis of any cancer (excluding non-melanoma skin cancer) (ICD 9 codes 140-172, 174-209; ICD 10 codes C00-C43, C45-C97), those who underwent pancreatectomy (ICD 9 procedure codes 52.5x-52.7x; for CCI and CCP codes, please see file “Pancreatectomy CCP & CII codes (August 11, 2014).xlsx in Dropbox), and congenital defects of the pancreas (ICD 9 code 751.7; ICD 10 codes Q45.0-Q45.3), all measured at any time prior to and including the date of study cohort entry
5. Exclude patients with less than 365 days of follow-up after study cohort entry (including study cohort entry date). Thus, patients with any of the 6 follow-up terminating criteria (events or censoring criteria) described below will be excluded if these occur within the first 365 days after study cohort entry.

**Complete Flowchart 3 for pancreatic cancer in the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx.**

Complete **“Patients Excluded”** Excel sheet in **“CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx”** based on exclusions in step 5 above**. (Table 8)**

1. **End of follow-up**

Follow-up will be from study cohort entry + 365 days until the earliest of the following:

1. An inpatient diagnosis of pancreatic cancer (defined below in section iii. Pancreatic cancer event definition])
2. Date of death (from any cause)
3. Date of emigration from your province
4. Date of first loss of continuous health plan or drug plan enrolment (or date no longer registered in the general practice for CPRD)
5. Entry into a long-term care facility
6. End of the study period (June 30, 2014, or the last date of data availability at your site)

**Note:** For pancreatic cancer, follow-up time starts at cohort entry date + 365 days. When calculating follow-up time, please use: ((Cohort exit date) – (Cohort entry date + 365) + 1).

**iii. Pancreatic cancer event definition**

Cases of pancreatic cancer on the basis of a first-ever inpatient diagnosis of pancreatic cancer (recorded in hospital databases [any type of code]: ICD-9 codes: 157.0-157.9; ICD-10 codes: C25.x) during follow-up.

**Note:** To be considered an event, the inpatient diagnosis of pancreatic cancer will need to be recorded within a hospitalization lasting at least 1 day (i.e. date of discharge – date of admission ≠ 0). If that criterion is not satisfied, this inpatient diagnosis of pancreatic cancer will not count as an event, and patient follow-up will continue until this event definition is satisfied or until one of the censoring events (whichever occurs first).

**iv. Rate of the outcome in study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* Pancreatic cancer rate **(Tables 9 and 10)**
  + If you choose, a program template (incretins\_template\_tables7\_and\_8.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names).

# Baseline covariates for pancreatic cancer

1. **Table of the baseline covariates**

**Note:** Please use all data sources at your disposal to define the covariates below; these include physician and hospitalization data sources.

**Note:** ICD-9 codes **bolded** with an **\*** should only be used with data that includes at least 4 digits. If physician billing is only available up to 3 digits, please restrict the covariate definition to hospitalization data (that contain at least 4 digits) for these codes. Three digit data can be used for the other components of such definitions.

| **Covariate** | **ICD-9 code** | **ICD-10 code** | **ATC code** | **Variable coding** | **Comment** |
| --- | --- | --- | --- | --- | --- |
| Age | - | - | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 18-25  2: 26-35  3: 36-45  4: 46-55  5: 56-65  6: 66-75  7: 76+ | Measured at study cohort entry |
| Calendar year | - | - | - | 2006…  2014 | Measured at study cohort entry |
| Duration of treated diabetes (years) | - | - | A10 | Continuous | (Date of cohort entry – date of first non-insulin prescription)/365.25 days |
| Sex | - | - | - | 1: M  0: F |  |
| Body mass index (kg/m2) | - | - | - | 1: <25  2: 25-29  3: ≥30  9: Missing | Last measure before study cohort entry (where available) |
| Hemoglobin A1c (%) | - | - | - | 1: ≤7  2: 8  3: >8  9: Missing | Last measure before study cohort entry (where available) |
| Excessive alcohol use | 291.x  303x  **571.0-571.3\*** **535.3\*** | F10x K70x K29.2 G31.2 G62.1 G72.1 I42.6 E24.4 K85.2 K86.0 Z50.2 Z71.4 | - | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Smoking status | - | - | - | 1: Yes  0: No  9: Missing | Last measure before study cohort entry (where available) |
| Acute or chronic pancreatitis | **577.0\***  **577.1\*** | K85.0 K85.1 K85.2 K85.3 K85.8 K85.9 K86.0 K86.1 | - | 1: Yes  0: No | Measured ever before and including study cohort entry date |
| Statins | - | - | C10AA C10BA C10BX | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Neuropathy | **357.2\*** | E11.4x  E13.4x  E14.4x  G59.0  G63.2 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Renal disease | 403.x  404.x  585.x  586.x  588.x  **250.4\*** | E11.2  E13.2  E14.2  I12.x  I13.x  N08.x  N18.x  N19.X | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Retinal disorders | 362.x | E11.3x  H36.0 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Peripheral arterial or vascular disease | **440.2\***  **440.8\***  **440.9\***  **557.1\***  **443.9\***  **444.2\*** | I70.0  I70.2  I70.8  I70.9  I73.1  I73.8  I73.9  K55.1 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Number of hospitalization episodes of care | - | -- | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before but excluding the date of study cohort entry |
| Number of unique non-anti-diabetic medications | - | - | Not A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before but excluding the date of study cohort entry; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |
| Pre-study cohort entry anti-diabetic medications | - | - | A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | From date of first non-insulin prescription to study cohort entry (but excluding study cohort entry date) ; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |

1. **Description of the study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* Description pancreatic cancer **(Table 11)**
  + If you choose, a program template (incretins\_template\_table9.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names). If your site does not contain some categories (i.e. if your data only have 66+ year olds or do not have the BMI, hemoglobin, and smoking status variables), we still want those categories in the table (just leave them blank) (the template is set up to account for this).

# Study cohort for congestive heart failure

1. **Study cohort assembly**

Using the base-cohort defined above, we will identify a study cohort of all patients who initiated a new anti-diabetic after incretin-based drugs entered the market in each respective CNODES site up until June 30, 2014 or the last date of data availability at your site.

The following **sequential** exclusions will be performed:

1. Exclude from the base-cohort all patients who died or left the cohort before the year the first incretin-based drug entered the market in your jurisdiction
2. Exclude patients who never added-on, switched to, or initiated a new anti-diabetic drug (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogs, alpha-glucosidase inhibitors, meglitinides, insulin) after incretin-based drugs entered the market in each respective CNODES site up until June 30, 2014 or the last date of data availability at your site
3. **Study cohort entry** will be defined by the date of dispensation (or prescription date in the CPRD) for the new anti-diabetic drug (i.e., the first anti-diabetic drug to which the patient switched to or added on to their existing anti-diabetic therapy after incretins entered the market)
4. Exclude patients with HIV (ICD 9 code 042; ICD 10 code B20.x-B24.x) or prescriptions for HAART (ATC codes J05AE03, J05AF01, J05AF04, J05AF05, J05AF06, J05AF07, J05AF09, J05AG01, J05AG03, J05AG05, J05AR01-J05AR11, J05AX11) ever before and including the date of study cohort entry. See HAART medication DIN list (excel file: incretin\_DIN\_list.xlsx).

Using the above study cohort, we will create two separate cohorts defined by the presence or absence of a previous history of CHF (ICD-9 code: 428.x; ICD-10 code: I50.x) at any time prior and including the date of study cohort entry.

**Complete the study cohort flowchart for congestive heart failure in the Excel workbook entitled “CNODES Incretins Flowchart and Tables”.**

1. **End of follow-up**

Follow-up will be from study cohort entry until the earliest of the following events:

1. Study outcome
   1. Cohort of patients with no history of CHF: A hospitalization for incident CHF, defined by a diagnostic code for CHF (ICD-9 code: 428.x; ICD-10 code: I50.x) appearing in any position in the hospitalization discharge abstract or hospitalization record during follow-up
   2. Cohort of patients with a previous history of CHF: A hospitalization for incident CHF, defined by a diagnostic code for CHF (ICD-9 code: 428.x; ICD-10 code: I50.x) appearing in the primary or most responsible position only\* in the hospitalization discharge abstract or hospitalization record during follow-up

\* Hospital Abstracts User’s Manual (HAUM) Diagnosis Types to include are:

‘M’ (most responsible)

\* Discharge Abstract Database (DAD) Diagnosis Types to include are:

‘M’ (most responsible)

1. Date of a new diagnosis of HIV (ICD 9 code 042; ICD 10 code B20.x-B24.x)
2. Date of a new prescription for HAART (ATC codes J05AE03, J05AF01, J05AF04, J05AF05, J05AF06, J05AF07, J05AF09, J05AG01, J05AG03, J05AG05, J05AR01-J05AR11, J05AX11)
3. Date of death (from any cause)
4. Date of emigration from your province
5. Date of first loss of continuous health plan or drug plan enrolment (or date no longer registered in the general practice for CPRD or HES linkable)
6. Entry into a long-term care facility
7. End of the study period (June 30, 2014, or the last date of data availability at your site)

**Note:** The minimum duration of follow-up for all patients is 1 day. Consequently, when calculating follow-up time for the CHF analyses, use ((Cohort exit date) – (Cohort entry date) + 1).

1. **Rate of the outcome in study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* CHF rate) **(Tables 12, 13, 14, and 15)**

* + If you choose, a program template (incretins\_template\_tables 10\_11\_12\_and\_13.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names).

# Baseline covariates for CHF

1. **Table of the baseline covariates**

**Note:** Please use all data sources at your disposal to define the covariates below; these include physician and hospitalization data sources.

**Note:** ICD-9 codes **bolded** with an **\*** should only be used with data that includes at least 4 digits. If physician billing is only available up to 3 digits, please restrict the covariate definition to hospitalization data (that contain at least 4 digits) for these codes. Three digit data can be used for the other components of such definitions.

| **Covariate** | **ICD-9 code** | **ICD-10 code** | **ICD-9 procedure code** | **CCI code** | **CCP code** | **ATC code** | **Variable**  **coding** | **Comment** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Age | - | - | - | - | - | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 18-25  2: 26-35  3: 36-45  4: 46-55  5: 56-65  6: 66-75  7: 76+ | Measured at study cohort entry |
| Calendar year | - | - | - | - | - | - | 2006…  2014 | Measured at study cohort entry |
| Duration of treated diabetes (years) | - | - | - | - | - | A10 | Continuous | (Date of cohort entry – date of first non-insulin prescription)/365.25 days |
| Sex | - | - | - | - | - | - | 1: M  0: F | - |
| Body mass index (kg/m2) | - | - | - | - | - | - | 1: <25  2: 25-29  3: ≥30  9: Missing | Last measure before study cohort entry (where available) |
| Hemoglobin A1c (%) | - | - | - | - | - | - | 1: ≤7  2: 8  3: >8  9: Missing | Last measure before study cohort entry (where available) |
| Excessive alcohol use | 291.x  303x  **571.0-571.3\*** **535.3\*** | F10x  K70x  K29.2  G31.2  G62.1  G72.1  I42.6  E24.4  K85.2  K86.0  Z50.2  Z71.4 | - | - | - | - | 1: Yes  0: No | Measured in the year before and including study cohort entry date |
| Smoking status | - | - | - | - | - | - | 1: Yes  0: No  9: Missing | Last measure before study cohort entry (where available) |
| Atrial fibrillation or flutter | **427.3x\*** | I48.x | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Cancer  (other than non-melanoma skin cancer) | 140-172 174-209 | C00-C43  C45-C97 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| COPD | 490.x  491.x  492.x  496.x | J40.x-J44.x | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Coronary artery disease | 410.x-414.x | I20-I25 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Dyslipidemia | 272.x | E78.x | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Hypertension | 401.x-405.x | I10.x-I15.x | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Neuropathy | **357.2\*** | E11.4x  E13.4x  E14.4x  G59.0  G63.2 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Renal disease | 403.x  404.x  585.x  586.x  588.x  **250.4\*** | E11.2  E13.2  E14.2  I12.x  I13.x  N08.x  N18.x  N19.X | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Retinal disorders | 362.x | E11.3x  H36.0 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Peripheral arterial or vascular disease | **440.2\***  **440.8\***  **440.9\***  **557.1\***  **443.9\***  **444.2\*** | I70.0  I70.2  I70.8  I70.9  I73.1  I73.8  I73.9  K55.1 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Previous coronary revascularization | - | - | 00.66  36.01  36.02  36.05  36.06  36.07  36.1x | 1IJ57LA.x 1IJ57VS.x 1IJ76.x 1IJ50.x 1IJ57G.x | 48.02 48.03  48.1  48.11 48.12 48.13 48.14 48.15 48.16 48.17 48.19 | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Previous myocardial infarction | 410.x  412.x | I21.x  I25.2 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| Previous stroke | 431  433.x  434.x  436 | I63.x  I65.x  I66.3  I61.x  I64 | - | - | - | - | 1: Yes  0: No | Measured ever before and including the date of study cohort entry |
| ACE inhibitors | - | - | - | - | - | C09A C09B | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| ARBs | - | - | - | - | - | C09C  C09D C09X | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| Beta-blockers | - | - | - | - | - | C07 | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| Calcium-channel blockers | - | - | - | - | - | C08 | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| Diuretics | - | - | - | - | - | C03 | 1: Yes  0: No | Measured in the year before study cohort entry |
| Statins | - | - | - | - | - | C10AA C10BA C10BX | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| Aspirin | - | - | - | - | - | A01AD05 B01AC06 N02BA01 N02BA01 N02BA01 M01BA03 B01AC56 N02BA51 N02BA71 C10BX02  C10BX05 C10BX01 C10BX04 | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| NSAIDs | - | - | - | - | - | M01A | 1: Yes  0: No | Measured in the year before and including the study cohort entry date |
| Number of hospitalization episodes of care | - | - | - | - | - | - | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before but excluding the date of study cohort entry |
| Number of unique non-anti-diabetic medications | - | - | - | - | - | Not A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | Measured in the year before but excluding the date of study cohort entry; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |
| Pre-study cohort entry anti-diabetic medications | - | - | - | - | - | A10 | Variable 1: Continuous  Variable 2:  Categorical:  1: 0  2: 1  3: 2  4: 3  5: 4+ | From date of first non-insulin prescription to study cohort entry (but excluding study cohort entry date) ; categorized by generic chemical name (combination pills contain 2 or more compounds, and each should be counted separately) |

1. **Description of the study cohort**

**Please enter information in the following worksheet of the Excel workbook entitled “CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx:**

* Description CHF **(Table 16)**
  + If you choose, a program template (incretins\_template\_table14.sas) has been provided in the Dropbox folder which will create this table. The program contains documentation at the top which explains the variables needed (you may either rename your variables to match this code, or modify the variable names with the program to match your variable names). If your site does not contain some categories (i.e. if your data only have 66+ year olds or do not have the BMI, hemoglobin, and smoking status variables), we still want those categories in the table (just leave them blank) (the template is set up to account for this).

# APPENDIX I: Site-specific protocol deviations

**Along with your Flow chart and Tables, please upload your site-specific protocol deviations as a separate word document to Dropbox.**

**Note:** A form for entering protocol deviations will be available in the Dropbox at a later date.

# APPENDIX II: Amendments

**Note:** Amendments in the analytical protocol are indicated in **blue** font.

**Version 1.3**

1. Rather than applying the HIV exclusion at the level of the base-cohort, it will be applied at study cohort entry for acute pancreatitis and CHF. In addition, it will be a new censoring criterion for these two study cohorts.
2. Examples for study cohort entry are provided.

**Version 1.4**

1. The end date for patient accrual will now be the last date of data availability. This date will also be used as a censoring criterion for end of follow-up. The earliest and latest date of data availability should now be entered in the new designated area in the ‘**Base-cohort flowchart**’ in the Excel worksheet located in Dropbox.
2. It is now clarified that patients entering the study cohorts are those who added-on, switched to, or initiated (i.e. newly-treated patients) an anti-diabetic drug class not previously used.
3. Cancer exclusion and covariate definitions should include the ICD-10 code C97.x as part of the range of diagnostic codes. C43 should also be included, but C44 should not. Thus, the correct ICD-10 code range is C00.x-C43.x, C45.x-C97.x.
4. ICD-10 codes used for the HIV exclusion and censoring for acute pancreatitis and CHF study cohorts should include B20.x-B24.x.
5. The ‘diagnosis types’ to use when defining acute pancreatitis and CHF have been clarified and now include:

Hospital Abstracts User’s Manual (HAUM) Diagnosis Types to include are:

‘M’ (most responsible)

‘P’ (primary)

‘C’ (condition arising in hospital)

‘A’ (admitting)

‘U’ – ‘Z’ (service transfer diagnosis code type)

\* Discharge Abstract Database (DAD) Diagnosis Types to include are:

‘M’ (most responsible)

‘2’ (post-admit comorbidity)

‘5’ (admitting)

‘W’ – ‘Y’ (service transfer diagnosis code type)

1. The ‘**Description base-cohort’** Excel worksheet now includes a new ‘Other anti-diabetic drugs monotherapy’ category. This new category is to account for additional drug classes, such as SGLT-2 inhibitors, which may be available at some sites. In addition, the labeling of the other categories has been revised to reflect that they are monotherapy. Please use the Excel workbook named, **“CNODES Incretins Flowchart and Tables (September 11, 2014).xlsx”** as it also includes small formatting changes.
2. Study flowcharts in the Excel workbook have been modified to include the number of patients excluded and remaining at each step. See **“CNODES Incretins Flowchart and Tables (September 11, 2014).xlsx”**.

**Version 1.5**

1. The Excel workbook has been modified and is now named. **“CNODES Incretins Flowchart and Tables (September 11, 2014).xlsx”** Modifications include:
   1. Removing drop down menus for dates and years.
   2. Ensuring that all sites are listed in the drop down menu for sites.
   3. In the drug utilization table, relabeling the unit for the total amount of follow-up time, which is now in person-days rather than person-years to match the provided SAS code.
   4. Changes have been made to the medication variables in all 3 tables describing the study cohorts, and inconsistencies between the protocol and Excel sheets regarding for these variables have been fixed.
      1. The variable “number of unique medications, mean (SD)” has been removed from Excel.
      2. The variable “number of unique non-anti-diabetic medications, mean (SD)” has been added to Excel.
      3. The variable “anti-diabetic medications” has been removed from the protocol.
      4. The variable “number of unique anti-diabetic medications, mean (SD)” has been renamed as “Pre-study cohort entry anti-diabetic medications, mean (SD)” in both Excel and the protocol.

The descriptions of these covariates found in the protocol have been modified accordingly.

* 1. In all 3 tables describing the study cohorts, an “Other” category was added for study cohort entry drugs.  The other anti-diabetic drugs monotherapy category was put in to capture any sites which might have prescriptions for additional drug classes (like SGLT-2 inhibitors).
  2. In the CHF rate, “Incidence rate of acute pancreatitis (per 1000 person-years)” now reads “Incidence rate of CHF hospitalization (per 1000 person-years)”. Both occurrences of this error have been corrected.
  3. In the table Description CHF, “Peripheral Vascular Disease” has been combined with “Peripheral arteriopathy” to create “Peripheral arterial or vascular disease”.  This labeling has also been revised for pancreatitis and pancreatic cancer.
  4. Cells that do not require data to be entered have been locked.

1. Please rename your Excel workbooks to include your site initials after the name to facilitate identification (e.g., Incretins Flowcharts and Tables\_ON.xlsx)
2. The minimum duration of follow-up for all patients is 1 day. Consequently, when calculating follow-up time for the acute pancreatitis and CHF analyses, please use: ((Cohort exit date) – (Cohort entry date) + 1).
3. For pancreatic cancer, follow-up time starts at cohort entry date + 365 days. When calculating follow-up time for the pancreatic cancer analyses, please use: ((Cohort exit date) – (Cohort entry date + 365) + 1).

**Version 1.6**

1. The pancreatic cancer definition has been updated. Events are now defined by hospitalization data only (see section VII.iii).
2. Two additional worksheets have been added to the Excel workbook in Dropbox (“**CNODES Incretins Flowchart and Tables (November 5, 2014).xlsx”**:
   1. Utilization base cohort 1987: please provide drug utilization information over a longer period of time
   2. Excluded patients: please report the number of pancreatic cancer events excluded in the year between study cohort entry and the start of follow-up.

Protocol sections IV.ii and VII.i have been updated accordingly.

1. Table numbers in the protocol and corresponding Excel workbook have been updated.

# APPENDIX III: Questions & Answers

**Q1. We do not have A10BC in the non-insulin DIN. Can you confirm?**

A1. That is correct. There are no A10BC products on Health Canada’s DPD. WHO lists glymidine as the only A10BC drug, which is not available in Canada. It is included in the list as two non-Canadian databases are being used.

**Q2. If one person enters the base cohort on day1 with drug class A and B, on day2 (which is after incretin-based drug enter the market), he had drug A, C, and D, then C and D will be considered as new add-on drugs and are counted in Table 6 (the study cohort entry drugs), in both C and D class. Is this correct?**

A2. That is correct. The first prescription date for new anti-diabetic drug class(es) (metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitors, GLP-1 analogs, alpha-glucosidase inhibitor, meglitinides, insulin) that occurs after the beginning of the year incretin-based products came to market are to be counted. So if they had more than one new class on that same prescription date then they will be counted in both class categories. Table 6 study cohort entry drug classes are not mutually exclusive. Importantly, Drug A in this example is not considered a study cohort entry drug as it was prescribed prior to cohort entry.

**Version 1.5**

**Q3. In Table 1, Baseline Characteristics of base cohort patients: According to the protocol, we are excluding patients with an insulin prescription ever before the first non-insulin prescription. Thus, we are having “0” patients in this category. Is this correct?**

A3. Yes, you should be getting "0" patients in the insulin monotherapy category for base-cohort entry drugs.

**Q4. In Table 1, Baseline Characteristics of base cohort patients: Would you please clarify what is “Other anti-diabetic drugs monotherapy” referring to?**

A4. The other anti-diabetic drugs monotherapy category was put in for sites to capture any prescriptions for additional drug classes (like SGLT-2 inhibitors). You may very well not have prescriptions for any additional anti-diabetic drugs that are not already listed and so you will have "0" patients for this category.

**Q5. If you were to start on Metformin and TZD on the same day (after incretins were available in your jurisdiction) and then never used another different type of anti-diabetic, does that mean that you are excluded?**

A5. If the patient is receiving the TZD and metformin as their first ever prescription and have at least 365 days of continuous coverage before this prescription (i.e., they are new users), they are eligible to enter the base cohort. If this first ever prescription is occurring after incretins have entered the market, this combination therapy prescription can result in both base cohort and study cohort entry as the therapy is initiated after incretins are available. If they do not have 365 days of database history prior to this prescription, they should be excluded as they are likely prevalent users. Otherwise, they enter both the base- and study cohorts simultaneously.

**Q6. What happens if a patient exits the base cohort prior to the availability of incretins in your jurisdiction?**

A6. If a patient is no longer in the database when incretins are available (and thus has no opportunity for exposure), they are excluded from the study cohorts.

**Q7. Hospitalization rates for CHF would substantially higher than expected among those with a history of CHF. Any suggestions?**

A7. While those with a history of CHF are expected to have a higher rate of hospitalization, please ensure than only diagnostic codes listed as the Most Responsible Diagnosis are included in the event definition for this sub-cohort. The two CHF sub-cohorts utilize different event definitions.