# Risk of Acute Pancreatitis Following SGLT2 Inhibitor Use in Patients with Type 2 Diabetes Mellitus

## HARPER Study Protocol

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## 1. Abstract

Based on review of the FDA Adverse Events Reporting System (FAERS), the FDA identified acute pancreatitis as a potential safety issue associated with use of sodium-glucose cotransporter-2 inhibitors (SGLT2i). To add evidence regarding this important safety concern, we aim to conduct an observational cohort study in the FDA Sentinel Real World Evidence Data Enterprise (RWE-DE) commercial network which leverages data linkages between insurance claims and electronic health records (EHRs) for 23 million people. This investigation is designed using the "PRocess guide for INferential studies using healthcare data from routine ClinIcal Practice to evaLuate causal Effects of Drugs" (PRINCIPLED) framework, which is a standard process proposed by Sentinel to conduct causal inferential studies of medication outcomes. This protocol outlines the specification and emulation of the target trial to answer the study question of interest.

## 2. Amendments and Updates

| Version Date | Version Number | Section of Protocol | Amendment or Update | Reason |
|---|---|---|---|---|
| May 16, 2024 | 1.0 (original) | | | |
| September 19, 2024 | 2.0 | Data Analysis | Added sensitivity analyses | Limits data missingness in important clinical variables; enables the detection of bias in the primary analysis, assuming shared confounding structure |

## 3. Milestones

*Table 1. Milestones and Timeline.*

| Milestone | Timeline |
|---|---|
| Initial Protocol | May 16, 2024 |

## 4. Rationale and Background

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have become one of the most widely used second-line treatments for Type 2 diabetes mellitus (T2DM) in the last decade likely owing to their beneficial effects on cardiovascular endpoints.[1] Based on review of the FDA Adverse Events Reporting System (FAERS), the FDA identified acute pancreatitis as a potential safety issue associated with use of SGLT2i. Ischemia and increased viscosity of pancreatic fluid related to the diuretic effects of SGLT2i, and bile stasis and cholelithiasis because of SGLT2i mediated lipolysis were noted as potential mechanisms for elevated risk of acute pancreatitis in FDA review.

Existing evidence regarding the association between SGLT2i and acute pancreatitis is limited. In a meta-analysis of 19 randomized controlled trials, Tang et al.[2] did not find an increased risk of acute pancreatitis with SGLT2i. However, most of the included trials were small and had limited follow-up time, which resulted in only 26 total observed acute pancreatitis events across the 19 included trials. Two prior observational studies have also indicated no excess risk in acute pancreatitis with SGLT2i compared to other antidiabetic treatments; although both these studies relied on diagnosis codes to assess acute pancreatitis.[3,4]Diagnosis codes are known to have poor positive predicted value (PPV) for acute pancreatitis (55-66%),[5] which raises concerns regarding the validity of prior studies due to outcome misclassification.

To add evidence regarding this important safety concern, we will conduct an observational cohort study in the FDA Sentinel Real World Evidence Data Enterprise (RWE-DE) commercial network. To address limitations of the previous studies, we will use a validated computable phenotyping algorithm for assessing acute pancreatitis events that has PPV of >90%.[5]

## 5. Research Question and Objectives

We will leverage the "PRocess guide for INferential studies using healthcare data from routine ClinIcal Practice to evaLuate causal Effects of Drugs" (PRINCIPLED) framework[6] to conduct the proposed study. Briefly, this framework features a pragmatic five step process (Figure 1) that

covers the range of considerations, including 1) formulating a well-defined causal question via specification of the target trial protocol, 2) Describing the emulation of each component of the target trial protocol and identifying fit-for-purpose data, 3) Assessing expected precision and conducting diagnostic evaluations, 4) Developing a plan for robustness assessments including deterministic sensitivity analyses, quantitative bias analyses, and net bias evaluation, and 5) inferential analyses.

*Figure 1: PRINCIPLED Process Overview.*

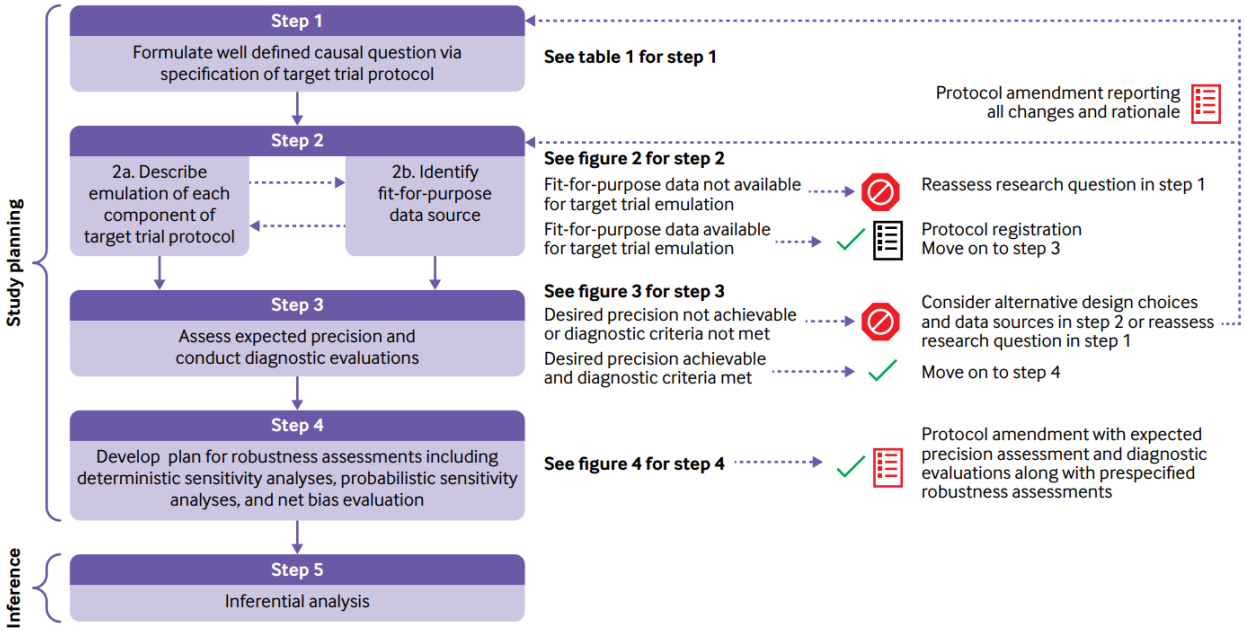



Table 2 summarizes the causal question being asked in the current study via specification of a target trial protocol (Step 1 of the process).

*Table 2. Step 1: Specification of the Target Trial Protocol.*

| Element | Specification of the hypothetical target trial | Emulation using real-world data sources |
|---|---|---|
| **Eligibility Criteria** | Patients with type 2 diabetes mellitus, no use of study medications before randomization, no history of end stage renal disease (ESRD), no history of HIV, no history of acute pancreatitis, no history of GLP-1 receptor agonist use<br><br>Continuous health plan enrollment and at least one recorded encounter in EHRs in 6 months prior to treatment initiation | Same as target trial |

| Element | Specification of the hypothetical target trial | Emulation using real-world data sources |
|---|---|---|
| **Treatment Strategies** | 1. Initiation SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin)<br>2. Initiation of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin) | Same as target trial |
| **Treatment Assignment** | Randomized non-blinded | Non-blinded and assumed to be randomized within levels of measured confounders* |
| **Follow-Up Start (Time 0)** | At assignment | Same as target trial |
| **Follow-Up End** | First of administrative end of follow-up (most recent data), loss to follow-up, death, or outcome occurrence | Same as target trial |
| **Primary Outcome** | Acute pancreatitis | Same as target trial |
| **Causal Contrast** | Intent to treat effect (effect of being assigned to the treatment)<br>Per protocol effect (effect of staying on the treatment) | Observational analogue of intent to treat effect<br>Observational analogue of per protocol effect |

# 6. Research Methods

Sections 6.1-6.5 correspond to Step 2a of the PRINCIPLED process, where we explicitly describe emulation of each component of the target trial protocol specified in Step 1.

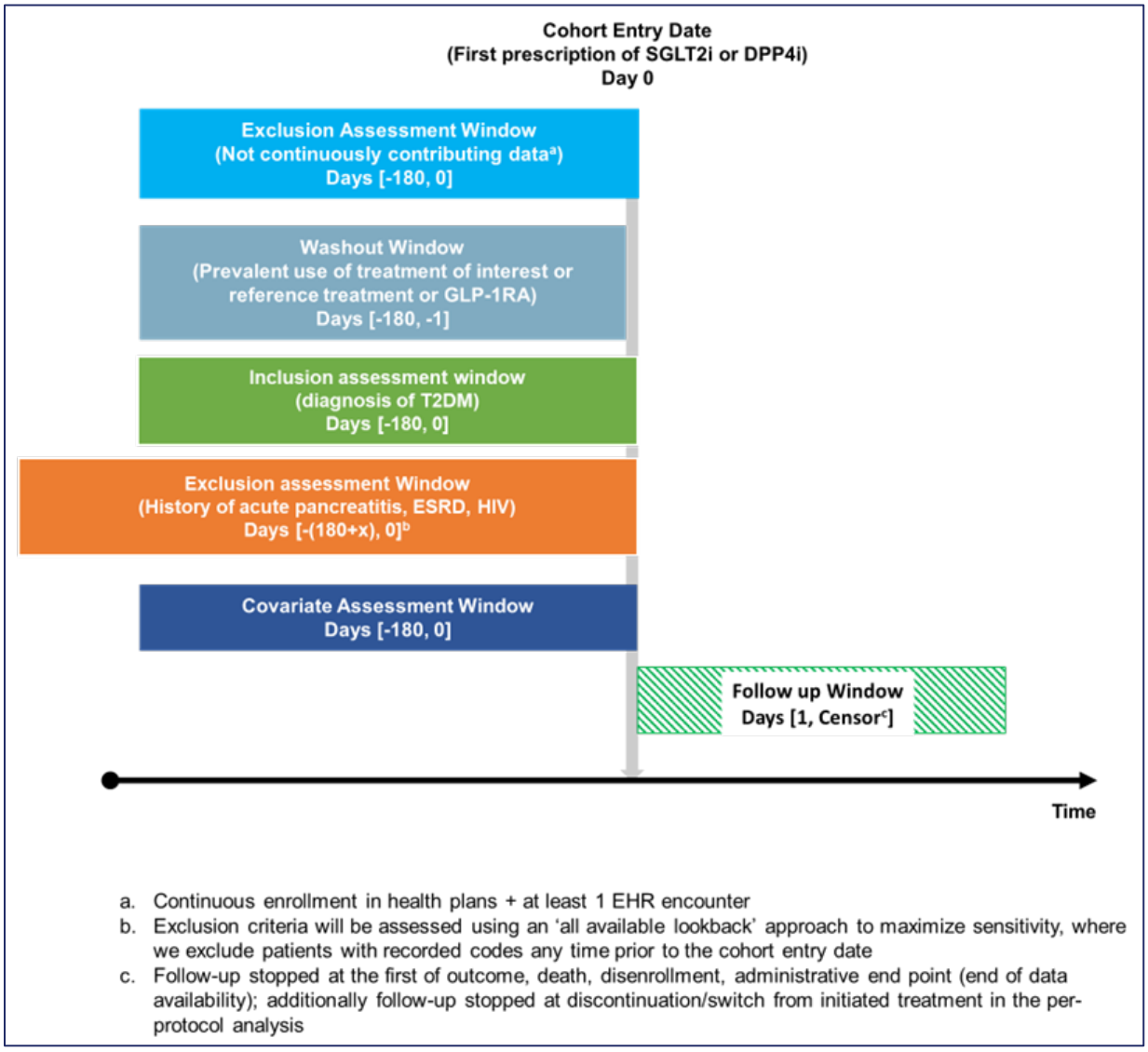
## 6.1. Study Design

**Research design:** New user active comparator cohort study.

**Rationale for study design choice:** This study design ensures homogenous patient population who are likely comparable and appropriate for evaluation of safety over the course of the treatment since initiation.

## 6.2. Study Design Diagram

*Figure 2. Visual Representation of Study Design.*




a. Continuous enrollment in health plans + at least 1 EHR encounter
b. Exclusion criteria will be assessed using an 'all available lookback' approach to maximize sensitivity, where we exclude patients with recorded codes any time prior to the cohort entry date
c. Follow-up stopped at the first of outcome, death, disenrollment, administrative end point (end of data availability); additionally follow-up stopped at discontinuation/switch from initiated treatment in the per-protocol analysis

## 6.3. Setting

### 6.3.1. Context and Rationale for Definition of Time 0 (and Other Primary Time Anchors) for Entry to the Study Population

Time 0 is the date of initiation of SGLT2 inhibitors or DPP-4 inhibitors and the time when patients enter the study population.

*Table 3. Operational Definition of Time 0 (Cohort Entry Date) and Other Primary Time Anchors.*

| Study Population Name(s) | Time Anchor Description (e.g., time 0) | Number of Entries | Type of Entry | Washout Window | Care Setting[1] | Code Type[2] | Diagnosis Position | Incident with Respect to... | Measurement Characteristics/ Validation | Source of Algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure:<br><br>SGLT2 inhibitors | Date of incident dispensation for SGLT2 inhibitors | Single | Incident | [-180, -1] | N/A | NDC | N/A | Any formulation of SGLT2 inhibitor or DPP-4 inhibitor | N/A | Investigator review of generic names |
| Reference:<br><br>DPP-4 inhibitors | Date of incident dispensation for DPP-4 inhibitors | Single | Incident | [-180, -1] | N/A | NDC | N/A | Any formulation of SGLT2 inhibitor or DPP-4 inhibitor | N/A | Investigator review of generic names |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

[2]See Appendix A for listing of clinical codes for each study parameter

### 6.3.2. Context and Rational for Study Inclusion Criteria

We require six months medical and prescription enrollment coverage prior to time 0 with an enrollment gap of 30 days as well as at least one electronic healthcare record (EHR) encounter. Requiring six months of medical and prescription coverage and having ≥ one EHR record encounter ensures that patients have observable time in the data where contact with the healthcare system will allow capture of clinical codes to measure inclusion-exclusion criteria and baseline covariates. We restrict the population to patients with type 2 diabetes mellitus. See Appendix A for listing of clinical codes for each study parameter.

*Table 4. Operational Definitions of Inclusion Criteria.*

| Criterion | Details | Order of Application | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Measurement Characteristics/ Validation | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|---|
| Observability related | Medical and prescription coverage (30 days maximum gaps allowed); at least 1 electronic healthcare record (EHR) encounter as operationalized by any entry in the lab or vital signs table of the Sentinel Common Data Model | Before selection of cohort entry date | [-180, 0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | N/A | N/A |
| Type 2 Diabetes Mellitus | | Before selection of cohort entry date | [-180, 0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | N/A | Investigator review of clinical codes |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### 6.3.3. Context and Rationale for Study Exclusion Criteria

We excluded patients if they had a history of acute pancreatitis; or if they had history of ESRD or HIV, as these patients have elevated risk of future acute pancreatitis event which may not be attributable to the treatment. We also excluded patients with Type 1 diabetes since the focus of this query

is on patients diagnosed with Type 2 diabetes. We further excluded patients who were treated with GLP1-RA prior to initiation of the study drugs as they share similar mechanism with DPP-4 inhibitors and there is uncertainty regarding the risk of pancreatitis after their use with some studies suggesting increased risk.[7,8] See Appendix A for listing of clinical codes for each study parameter.

*Table 5. Operational Definitions of Exclusion Criteria.*

| Criterion | Details | Order of Application | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Measurement Characteristics / Validation | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|---|
| Type 1 Diabetes Mellitus | Pathophysiology and treatment differs in comparison to T2DM | Before selection of cohort entry date | Any time prior to and including cohort entry date | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | N/A | Investigator review of clinical codes |
| Acute pancreatitis | Excluded as these patients have elevated risk of future acute pancreatitis event | Before selection of cohort entry date | Any time prior to and including cohort entry date | Any | ICD-9-CM, ICD-10-CM, lipase/ amylase laboratory test results | Any | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | PPV 91% | Carrell et al. In Review. |
| End stage renal disease (ESRD) | Excluded as these patients have elevated risk of future acute pancreatitis event | Before selection of cohort entry date | Any time prior to and including cohort entry date | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | N/A | Investigator review of clinical codes |
| Human Immuno-deficiency Virus (HIV) | Excluded as these patients have elevated risk of future | Before selection of cohort entry date | Any time prior to and including | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors | N/A | Investigator review of clinical codes |

| Criterion | Details | Order of Application | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Measurement Characteristics / Validation | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|---|
| | acute pancreatitis event | | cohort entry date | | | | Reference: DPP-4 inhibitors | | |
| GLP-1 RA use | Excluded as these patients may have elevated risk of future acute pancreatitis event | Before selection of cohort entry date | [-180, 0] | Any | NDC | NA | Exposure: SGLT2 inhibitors<br>Reference: DPP-4 inhibitors | N/A | Investigator review of generic names |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

## 6.4. Variables

### 6.4.1. Context and Rational for Exposure(s) of Interest

We focus on new initiators of drugs which are commonly used anti-diabetic drugs at similar stage of type 2 diabetes mellitus. This study design ensures homogenous patient population who are likely comparable and appropriate for evaluation of safety over the course of the treatment since initiation.

**Algorithm to define duration of exposure effect:** Assuming the effect of therapies lasts for 30 days after the days' supply, we allow 30 days gap between the dispensation (grace period) and also add 30 days at the end of days' supply of dispensation (exposure risk window).

*Table 6. Operational Definitions of Exposure.*

| Exposure Group Name(s) | Details | Washout Window | Assessment Window | Care Setting[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Incident with Respect to… | Measurement Characteristics/ Validation | Source of Algorithm |
|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure | N/A | [-180, -1] | [1, censor] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors | Both drug classes | N/A | Investigators review of generic names |
| Comparator | N/A | [-180, -1] | [1, censor] | N/A | NDC | N/A | Comparator: DPP-4 inhibitors | Both drug classes | N/A | Investigators review of generic names |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### 6.4.2. Context and Rationale for Outcome(s) of Interest

*Table 7. Operational Definitions of Outcome.*

| Outcome Name | Details | Primary Outcome? | Type of Outcome | Washout Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Measurement Characteristics/ Validation | Source of Algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Acute pancreatitis | A probabilistic phenotyping algorithm developed by Carrell et al. | Yes | Time-to-event | Any time prior to cohort entry | Any | ICD-9-CM, ICD-10-CM, laboratory test results, features extracted from free text | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Positive Predicted Value of 91% | Carrell et al. In Review<br><br>*Note: supplementary materials used to conduct the probabilistic phenotyping will be provided in Appendix B once above publication is available.* |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

### 6.4.3. Context and Rationale for Follow Up

We will conduct both an intent to treat and a per protocol analysis.

*Table 8. Operational Definitions of Follow Up.*

| | | |
|---|---|---|
| **Follow up start** | 1 | |
| **Follow up end**[1] | **Select all that apply** | **Specify** |
| **Date of outcome** | Yes | Table 8 |
| **Date of death** | Yes | As recorded in data sources |
| **End of observation in data** | Yes | Allow 30-day gaps in enrollment |
| **Day X following cohort entry date** *(specify day)* | No | - |
| **End of study period** *(specify date)* | Yes | Most recent data available within each data partner |
| **End of exposure** *(specify operational details, e.g., stockpiling algorithm, grace period)* | Yes (only in the per protocol analysis) | **Stockpiling algorithm:** a stockpiling algorithm is used to account for dispensings with overlapping days of supply by adjusting the date of the subsequent overlapping dispensing.<br>**Episode gap:** 30 days<br>**Episode extension:** 30 days |
| **Date of add to/switch from exposure** *(specify algorithm)* | Yes (only in the per protocol analysis) | On the day of the switch |
| **Other date** *(specify)* | N/A | N/A |

[1]Follow up ends at the first occurrence of any of the selected criteria that end follow up.

### 6.4.4. Context and Rationale for Covariates (Confounding Variables and Effect Modifiers, e.g., Risk Factors, Comorbidities, Comedications)

We identified demographic, comorbidity, healthcare utilization, frailty, and markers of healthy behaviors (e.g., use of preventative services) as confounding variables of interest.

*Table 9. Operational Definitions of Covariates: From Claims Data.*

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Age | (Cohort entry year - year of birth) | Continuous | [0,0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | |
| Sex | Male, Female | Categorical | [0, 0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | |
| Region | Northeast, South, Midwest, West, Other, Missing, Invalid | Categorical | [0, 0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | |
| Race (only available for TriNetX data source) | White, Black, Others | Categorical | [0, 0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | |
| Calendar Year | Date of cohort entry | Categorical | [0, 0] | N/A | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Hypertension | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Hyperlipidemia | | Binary | [-180, 0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Myocardial Infarction (MI) | Defined by acute MI/ old MI | Binary | [-180, 0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Tobacco Use | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Desai RJ et al.[9] |
| Obesity | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 and Investigators review of clinical codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Alcohol Abuse or Dependence | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 and Investigators review of clinical codes |
| Gallstones | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigator review of codes |
| Cancer | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] |
| Stable Angina | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Unstable Angina | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] |
| Coronary Revascularization | | Binary | [-180,0] | Any | ICD-9-CM, | Any | Exposure: SGLT2 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | ICD-10-CM | | Comparator: DPP-4 inhibitors | |
| Coronary Atherosclerosis | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Other Forms of Chronic Ischemic Heart Disease | | Binary | [-180 0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| History of Coronary-Artery Bypass Grafting (CABG)/ Percutaneous Transluminal Coronary Angioplasty (PTCA) | | Binary | [-180, 0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Any Stroke | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Transient Ischemic Attack | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Late Effects of Cerebrovascular Disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE Investigator review of codes |
| Valve Disorders | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Peripheral Vascular Disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE Investigator review of codes |
| Heart Failure | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Mahesri et al.[11] |
| Atrial Fibrillation | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 and RCT DUPLICATE Investigator review of codes |
| Other Cardiac Dysrhythmia | | Binary | [-180,0] | Any | ICD-9-CM, | Any | Exposure: SGLT2 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic- |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | ICD-10-CM | | Comparator: DPP-4 inhibitors | packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 and RCT DUPLICATE Investigator review of codes |
| Cardiomyopathy | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Mahesri et al.[11] |
| Hypertensive Nephropathy | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Acute Kidney Injury | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Chronic Kidney Disease, Stage 1-2 | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of codes |
| Chronic Kidney Disease, Stage 3-5 | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Paik et al.[12] |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Anemia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Miscellaneous renal disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Chronic obstructive pulmonary disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Pulmonary Hypertension | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Obstructive Sleep Apnea | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Asthma | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=r |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | efs%2Fheads%2Fcder_sir_wp002 |
| Osteoporosis | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Osteoarthrosis | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Syncope | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigator review of codes |
| Falls | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigator review of codes |
| Nonalcoholic Steatohepatitis (NASH)/ Nonalcoholic Fatty Liver Disease (NAFLD) | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE<br>Investigator review of codes |
| Alzheimer's Disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=r |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Comparator: DPP-4 inhibitors | efs%2Fheads%2Fcder_sir_wp002 |
| Parkinson's Disease | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Other Dementia Types | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Psychosis | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of codes |
| Delirium | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of codes |
| Depression | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Anxiety | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of codes |
| Hyperkalemia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Hypotension | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Deep Venous Thrombosis or Pulmonary Embolism | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Oedema | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Vertebral and Non-Vertebral Fractures | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Pneumonia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Frailty Score | | Continuous | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Kim DH et al[13] |
| Combined Comorbidity Score | | Continuous | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Gagne J et al.[14] |
| Type 2 Diabetes Mellitus without Mention of Complications | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Diabetic Nephropathy | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Diabetes with Peripheral Circulatory Disorders | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Diabetic Foot | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Diabetic Neuropathy | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Diabetic Retinopathy | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Type 2 Diabetes with Unspecified Complications | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Lower Limb Amputations | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Hyperglycemia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigator review of ICD-10 codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Hypoglycemia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Hyperosmolar Hyperglycemic Nonketotic Syndrome | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Hypertriglyceridemia | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| History of Autoimmune Diseases: Inflammatory Bowel Disease, Primary Biliary Cholangitis, Rheumatoid Arthritis, Sarcoidosis, Sjogren's Syndrome | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Urinary Tract or Fungal Infection History | | Binary | [-180,0] | Any | ICD-9-CM, ICD-10-CM | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Number of Antidiabetic Drugs | | Continuous | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors | |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Comparator: DPP-4 inhibitors | |
| Metformin Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Metformin Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day<br>2. Current use is defined as patients who have days' supply over lapping cohort entry day | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Sulfonylureas Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Sulfonylurea's Concomitant/ Current use | 1. Concomitant initiation is defined as patients who | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | "start" the prescription on cohort entry day<br>2. Current use is defined as patients who have days' supply over lapping cohort entry day | | | | | | Comparator: DPP-4 inhibitors | |
| Thiazolidinediones, Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Thiazolidinediones, Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day<br>2. Current use is defined as patients who have days' supply over lapping cohort entry day | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Alpha-Glucosidase Inhibitors, Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Alpha-Glucosidase Inhibitors, Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day<br><br>2. Current use is defined as patients who have days' supply overlapping cohort entry day | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Meglitinides, Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Meglitinides Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | cohort entry day<br><br>2. Current use is defined as patients who have days' supply overlapping cohort entry day | | | | | | | |
| Amylin Analog, Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Amylin Analog, Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day<br><br>2. Current use is defined as patients who have days' supply overlapping cohort entry day | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Insulin Past Use | | Binary | [-180,-1] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Insulin Concomitant/ Current Use | 1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day<br><br>2. Current use is defined as patients who have days' supply over lapping cohort entry day | Binary | [0,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Anticoagulants | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Antiarrhythmics | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Angiotensin Converting Enzyme (ACE) Inhibitors/ Angiotensin Receptor Blockers (ARBs) | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Beta Blockers | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Calcium Channel Blockers | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Thiazides | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Diuretics | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Digoxin | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (without aspirin) | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Aspirin | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Opioids | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Statins | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Other Lipid Lowering Drugs | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Anticonvulsants | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Antidepressants | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Antiosteoporosis Medications | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Anxiolytics/ Hypnotics | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Antipsychotics | Both typical and atypical | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Antiparkinsonian Medications | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |
| Benzodiazepine | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10]<br>Investigator review of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Dementia Medications | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Proton Pump Inhibitors (PPIs) | | Binary | [-180,0] | N/A | NDC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator review of codes |
| Number of Prescriptions | | Continuous | [-180,0] | N/A | | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |
| Number of Generics | | Continuous | [-180,0] | N/A | | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |
| Number of AV visits | | Continuous | [-180,0] | N/A | | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |
| Number of OA Visits | | Continuous | [-180,0] | N/A | | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Number of Hospital Visits | | Continuous | [-180,0] | N/A | | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |
| Number of ED Visits | | Continuous | [-180, 0] | ED | N/A | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | N/A |
| Number of HbA1C Tests | | Continuous | [-180, 0] | Any | LOINC | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Number of Microalbuminuria Tests | | Continuous | [-180, 0] | Any | LOINC | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Number of Creatinine Tests | | Continuous | [-180, 0] | Any | LOINC | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Colonoscopy | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator choice of codes |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| Fecal Occult Blood Test | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Investigators review of clinical codes |
| Flu Vaccination | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator choice of codes |
| Mammography | Only among females | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Pap Smear Test | Only among female patients | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002 |
| Pneumococcal Vaccine | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator choice of codes |
| Prostate Specific Antigen Test | Only among male patients | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors | https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_s |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Source for Algorithm |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Comparator: DPP-4 inhibitors | ir_wp002 and RCT DUPLICATE[10] Investigator choice of codes |
| Bone Mineral Density Test | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator choice of codes |
| Metabolic Blood Chemistry Test | | Binary | [-180, 0] | Any | CPT, HCPCS | Any | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | RCT DUPLICATE[10] Investigator choice of codes |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

*Table 10. Operational Definitions of Covariates: From Electronic Healthcare Record (EHR) Data.*

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Handling of Missingness | Handling of Multiple Values Over Time |
|---|---|---|---|---|---|---|---|---|---|
| HbA1c | Based on structured EHRs | Continuous | [-180,0] | Any | LOINC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |
| Serum Creatinine | Based on structured EHRs | Continuous | [-180,0] | Any | LOINC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |
| Triglycerides | Based on structured EHRs | Continuous | [-180,0] | Any | LOINC | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |
| Body mass Index (BMI) (Weight/ Height) | Based on structured EHRs | Continuous | [-180,0] | Any | Sentinel Common Data Model Vitals Table | N/A | Exposure: SGLT2 inhibitors<br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |

| Characteristic | Details | Type of Variable | Assessment Window | Care Settings[1] | Code Type[2] | Diagnosis Position[3] | Applied to Study Populations: | Handling of Missingness | Handling of Multiple Values Over Time |
|---|---|---|---|---|---|---|---|---|---|
| Systolic Blood Pressure | Based on structured EHRs | Continuous | [-180,0] | Any | Sentinel Common Data Model Vitals Table | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |
| Diastolic Blood Pressure | Based on structured EHRs | Continuous | [-180,0] | Any | Sentinel Common Data Model Vitals Table | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | Mechanism for missingness to be investigated using smdi | Selected closest value to the cohort entry date |
| Tobacco Use | Based on structured EHRs | Binary | [-180,0] | Any | Sentinel Common Data Model Vitals Table | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | N/A | Selected closest value to the cohort entry date |
| Total Number of EHR Encounters | Based on structured EHRs | Count | [-180, 0] | Any | Sentinel Common Data Model Tables | N/A | Exposure: SGLT2 inhibitors<br><br>Comparator: DPP-4 inhibitors | N/A | Sum |

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2]See Appendix A for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

## 6.5. Data Analysis

### 6.5.1. Context and Rationale for Analysis Plan

We will use propensity score (PS) based fine-stratification weighting method with 50 strata for confounding adjustment by measured factors.[15] PS will be estimated as the probability of initiating SGLT2i versus DPP-4i given the baseline patient characteristics using multivariable logistic regression models. Fifty strata will be created based on the distribution of PS in SGLT2i-treated patients, and DPP-4i initiators will be assigned into these strata based on their PS resulting in 50 unequally sized strata. In the weighting step, DPP-4i initiators in each stratum will be weighted proportional to the number of SGLT2i patients to account for stratum membership and achieve balance. As diagnostics for PS models, we will evaluate distributional overlap, weight distribution, and covariate balance using standardized differences post-weighting. In the weighted population, we will estimate the hazard ratio for SGLT2i versus DPP-4 inhibitor on acute pancreatitis using a Cox proportional hazards model. Cumulative incidence at various time points during follow-up will be calculated using cumulative incidence functions[16] and reported stratified by treatment groups.

In addition to claims-based variables, we intend to use numerous EHR based variables for confounding adjustment. Missingness in these variables is common and expected. We will use a recently developed R Package, smdi,[17] for principled missing data investigations on partially observed confounders and implement functions to visualize, describe, and infer potential missingness patterns and mechanisms based on observed data. After verifying assumptions based on this diagnostic evaluation, we will proceed to use multiple imputation methods to analytically address missingness in key confounding variables including HbA1c and BMI. Figure 3 provides an overview of the analytic workflow. Briefly, we will create 20 imputed datasets where missing confounders will be imputed based on random forest algorithms. In each of the imputed dataset, we will fit the PS models and conduct fine stratification to calculate adjusted treatment effect estimates. The final results will be reported after pooling results using Rubin's rule to account for variance both in the within and across the imputed datasets.

*Figure 3. Analytic Workflow.*

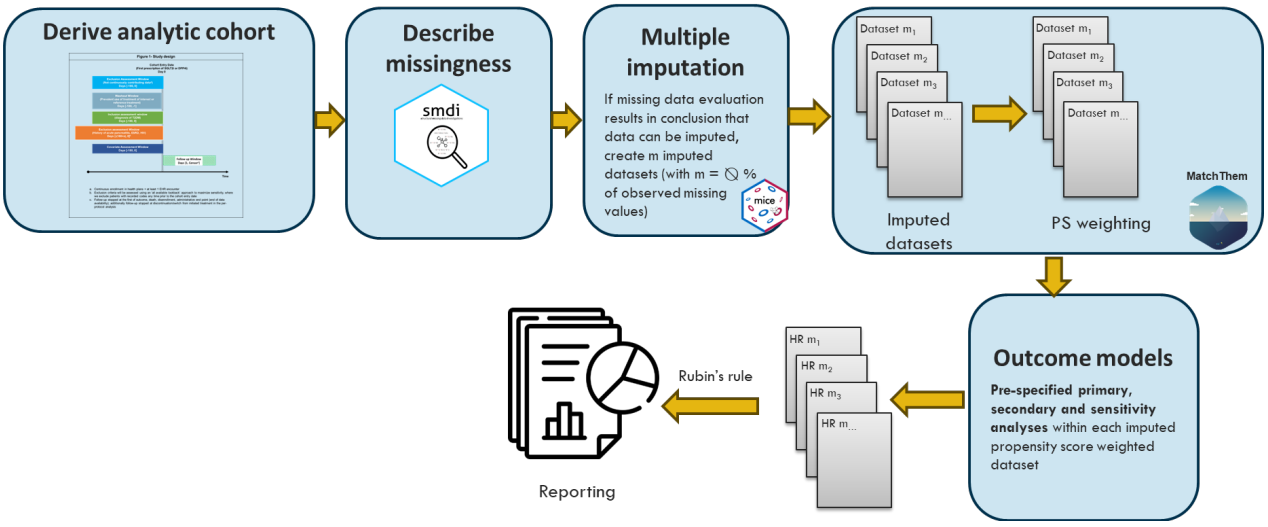


*Table 11. Primary, Secondary, and Subgroup Analysis Specification.*

| | |
|---|---|
| **Hypothesis:** | SGLT2 inhibitors increases the risk of acute pancreatitis compared to DPP-4 inhibitors |
| **Exposure contrast:** | SGLT2 inhibitor vs. DPP-4 inhibitor |
| **Outcome:** | Acute pancreatitis |
| **Analytic software:** | R |
| **Model(s):** ***(provide details or code)*** | R packages: smdi, mice, MatchThem |
| **Confounding adjustment method** | ***Propensity score fine stratification*** |
| **Missing data methods** | ***Multiple imputations with random forests*** |
| **Subgroup Analyses** | ***List all subgroups*** |
| | 1. Sex (Male/Female)<br>2. Age (<65, >=65)<br>3. History of risk factors for acute pancreatitis |

*Table 12. Sensitivity Analyses: Rationale, Strengths, and Limitations.*

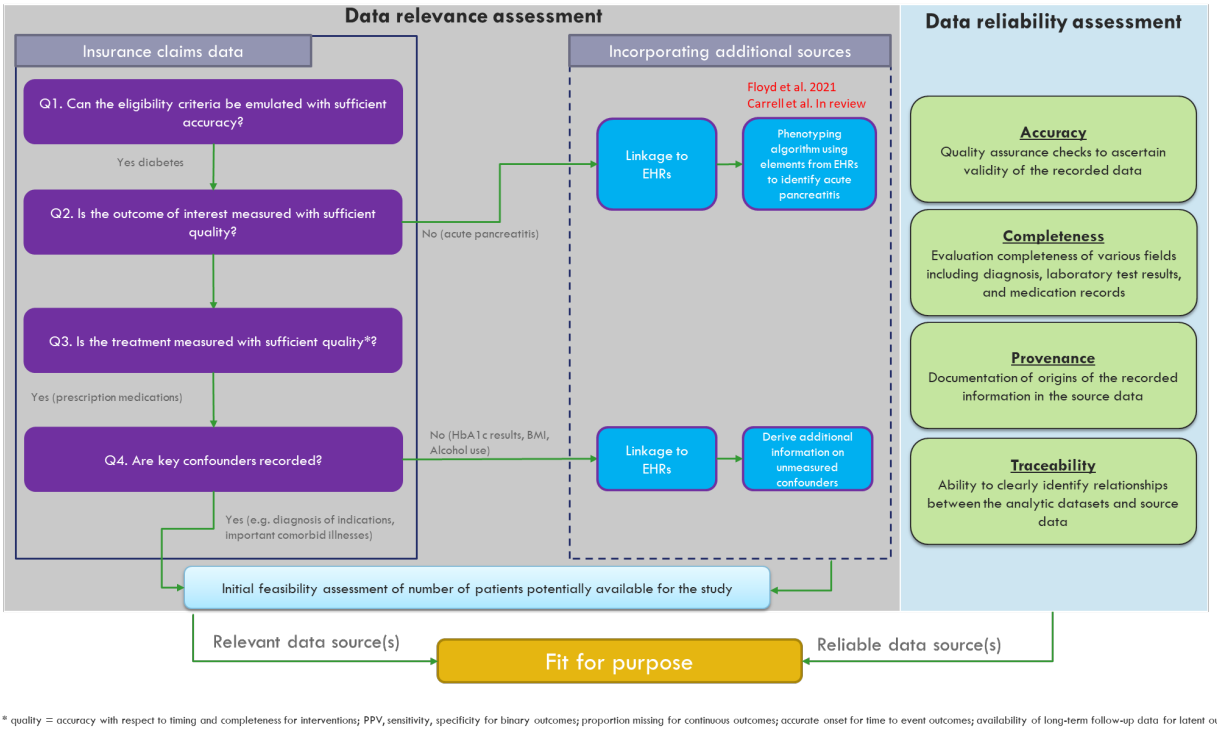
| | **What is being varied? How?** | **Why? (What do you expect to learn?)** | **Strengths of the sensitivity analysis compared to the primary** | **Limitations of the sensitivity analysis compared to the primary** |
|---|---|---|---|---|
| Baseline window | Increase baseline window to 12 months for EHR measurements | Greater capture of some of the EHR recorded confounding variables | Less degree of missingness in important clinical variables | EHR information recorded in distant past (>180 days before) may have changed and not relevant at the time of treatment initiation |
| Restricted to high EHR continuity | Based on Lin et al. algorithm,[18] restrict the analysis to subjects predicted to have high EHR continuity in the source systems | Greater capture of confounders, less potential for missingness in outcome events | Limiting missingness in important clinical variables | Compromised sample size |
| Control outcome | Use ischemic stroke as a negative control outcome[19] | Net bias analysis | Enables the detection of bias in the primary analysis, assuming shared confounding structure | N/A |

# 6.6. Data Sources

## 6.6.1. Context and Rationale for Data Sources

This section corresponds to Step 2b of the PRINCIPLED framework: selecting fit-for-purpose data. Figure 4 outlines the general considerations for our research question.

*Figure 4. Consideration in Selecting Fit-for-Purpose Data.*




* quality = accuracy with respect to timing and completeness for interventions; PPV, sensitivity, specificity for binary outcomes; proportion missing for continuous outcomes; accurate onset for time to event outcomes; availability of long-term follow-up data for latent outcomes

Two key considerations for determining fitness-for-purpose of data sources are data relevance and data reliability. Within Sentinel, reliability evaluations are performed upstream when converting raw data from contributing sources to the Sentinel common data model—which is then used for all subsequent analyses.

For determination of relevance, we consider the context of Sentinel where most of the data come from insurance claims, and ancillary sources (including electronic health records) provide opportunities for augmentation. Relevance determination depends on a series of questions focused on measurement characteristics of four variable types central to the research question of interest in insurance claims data: eligibility criteria, outcome, treatment, and key confounders. For the current question, the outcome of interest (acute pancreatitis) and confounders (HbA1c, BMI, alcohol use) are deemed to be insufficiently measured in insurance claims data. Therefore, insurance claims linked with electronic health records, where the confounders are recorded with higher validity than claims as well as acute pancreatitis[5] can be identified by implementing a phenotyping algorithm, in combination were considered fit-for-purpose. Specifically, we used the FDA Sentinel Real-World Evidence Data Enterprise (RWE-DE) commercial network, includes HealthVerity and TriNetX data sources, for this study.

## Data source provenance/curation:

*Table 13. Metadata About Data Sources and Software.*

| | |
|---|---|
| **Data Source(s):** | HealthVerity: EHRs from three sources (Veradigm, Amazing Charts, and Source 42) linked to closed medical claims (Inovalon) and closed pharmacy claims (Evernorth)<br><br>TriNetX: EHRs from 20 unique health care organizations (HCOs) linked to closed claims data from more than 150 payers |
| **Study Period:** | 2018-2020 (HealthVerity)<br><br>2013-2023 (TriNetX) |
| **Eligible Cohort Entry Period:** | 2018-2020 (HealthVerity)<br><br>2013-2023 (TriNetX) |
| **Data Version (or date of last update):** | HealthVerity: ETL 2<br><br>TriNetX: ETL 2 |
| **Data sampling/ extraction criteria:** | HealthVerity: We non-randomly sampled 10 million unique patients in the source population out of ~23 million total available patients meeting inclusion criteria in the HealthVerity real-world data ecosystem. To enrich the sample with patients who have more person-time overlap between claims and EHRs, the following sampling criteria were used 1) at least one EHR encounter from 2018-2019, 2) at least one index encounter in EHR with a medical claim on same date of service, 3) continuous medical and drug coverage 30 days pre- and post-index, 4) at least one pharmacy claim within 30 days pre- or post-index, and 5) sampling remaining population for greatest number of unique indexed EHR encounters with medical claim on same date of service. Due to the non-random selection, this sample likely overestimates prevalence of medical conditions; however, most pertinent information for Sentinel, which includes descriptive characteristics of users of medications and causal questions related to medication outcomes, are likely unaffected by these sampling choices.<br><br>TriNetX: No sampling was performed. All patients with linkage between EHRs and claims were included in the source population. |
| **Type(s) of data:** | Medical claims; electronic health records (EHRs) |
| **Data linkage:** | EHR data linked with insurance claims data |
| **Conversion to CDM:** | Sentinel Common Data Model 8.0.0[20] |
| **Software for data management:** | SAS |

## 6.7. Data Management
N/A

## 6.8. Quality Control
Both data sources had their ETL approved using a standard Sentinel Quality Assurance review process.

## 6.9. Study Size and Feasibility
TBD; this study corresponds to Step 4 of the PRINCIPLED process and will be populated in the amended protocol along with any study adaptations as required.

# 7. Limitation of the Methods
TBD

# 8. Protection of Human Subjects
This project was approved under 'Public Health Surveillance exemption' by Mass General Brigham IRB.

# 9. Reporting of Adverse Events
N/A

# 10. References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# 11. Appendices

## 11.1 Appendix A. List of Medical Codes Used to Define Clinical Concepts in this Study

Please refer to the attached spreadsheet for a complete list of medical codes used to define concepts in this analysis.

## 11.2 Appendix B. Supplementary Materials Used to Conduct Probabilistic Phenotyping Algorithm for "Acute Pancreatitis"

These materials will become available in an upcoming study protocol amendment, pending availability of Floyd et al. manuscript.