

Strengthening Inferential Studies in the U.S. FDA Sentinel Initiative: A Methodological Demonstration Project

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” (PRINCIPILED) 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
July 17, 2025	3.0	Title Page	Updated project title	Project title was updated to align with final report

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 “PProcess guide for INferential studies using healthcare data from routine Clinical Practice to evaluate causal Effects of Drugs” (PRINCIPLED) framework⁶ 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.

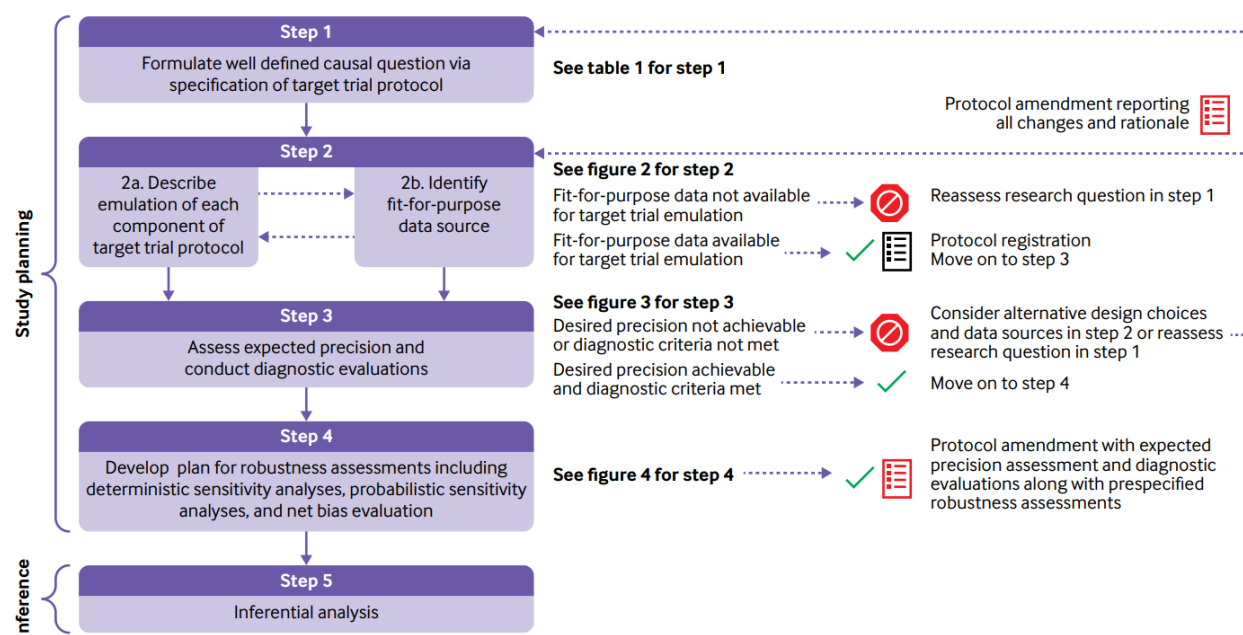


Table 2 summarizes the causal question being asked in the current study via specification of a target trial protocol (Step 1 of the process).

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 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) 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) Per protocol effect (effect of staying on the treatment)	Observational analogue of intent to treat effect 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.

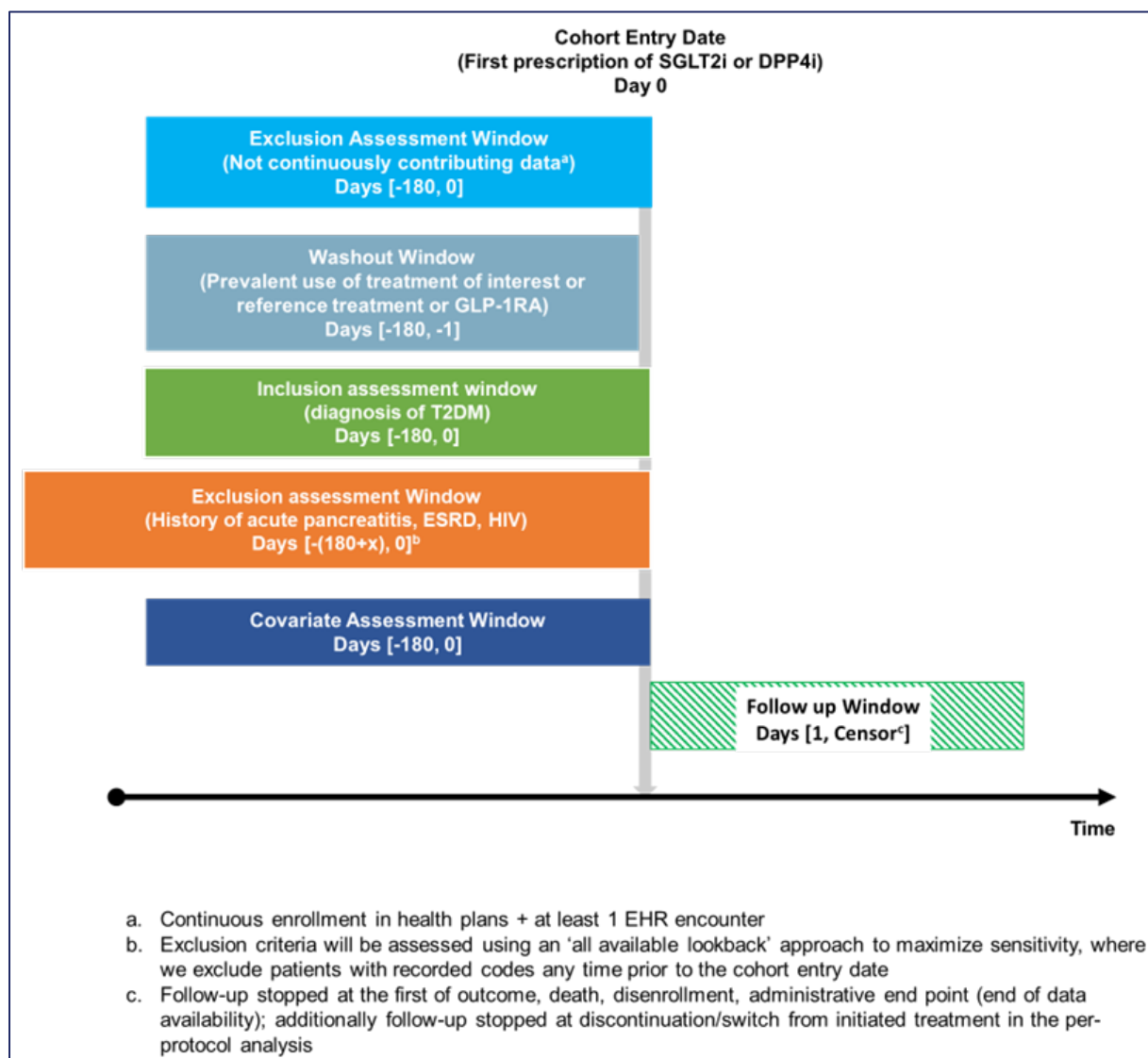
6.1. Study Design

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.



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: 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: 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

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

²See 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 $\geq$ 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 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 Reference: DPP-4 inhibitors	N/A	Investigator review of clinical codes

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

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

³Specify 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 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 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 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 Reference: DPP-4 inhibitors	N/A	Investigator review of generic names

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

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

³Specify 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
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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

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

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

³Specify 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 Comparator: DPP-4 inhibitors	Positive Predicted Value of 91%	Carrell et al. In Review <i>Note: supplementary materials used to conduct the probabilistic phenotyping will be provided in Appendix B once above publication is available.</i>

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

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

³Specify 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 end¹	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. Episode gap: 30 days 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

¹Follow 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 Comparator: DPP-4 inhibitors	
Sex	Male, Female	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	
Region	Northeast, South, Midwest, West, Other, Missing, Invalid	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	
Calendar Year	Date of cohort entry	Categorical	[0, 0]	N/A	N/A	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Hyperlipidemia		Binary	[-180, 0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Myocardial Infarction (MI)	Defined by acute MI/ old MI	Binary	[-180, 0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Tobacco Use		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Desai RJ et al. ⁹
Obesity		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_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 Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002 and Investigators review of clinical codes
Gallstones		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigator review of codes
Cancer		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰
Stable Angina		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 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 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 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 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 Comparator: DPP-4 inhibitors	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Transient Ischemic Attack		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel.system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_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 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 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 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 Comparator: DPP-4 inhibitors	Mahestri et al. ¹¹
Atrial Fibrillation		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcd_r_wp002 and RCT DUPLICATE Investigator review of codes
Other Cardiac Dysrhythmia		Binary	[-180,0]	Any	ICD-9-CM,	Any	Exposure: SGLT2 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcd_r_wp002

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%2Fcdcr_sir_wp002 and RCT DUPLICATE Investigator review of codes
Cardiomyopathy		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Mahealani et al. ¹¹
Hypertensive Nephropathy		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 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 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 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 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 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 Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdcr_sir_wp002
Pulmonary Hypertension		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 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 Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcdcr_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
								efs%2Fheads%2Fcder_sir_wp002
Osteoporosis		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Osteoarthritis		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Syncope		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigator review of codes
Falls		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE Investigator review of codes
Alzheimer's Disease		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors	https://dev.sentinel-system.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 Comparator: DPP-4 inhibitors	https://dev.sentinel.system.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 Comparator: DPP-4 inhibitors	https://dev.sentinel.system.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 Comparator: DPP-4 inhibitors	Investigators review of codes
Delirium		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigators review of codes
Depression		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	Investigators review of codes
Hyperkalemia		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Hypotension		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Oedema		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 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 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 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 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 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 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 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Diabetic Neuropathy		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Diabetic Retinopathy		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Type 2 Diabetes with Unspecified Complications		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Lower Limb Amputations		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Hyperglycemia		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Hyperosmolar Hyperglycemic Nonketotic Syndrome		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Hypertriglyceridemia		Binary	[-180,0]	Any	ICD-9-CM, ICD-10-CM	Any	Exposure: SGLT2 inhibitors 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Amylin Analog, Concomitant/ Current Use	1. Concomitant initiation is defined as patients who "start" the prescription on cohort entry day 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 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
Insulin Past Use		Binary	[-180,-1]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Anticoagulants		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Antiarrhythmics		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Beta Blockers		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Thiazides		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Diuretics		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Digoxin		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Aspirin		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Opioids		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Statins		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Anticonvulsants		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Antiosteoporosis Medications		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Anxiolytics/ Hypnotics		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Antipsychotics	Both typical and atypical	Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Antiparkinsonian Medications		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Benzodiazepine		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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
Dementia Medications		Binary	[-180,0]	N/A	NDC	N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator review of codes
Number of Prescriptions		Continuous	[-180,0]	N/A		N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	N/A
Number of Generics		Continuous	[-180,0]	N/A		N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	N/A
Number of AV visits		Continuous	[-180,0]	N/A		N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	N/A
Number of OA Visits		Continuous	[-180,0]	N/A		N/A	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	N/A
Number of ED Visits		Continuous	[-180, 0]	ED	N/A	N/A	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	N/A
Number of HbA1C Tests		Continuous	[-180, 0]	Any	LOINC	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Number of Microalbuminuria Tests		Continuous	[-180, 0]	Any	LOINC	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Number of Creatinine Tests		Continuous	[-180, 0]	Any	LOINC	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Colonoscopy		Binary	[-180, 0]	Any	CPT, HCPCS	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	Investigators review of clinical codes
Flu Vaccination		Binary	[-180, 0]	Any	CPT, HCPCS	Any	Exposure: SGLT2 inhibitors 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 Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Pap Smear Test	Only among female patients	Binary	[-180, 0]	Any	CPT, HCPCS	Any	Exposure: SGLT2 inhibitors Comparator: DPP-4 inhibitors	https://dev.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002
Pneumococcal Vaccine		Binary	[-180, 0]	Any	CPT, HCPCS	Any	Exposure: SGLT2 inhibitors 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.sentinel-system.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcders_ir_wp002

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 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 Comparator: DPP-4 inhibitors	RCT DUPLICATE ¹⁰ Investigator choice of codes

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

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

³Specify 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 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 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 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 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 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 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 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 Comparator: DPP-4 inhibitors	N/A	Sum

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

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

³Specify 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 functions¹⁶ 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.

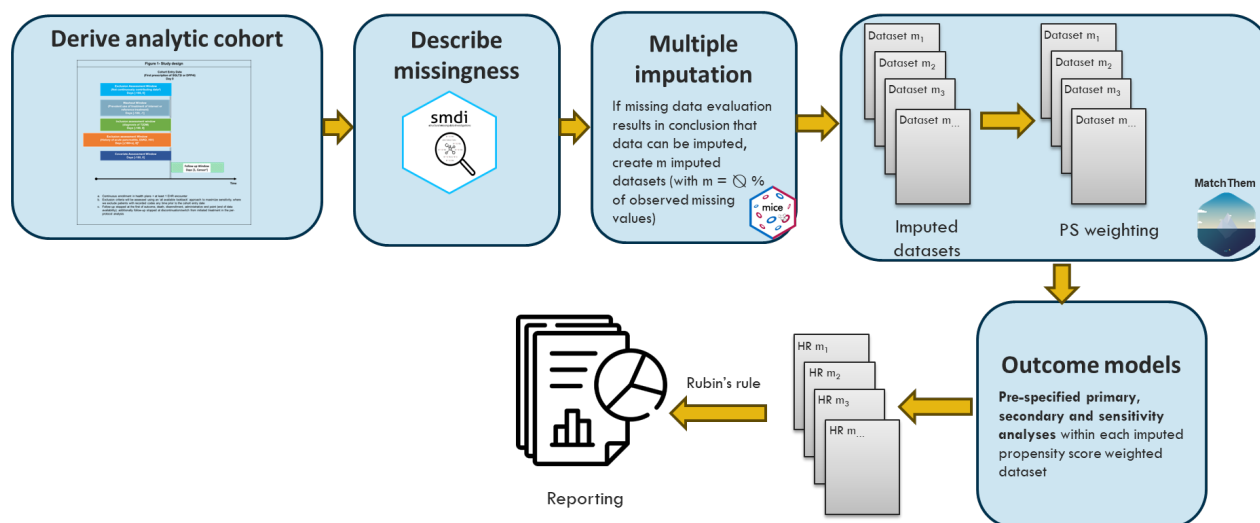


Table 11. Primary, Secondary, and Subgroup Analysis Specification.

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): <i>(provide details or code)</i>	R packages: smdi, mice, MatchThem
Confounding adjustment method	<i>Propensity score fine stratification</i>
Missing data methods	<i>Multiple imputations with random forests</i>
Subgroup Analyses	<i>List all subgroups</i>
	1. Sex (Male/Female) 2. Age (<65, >=65) 3. History of risk factors for acute pancreatitis

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

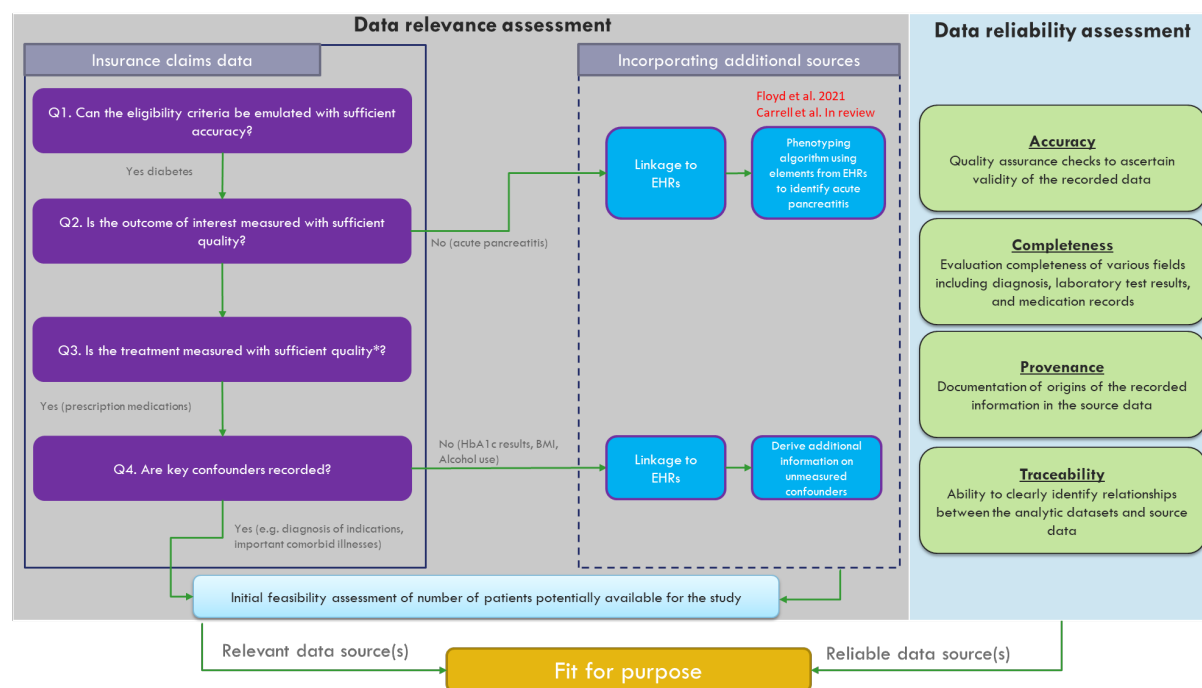
	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Baseline window	Increase baseline window to 12 months for EHR measurements	Greater capture of some of the EHR recorded 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 pancreatitis⁵ 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) TriNetX: EHRs from 20 unique health care organizations (HCOs) linked to closed claims data from more than 150 payers
Study Period:	2018-2020 (HealthVerity) 2013-2023 (TriNetX)
Eligible Cohort Entry Period:	2018-2020 (HealthVerity) 2013-2023 (TriNetX)
Data Version (or date of last update):	HealthVerity: ETL 2 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. 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

1. Abrahami D, D'Andrea E, Yin H, et al. Contemporary trends in the utilization of second-line pharmacological therapies for type 2 diabetes in the United States and the United Kingdom. *Diabetes Obes Metab*. Oct 2023;25(10):2980-2988. doi:10.1111/dom.15196
2. Tang H, Yang K, Li X, Song Y, Han J. Pancreatic safety of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf*. Feb 2020;29(2):161-172. doi:10.1002/pds.4943
3. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *Bmj*. Nov 14 2018;363:k4365. doi:10.1136/bmj.k4365
4. Patil T, Cook M, Hobson J, Kaur A, Lee A. Evaluating the Safety of Sodium-Glucose Cotransporter-2 Inhibitors in a Nationwide Veterans Health Administration Observational Cohort Study. *The American journal of cardiology*. Aug 15 2023;201:281-293. doi:10.1016/j.amjcard.2023.06.016
5. Floyd JS, Bann MA, Felcher AH, et al. Validation of Acute Pancreatitis Among Adults in an Integrated Healthcare System. *Epidemiology*. Jan 1 2023;34(1):33-37. doi:10.1097/ede.0000000000001541
6. Desai RJ, Wang SV, Sreedhara SK, et al. Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center. *Bmj*. Feb 12 2024;384:e076460. doi:10.1136/bmj-2023-076460
7. Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M. Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. *Jama*. Nov 14 2023;330(18):1795-1797. doi:10.1001/jama.2023.19574
8. Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. *Endocrine*. Jun 2020;68(3):518-525. doi:10.1007/s12020-020-02223-6
9. Desai RJ, Solomon DH, Shadick N, Iannaccone C, Kim SC. Identification of smoking using Medicare data - a validation study of claims-based algorithms. *Pharmacoepidemiol Drug Saf*. Apr 2016;25(4):472-5. doi:10.1002/pds.3953
10. Wang SV, Schneeweiss S, Franklin JM, et al. Emulation of randomized clinical trials with nonrandomized database analyses: results of 32 clinical trials. *Jama*. 2023;329(16):1376-1385.
11. Mahesri M, Chin K, Kumar A, et al. External validation of a claims-based model to predict left ventricular ejection fraction class in patients with heart failure. *PloS one*. 2021;16(6):e0252903. doi:10.1371/journal.pone.0252903
12. Paik JM, Patorno E, Zhuo M, et al. Accuracy of identifying diagnosis of moderate to severe chronic kidney disease in administrative claims data. *Pharmacoepidemiol Drug Saf*. Apr 2022;31(4):467-475. doi:10.1002/pds.5398
13. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in medicare data: development and validation of a claims-based frailty index. *The Journals of Gerontology: Series A*. 2017;73(7):980-987.
14. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. Jul 2011;64(7):749-59. doi:10.1016/j.jclinepi.2010.10.004
15. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A Propensity score based fine stratification approach for confounding adjustment when exposure is infrequent. *Epidemiology (Cambridge, Mass)*. 2017;28(2):249-257.
16. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601-609.

17. Weberpals J, Raman SR, Shaw PA, et al. smdi: an R package to perform structural missing data investigations on partially observed confounders in real-world evidence studies. *JAMIA Open*. Apr 2024;7(1):00ae008. doi:10.1093/jamiaopen/00ae008
18. Lin KJ, Glynn RJ, Singer DE, Murphy SN, Lii J, Schneeweiss S. Out-of-system care and recording of patient characteristics critical for comparative effectiveness research. *Epidemiology (Cambridge, Mass)*. 2018;29(3):356-363.
19. Fu EL, Patorno E, Everett BM, et al. Sodium–glucose cotransporter 2 inhibitors vs. sitagliptin in heart failure and type 2 diabetes: an observational cohort study. *European heart journal*. 2023;44(24):2216-2230.
20. The Sentinel Common Data Model. Available at https://dev.sentinelssystem.org/projects/SCDM/repos/sentinel_common_data_model/browse, Accessed 5/1/2025.

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.