BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

BMJ Open

Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057977
Article Type:	Protocol
Date Submitted by the Author:	04-Nov-2021
Complete List of Authors:	Khera, Rohan; Yale School of Medicine, Internal Medicine/Cardiology; Yale University School of Medicine, Schuemie, Martijn; Observational Health Data Sciences and Informatics, Epidemiology Analytics; University of California, Los Angeles, Department of Biostatistics Lu, Yuan; Yale University School of Medicine, Internal Medicine; Yale University Ostropolets, Anna; Columbia University Chen, RuiJun; Geisinger Hripcsak, George; Columbia University Ryan, Patrick; Janssen Research and Development LLC, Observational Health Data Analytics; Columbia University Irving Medical Center, Department of Biomedical Informatics Krumholz, Harlan; Yale School of Medicine, Suchard, MA; University of California Los Angeles,
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, DIABETES & ENDOCRINOLOGY, Cardiology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

RESEARCH PROTOCOL

Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus

Rohan Khera MD MS[1,2], Martijn J Schuemie PhD[3,4], Yuan Lu ScD[1,2] Anna Ostropolets MD[5], Ruijun Chen MD[6], George Hripcsak MD MS [5,7], Patrick B Ryan PhD[3,5], Harlan M Krumholz MD SM [1,2], Marc A Suchard MD PhD [4,8,9,10]

1. Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT
2. Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT
3. Epidemiology Analytics, Janssen Research and Development, Titusville, NJ
4. Department of Biostatistics, UCLA Fielding School of Public Health, University of California, Los Angeles, CA
5. Department of Biomedical Informatics, Columbia University Medical Center, New York, NY
6. Department of Translational Data Science and Informatics, Geisinger, Danville, PA
7. New York-Presbyterian Hospital, New York, NY
8. Department of Biomathematics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA
9. Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA
10. VA Informatics and Computing Infrastructure, US Department of Veterans Affairs, Salt Lake City, UT

Corresponding author:
Marc A Suchard, MD PhD
6558 Gonda Building, 695 Charles E. Young Drive
South Los Angeles, CA 90095-1766
Email: msuchard@ucla.edu
Tel (310) 825-7442; Fax (310) 825-8685

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Abstract

Introduction: Therapeutic options for type 2 diabetes mellitus (T2DM) have expanded over the last decade with the emergence of cardioprotective novel agents, but without such data for older drugs, leaving a critical gap in our understanding of the relative effects of T2DM agents on cardiovascular risk.

Methods and Analysis: The Large-Scale Evidence Generations Across a Network of Databases for T2DM (LEGEND-T2DM) initiative is a series of systematic, large-scale, multinational, real-world comparative cardiovascular effectiveness and safety studies of all 4 major second-line anti-hyperglycemic agents including SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor and sulfonylureas. LEGEND-T2DM will leverage the OHDSI community that provides access to a global network of administrative claims and electronic health record (EHR) data sources, representing 190 million patients in the US and about 50 million internationally. LEGEND-T2DM will identify all adult, T2DM patients who newly initiate a traditionally second-line T2DM agent. Using an active comparator, new-user cohort design, LEGEND-T2DM will execute all pairwise class-vs-class and drug-vs-drug comparisons in each data source, producing extensive study diagnostics that assess reliability and generalizability through cohort balance and equipoise to examine the relative risk of cardiovascular and safety outcomes. The primary cardiovascular outcomes include a composite of major adverse cardiovascular events and a series of safety outcomes. The study will pursue data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias.

Ethics and Dissemination: The study ensures data safety through a federated analytic approach and follows research best practices, including prespecification and full disclosure of hypotheses tested and their results. LEGEND-T2DM is dedicated to open science and transparency and will publicly share all analytic code from reproducible cohort definitions through turn-key software, enabling other research groups to leverage our methods, data, and results in order to verify and extend our findings.

For peer review only

Strengths and limitations of this study

- The proposal seeks to determine real-world comparative effectiveness and safety of traditionally second-line T2DM agents using health information encompassing millions of patients with T2DM, with a focus on individuals at moderate cardiovascular risk and other key subgroups.
- We will conduct three large-scale, systematic, observational studies to make pairwise comparisons of all SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor and sulfonylurea agents at the drug-, class- and population subgroup-level within our proposed Large-Scale Evidence Generations Across a Network of Databases for T2DM (LEGEND-T2DM) initiative.
- LEGEND-T2DM will leverage the Observational Health Data Science and Informatics (OHDSI) community that provides access to a standing global network of administrative claims and electronic health record (EHR) data sources, representing the 13 data sources already committed to LEGEND-T2DM cover over 190 million patients in the US and about 50 million internationally, and include two academic medical centers, IBM MarketScan and Optum databases, and the US Department of Veterans Affairs. All adults with type 2 diabetes across data sources are included. The outcomes of interest include a composite of major adverse cardiovascular events, and secondary effectiveness and safety outcomes, guided by stakeholders.
- The studies represent an observational, active-comparator, new-user cohort design with a systematic framework to address residual confounding, publication bias, and p-hacking using data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, prespecification and full disclosure of hypotheses tested and their results. These approaches capitalize on mature OHDSI open-source resources and a large body of clinical and quantitative research that the LEGEND-T2DM investigators originated and continue to drive.
- LEGEND-T2DM is dedicated to open science and transparency and will publicly share all our analytic code from reproducible cohort definitions through turn-key software,

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

enabling other research groups to leverage our methods, data, and results in order to verify and extend our findings.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1 Rationale and Background

The landscape of therapeutic options for type 2 diabetes mellitus (T2DM) has been dramatically transformed over the last decade [1]. The emergence of drugs targeting the sodium-glucose co-transporter-2 (SGLT2) and the glucagon-like peptide-1 (GLP1) receptor has expanded the role of T2DM agents from lowering blood glucose to directly reducing cardiovascular risk [2]. A series of large randomized clinical trials designed to evaluate the cardiovascular safety of SGLT2 inhibitors and GLP1 receptor agonists found that use of many of these agents led to a reduction in major adverse cardiovascular events, including myocardial infarction, hospitalization for heart failure, and cardiovascular mortality [3–6]. However, other T2DM drugs widely used before the introduction of these novel agents, such as sulfonylureas, did not undergo similarly comprehensive trials to evaluate their cardiovascular efficacy or safety. Moreover, direct comparisons of newer agents with dipeptidyl peptidase-4 (DPP4) inhibitors, with neutral effects on major cardiovascular outcomes [7–10], have not been conducted. Nevertheless, DPP4 inhibitors and sulfonylureas continue to be used in clinical practice and are recommended as second-line T2DM agents in national clinical practice guidelines.

Several challenges remain in formulating T2DM treatment recommendations based on existing evidence [11]. First, trials of novel agents did not pursue head-to-head comparisons to older agents and were instead designed as additive treatments on the background of commonly used T2DM agents. Therefore, the relative cardiovascular efficacy and safety of novel compared with older agents is not known, and indirect estimates have relied on summary-level data restricted to common comparators [12–14] and are less reliable [15,16]. Second, trials of novel agents have tested individual drugs against placebo, but have not directly compared SGLT2 inhibitors with GLP1 receptor agonists in reducing adverse cardiovascular event risk. Moreover, there is no evidence to guide the use of individual drugs within each class and across different drug classes, particularly among patients at lower cardiovascular risk than recruited in clinical trials. Third, randomized trials focused on cardiovascular efficacy and safety, but were not powered to adequately assess the safety of these agents across a spectrum of non-cardiovascular outcomes.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Finally, restricted enrollment across regions, and subgroups of age, sex, and race further limits the efficacy and safety assessment that may guide individual patients' treatment.

Evidence gaps from these trials also pose a challenge in designing treatment algorithms, which rely on comparative effectiveness and safety of drugs. Perhaps, as a result, there is large variation in clinical practice guidelines and in clinical practice with regard to these medications, with many patients initiated on the newer therapies and many others treated with older regimens [17–21]. Among the second-line options, there is much variation with respect to the order of drugs used. This lack of consensus about the best approach provides an opportunity for systematic, large-scale observational studies.

2 Study Objectives

To inform critical decisions facing patients with diabetes, their caregivers, clinicians, policymakers and healthcare system leaders, we have launched the Large-Scale Evidence Generation and Evaluation across a Network of Databases for Diabetes (LEGEND-T2DM) initiative to execute a series of comprehensive observational studies to compare cardiovascular outcome rates and safety of second-line T2DM glucose-lowering agents. Specifically, these studies aim

1. To determine, through systematic evaluation, the comparative effectiveness of traditionally second-line T2DM agents, SGLT2 inhibitors and GLP1 receptor agonists, with each other and with DPP4 inhibitors and sulfonylureas, for cardiovascular outcomes.
2. To determine, through systematic evaluation, the comparative safety of traditionally second-line T2DM agents among patients with T2DM.
3. To assess heterogeneity in effectiveness and safety of traditionally second-line T2DM agents among key patient subgroups: Using stratified patient cohorts, we will quantify differential effectiveness and safety across subgroups of patients based on age, sex, race, renal impairment, and baseline cardiovascular risk.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3 Research Methods

LEGEND-T2DM will execute three systematic, large-scale observational studies of second-line T2DM agents to estimate the relative risks of cardiovascular effectiveness and safety outcomes.

1. The **Class-vs-Class Study** will provide all pairwise comparisons between the four major T2DM agent classes to evaluate their comparative effects on cardiovascular risk (Objective 1) and patient-centered safety outcomes (Objective 2);
2. The **Drug-vs-Drug Study** will furnish head-to-head pairwise comparisons between individual agents within and across classes (both Objectives 1 and 2); and
3. The **Heterogeneity Study** will refine these comparisons for T2DM patients for important subgroups (Objective 3). In contrast to a single comparison approach, LEGEND-T2DM will provide a comprehensive view of the findings and their consistency across populations, drugs, and outcomes. We will model each study on our successful collaborative research evaluating the comparative effectiveness of antihypertensives recently published in *The Lancet* [22].

Table 1 list the four major T2DM agent classes and the individual agents licensed in the U.S. within each class. We will examine all $\binom{4}{2} = 6$ class-wise comparisons and all $\binom{5+6+4+7}{2} = 231$ ingredient-wise comparisons.

For each comparison, we are interested in the relative risk of each of the cardiovascular and safety outcomes described in the Outcomes Section.

3.1 Study Design

For each study, we will employ an active comparator, new-user cohort design [23–25]. New-user cohort design is advocated as the primary design to be considered for comparative effectiveness and drug safety [26–28]. By identifying patients who start a new treatment course and using therapy initiation as the start of follow-up, the new-user design models an randomized controlled trial (RCT) where treatment commences at the index study visit. Exploiting such an index date allows a clear separation of baseline patient

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

characteristics that occur prior to index date and are usable as covariates in the analysis without concern of inadvertently introducing mediator variables that arise between exposure and outcome [29]. Excluding prevalent users as those without a sufficient washout period prior to first exposure occurrence further reduces bias due to balancing mediators on the causal pathway, time-varying hazards, and depletion of susceptibles [28,30]. Our systematic framework across studies further will address residual confounding, publication bias, and p-hacking using data-driven, large-scale propensity adjustment for measured confounding [31], a large set of negative control outcome experiments to address unmeasured and systematic bias [32–34], and full disclosure of hypotheses tested [35]. Figure 1 illustrates our design for all studies that the following sections describe in more detail.

3.2 Data Sources

We will execute LEGEND-T2DM as a series of OHDSI network studies. All data partners within OHDSI are encouraged to participate voluntarily and can do so conveniently, because of the community's shared Observational Medical Outcomes Partnership (OMOP) common data model (CDM) and OHDSI tool-stack. Many OHDSI community data partners have already committed to participate and we will recruit further data partners through OHDSI's standard recruitment process, which includes protocol publication on OHDSI's GitHub, an announcement in OHDSI's research forum, presentation at the weekly OHDSI all-hands-on meeting and direct requests to data holders.

Table 2 lists the 13 already committed data sources for LEGEND-T2DM; these sources encompass a large variety of practice types and populations. For each data source, we report a brief description and size of the population it represents and its patient capture process and start date. While the earliest patient capture begins in 1989 (CUIMC), the vast majority come from the mid-2000s to today, providing almost two decades of T2DM treatment coverage. US populations include those commercially and publicly insured, enriched for older individuals (MDCR, VA), lower socioeconomic status (MDCD), and racially diverse (VA >20% Black or African American, CUIMC 8%). The US data sources may capture the same patients across multiple sources. Different views of the same patients are

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

an advantage in capturing the diversity of real-world health events that patients experience. Across CCAE (commercially insured), MCDR (Medicare) and MCDC (Medicaid), we expect little overlap in terms of the same observations recorded at the same time for a patient; patients can flow between sources (e.g., a CCAE patient who retires can opt-in to become an MDCR patient), but the enrollment time periods stand distinct. On the other hand, Optum, PanTher, OpenClaims, CUIMC and YNHHS may overlap in time with the other US data sources. While it remains against licensing agreements to attempt to link patients between most data sources, Optum reports <20% overlap between their claims and EHR data sources that is reassuringly small. All data sources will receive institutional review board approval or exemption for their participation before executing LEGEND-T2DM.

3.3 Study Population

We will include all subjects in a data source who meet inclusion criteria for one or more traditionally second-line T2DM agent exposure cohorts. Broadly, these cohorts will consist of T2DM patients either with or without prior metformin monotherapy who initiate treatment with one of the 22 drug ingredients that comprise the DPP4 inhibitor, GLP1 receptor agonist, SGT2 inhibitor and sulfonylurea drug classes (Table 1). We do not consider thiazolidinediones given their known association with a risk of heart failure and bladder cancer [36,37]. We describe specific definitions for exposure cohorts for each study in the following sections.

3.4 Exposure Comparators

3.4.1 Class-vs-Class Study comparisons

The **Class-vs-Class** Study will construct four exposure cohorts for new-users of any drug ingredient within the four traditionally second-line drug classes in Table 1. Cohort entry (index date) for each patient is their first observed exposure to any drug ingredient for the four second-line drug classes. Consistent with an idealized target trial for T2DM therapy and cardiovascular risk [38,39], inclusion criteria for patients based on the index date will include:

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

- T2DM diagnosis and no Type 1 or secondary diabetes mellitus diagnosis before the index date;
- At least 1 year of observation time before the index date (to improve new-user sensitivity); and
- No prior drug exposure to a comparator second-line or other antihyperglycemic agent (i.e. thiazolidinediones, acarbose, acetohexamide, bromocriptine, glibornuride, miglitol and nateglinide) or $>$ 30 days insulin exposure before index date.

We will construct and compare separately cohorts patients either with

- At least 3 months of metformin use before the index date,

or

- No prior metformin use before the index date.

In the first case, three months of metformin is consistent with ADA guidelines [40]. In the second case, we are interested in relative effectiveness and safety of these traditionally second-line agents in patients who initiate their treatments without first using metformin. We purposefully do not automatically exclude or restrict to patients with a history of myocardial infarction, stroke or other major cardiovascular events, which will allow us to report relative effectiveness and safety for individuals with both low or moderate and high cardiovascular risk. Likewise, we do not automatically exclude or restrict to individuals with severe renal impairment [41]. We will use cohort diagnostics, such as achieving covariate balance and clinical empirical equipoise between exposure cohorts (Section 4) and stakeholder input to guide the possible need to exclude other prior diagnoses, such as congestive heart failure, pancreatitis or cancer [41].

Appendix A.1 reports the complete OHDSI ATLAS cohort description for new-users of DDP4 inhibitors with prior metformin use. This description lists complete specification of cohort entry events, additional inclusion criteria, cohort exit events, and all associated standard OMOP CDM concept code sets used in the definition. We generate programmatically equivalent cohort definitions for new-others of each drug class with and without prior metformin use. ATLAS then automatically translates these definitions into network-

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

deployable SQL source code. Appendix A.2 lists the inclusion criteria modifier for no prior metformin use.

Of note, the inclusion criteria do not directly incorporate quantitative measures of poor glycemic control, such as one or more elevated serum HbA1c measurements; such laboratory values are irregularly captured in large claims and even EHR data sources. Older ADA guidelines (but not since 2020 for patients with cardiovascular disease [42]) advise escalating to a second-line agent only when glycemic control is not met with metformin monotherapy, nicely mirroring our cohort design for our historical data. We will conduct sensitivity analyses involving available HbA1c measurements to demonstrate their balance between exposure cohorts (described later in Section 4). In the unlikely event that balance is not met, we will consider an inclusion criterion of at least two HbA1c measurements $\geq$ 7% within 6 months before the index [39]. We will also conduct sensitivity analyses to assess prior insulin use exclusions, bearing in mind difficulties in assessing insulin use end-dates.

For each data source, we will then execute all $2 \times \binom{4}{2} = 6$ pairwise class comparisons for which the data source yields $\geq$ 1,000 patients in each arm. Significantly fewer numbers of patients strongly suggest data source-specific differences in prescribing practices that may introduce residual bias and sufficient samples sizes are required to construct effective propensity score models [43].

3.4.2 Drug-vs-Drug Study comparisons

The **Drug-vs-Drug Study** will construct 2×22 exposure cohorts for new-users of each drug ingredient in Table 1. We will apply the same cohort definition, inclusion criteria and patient count minimum as described in Section 3.4.1.

For each data source, we will then execute all $2 \times \binom{22}{2} = 462$ pairwise drug comparisons. While we will publicly report studies results for all pairwise comparisons, we will focus primary clinical interpretation and scientific publishing to the $2 \times \binom{5}{2}$ [within DPP4Is]

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

$+2 \times \binom{6}{2}$ [within GLPR1RAs] $+2 \times \binom{4}{2}$ [within SGLT2Is] $+2 \times \binom{7}{2}$ [within SUs] $= 104$

comparisons that pit drugs within the same class against each other, as well as across-class comparisons that stakeholders deem pertinent given their experiences.

Appendix A.5 reports the complete OHDSI ATLAS cohort description for new-users of aloglipitin with prior metformin use. Again, we programmatically construct all new-user drug-level cohort and automatically translate into SQL.

3.4.3 Heterogeneity Study comparisons

The **Heterogeneity Study** will further stratify all 237 class- and drug-level exposure cohorts in Sections 3.4.1 and 3.4.2 by clinically important patient characteristics that modify cardiovascular risk or relative treatment heterogeneity to provide patient-focused treatment recommendations. These factors will include:

- Age (18 - 44 / 45 - 64 / $\geq$ 65 at the index date)
- Gender (women / men)
- Race (African American or black)
- Cardiovascular risk (low or moderate/high, defined by established cardiovascular disease at the index date)
- Renal impairment (at the index date)

We will define patients at high cardiovascular risk as those who fulfill at index date an established cardiovascular disease (CVD) definition that has been previously developed and validated for risk stratification among new-users of second-line T2DM agents [44]. Under this definition, established CVD means having at least 1 diagnosis code for a condition indicating cardiovascular disease, such as atherosclerotic vascular disease, cerebrovascular disease, ischemic heart disease or peripheral vascular disease, or having undergone at least 1 procedure indicating cardiovascular disease, such as percutaneous coronary intervention, coronary artery bypass graft or revascularization, any time on or prior to the exposure start. Likewise, we will define renal impairment through diagnosis codes for chronic kidney disease and end-stage renal disease, dialysis procedures, and

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

laboratory measurements of estimated glomerular filtration rate, serum creatinine and urine albumin.

Appendix A.4 presents complete OHDSI ATLAS specifications for these subgroups, including all standard OMOP CDM concept codes defining cardiovascular risk and renal disease.

3.4.4 Validation

We will validate exposure cohorts and aggregate drug utilization using comprehensive cohort characterization tools against both claims and EHR data sources. Chief among these tools stands OHDSI's `CohortDiagnostic` package (github). For any cohort and data source mapped to OMOP CDM, this package systematically generates incidence new-user rates (stratified by age, gender, and calendar year), cohort characteristics (all comorbidities, drug use, procedures, health utilization) and the actual codes found in the data triggering the various rules in the cohort definitions. This can allow researchers and stakeholders to understand the heterogeneity of source coding for exposures and health outcomes as well as the impact of various inclusion criteria on overall cohort counts (details described in Section 4).

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.5 Outcomes

Across all data sources and pairwise exposure cohorts, we will assess relative risks of 32 cardiovascular and patient-centered outcomes (Table 3). Primary outcomes of interest are:

- 3-point major adverse cardiovascular events (MACE), including acute myocardial infarction, stroke, and sudden cardiac death, and
- 4-point MACE that additionally includes heart failure hospitalization.

Secondary outcomes include:

- individual MACE components,
- acute renal failure,
- revascularization

In data sources with laboratory measurements, secondary outcomes further include:

- glycemic control, and
- measured renal dysfunction

We will also study second-line T2DM drug side-effects and safety concerns highlighted in the 2018 ADA guidelines [40] and from RCTs, including:

- abnormal weight change,
- genitourinary (GU) infection,
- various cancers, and
- hypoglycemia.

We will employ the same level of systematic rigor in studying outcomes regardless of their primary or secondary label.

A majority of outcome definitions have been previously implemented and validated in our own work [22,44–48] based heavily on prior development by others (see references in Table 3 [44–101]). To assess across-source consistency and general clinical validity, we will characterize outcome incidence, stratified by age, sex and index year for each data source.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.6 Analysis

3.6.1 Contemporary utilization of drug classes and individual agents

For all cohorts in the three studies, we will describe overall utilization as well as temporal trends in the use of each drug class and agents within the class. Further, we will evaluate these trends in patient groups by age (18-44 / 45-64 / ≥ 65 years), gender, race and geographic regions. Since the emergence of novel medications in the management of type 2 DM in 2014, there has been a rapid expansion in both the number of drug classes and individual agents. These data will provide insight into the current patterns of use and possible disparities. These data are critical to guide the real-world application of treatment decision pathways for the treatment of T2DM patients.

Specifically, we will calculate and validate aggregate drug utilization using the OHDSI's CohortDiagnostic package against both claims and EHR data sources. The CohortDiagnostics package works in two steps: 1) Generate the utilization results and diagnostics against a data source and 2) Explore the generated utilization and diagnostics in a user-friendly graphical interface R-Shiny app. Through the interface, one can explore patient profiles of a random sample of subjects in a cohort. These diagnostics provide a consistent methodology to evaluate cohort definitions/phenotype algorithms across a variety of observational databases. This will enable researchers and stakeholders to become informed on the appropriateness of including specific data sources within analyses, exposing potential risks related to heterogeneity and variability in patient care delivery that, when not addressed in the design, could result in errors such as highly correlated covariates in propensity score matching of a target and a comparator cohort. Thus, the added value of this approach is two-fold in terms of exposing data quality for a study question and ensuring face validity checks are performed on proposed covariates to be used for balancing propensity scores.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.6.2 Relative risk of cardiovascular and patient-centered outcomes

For all three studies, we will execute a systematic process to estimate the relative risk of cardiovascular and patient-centered outcomes between new-users of second-line T2DM agents. The process will adjust for measured confounding, control from further residual (unmeasured) bias and accommodate important design choices to best emulate the nearly impossible to execute, idealized RCT that our stakeholders envision across data source populations, comparators, outcomes and subgroups.

To adjust for potential measured confounding and improve the balance between cohorts, we will build large-scale propensity score (PS) models [102] for each pairwise comparison and data source using a consistent data-driven process through regularized regression [31]. This process engineers a large set of predefined baseline patient characteristics, including age, gender, race, index month/year and other demographics and prior conditions, drug exposures, procedures, laboratory measurements and health service utilization behaviors, to provide the most accurate prediction of treatment and balance patient cohorts across many characteristics. Construction of condition, drug, procedures and observations include occurrences within 365, 180 and 30 days prior to index date and are aggregated at several SNOMED (conditions) and ingredient/ATC class (drugs) levels. Other demographic measures include comorbidity risk scores (Charlson, DCSI, CHADS2, CHAD2VASc). From prior work, feature counts have ranged in the 1,000s - 10,000s, and these large-scale PS models have outperformed hdPS [103] in simulation and real-world examples [31].

We will:

- Exclude patients who have experienced the outcome prior to their index date,
- Stratify and variable-ratio match patients by PS, and
- Use Cox proportional hazards models

to estimate hazard ratios (HRs) between alternative target and comparator treatments for the risk of each outcome in each data source. The regression will condition on the PS strata/matching-unit with treatment allocation as the sole explanatory variable and censor

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

patients at the end of their time-at-risk (TAR) or data source observation period. We will prefer stratification over matching if both sufficiently balance patients (see Section 4), as the former optimizes patient inclusions and thus generalizability.

We will execute each comparison using three different TAR definitions, reflecting different and important causal contrasts:

- Intent-to-treat (TAR: index + 1 → end of observation) captures both direct treatment effects and (long-term) behavioral/treatment changes that initial assignment triggers [104];
- On-treatment-1 (TAR: index + 1 → treatment discontinuation) is more patient-centered [105] and captures direct treatment effect while allowing for escalation with additional T2DM agents; and
- On-treatment-2 (TAR: index + 1 → discontinuation or escalation with T2DM agents) carries the least possible confounding with other concurrent T2DM agents.

Our "on-treatment" is often called "per-protocol" [106]. Systematically executing with multiple causal contrasts enables us to identify potential biases that missing prescription data, treatment escalation and behavioral changes introduce, while preserving the ease of intent-to-treat interpretation and power if the data demonstrate them as unbiased. Appendix A.3 reports the modified cohort exit rule for the on-treatment-2 TAR.

We will aggregate HR estimates across non-overlapping data sources to produce meta-analytic estimates using a random-effects meta-analysis [107]. This classic meta-analysis assumes that per-data source likelihoods are approximately normally distributed [108]. This assumption fails when outcomes are rare as we expect for some safety events. Here, our recent research shows that as the number of data sources increases, the non-normality effect increases to where coverage of 95% confidence intervals (CIs) can be as low as 5%. To counter this, we will also apply a Bayesian meta-analysis model [109,110] that neither assumes normality nor requires patient-level data sharing by building on composite likelihood methods [111] and enables us to introduce appropriate overlap weights between data sources.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Residual study bias from unmeasured and systematic sources often remains in observational studies even after controlling for measured confounding through PS-adjustment [32,33]. For each comparison-outcome effect, we will conduct negative control (falsification) outcome experiments, where the null hypothesis of no effect is believed to be true, using approximately 100 controls. We identified these controls through a data-rich algorithm [112] that identifies prevalent OMOP condition concept occurrences that lack evidence of association with exposures in published literature, drug-product labeling and spontaneous reports, and were then adjudicated by clinical review. We previously validated 60 of the controls in LEGEND-HTN [22]. Appendix C lists these negative controls and their OMOP condition concept IDs.

Using the empirical null distributions from these experiments, we will calibrate each study effect HR estimate, its 95% CI and the p-value to reject the null hypothesis of no differential effect [34]. We will declare an HR as significantly different from no effect when its calibrated $p < 0.05$ without correcting for multiple testing. Finally, blinded to all trial results, study investigators will evaluate study diagnostics for all comparisons to assess if they were likely to yield unbiased estimates (Section 4).

3.6.3 Sensitivity analyses and missingness

Because of the potential confounding effect of glycemic control at baseline between treatment choice and outcomes and to better understand the impact of limited glucose level measurements on effectiveness and safety estimation that arises in administrative claims and some EHR data, we will perform pre-specified sensitivity analyses for all studies within data sources that contain reliable glucose or hemoglobin A1c measurements. Within a study, for each exposure pair, we will first rebuild PS models where we additionally include baseline glucose or hemoglobin A1c measurements as patient characteristics, stratify or match patients under the new PS models that directly adjust for potential confounding by glycemic control and then estimate effectiveness and safety HRs.

A limitation of the Cox model is that no doubly robust procedure is believed to exist for estimating HRs, due to their non-collapsibility [113]. Doubly robust procedures combine baseline patient characteristic-adjusted outcome and PS models to control for confounding

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

and, in theory, remain unbiased when either (but not necessarily both) model is correctly specified [114]. Doubly robust procedures do exist for hazard differences [113] and we will validate the appropriateness of our univariable Cox modeling by comparing estimate differences under an additive hazards model [116] with and without doubly robust-adjustment [117]. In practice, however, neither the outcome nor PS model is correctly specified, leading to systematic error in the observational setting.

Missing data of potential concern are patient demographics (gender, age, race) for our inclusion criteria. We will include only individuals whose baseline eligibility can be characterized that will most notably influence race subgroup assessments in the **Heterogeneity Study**. No further missing data can arise in our large-scale PS models because all features, with the exception of demographics, simply indicate the presence or absence of health records in a given time-period. Finally, we limit the impact of missing data, such as prescription information, relating to exposure time-at-risk by entertaining multiple definitions [29]. In all reports, we will clearly tabulate numbers of missing observations and patient attrition.

4 Sample Size and Study Power

Within each data source, we will execute all comparisons with $\geq$ 1,000 eligible patients per arm. Blinded to effect estimates, investigators and stakeholders will evaluate extensive study diagnostics for each comparison to assess reliability and generalizability, and only report risk estimates that pass [25,35]. These diagnostics will include

1. Minimum detectable risk ratio (MDRR) as a typical proxy for power,
2. Preference score distributions to evaluate empirical equipoise10 and population generalizability,
3. Extensive patient characteristics to evaluate cohort balance before and after PS-adjustment,
4. Negative control calibration plots to assess residual bias, and
5. Kaplan-Meier plots to examine hazard ratio proportionality assumptions.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

We will define cohorts to stand in empirical equipoise if the majority of patients carry preference scores between 0.3 and 0.7 and to achieve balance if all after-adjustment characteristics return absolute standardized mean differences < 0.1 [118].

5 Strengths and Limitations

5.1 Strengths

LEGEND-T2DM is, to our knowledge, the largest and most comprehensive study to provide evidence about the comparative effectiveness and safety of second-line T2DM agents. The LEGEND-T2DM studies will encompass over 1 million patients initiating second-line T2DM agents across at least 13 databases from 5 countries and will examine all pairwise comparisons between the four second-line drug classes against a panel of TODO health outcomes. Through an international network, LEGEND-T2DM seeks to take advantage of disparate health databases drawn from different sources and across a range of countries and practice settings. These large-scale and unfiltered populations better represent real-world practice than the restricted study populations in prescribed treatment and follow-up settings from RCTs. Our use of the OMOP CDM allows extension of the LEGEND-T2DM experiment to future databases and allows replication of these results on licensable databases that were used in this experiment, while still maintaining patient privacy on patient-level data.

LEGEND-T2DM further advances the statistically rigorous and empirically validated methods we have developed in OHDSI that specifically address bias inherent in observational studies and allow for reliable causal inference. Patient characteristics and their treatment choices are likely to confound comparative effectiveness and safety estimates. Our approach combines active comparator new-user designs that emulate randomized clinical trials with large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, and full disclosure of hypotheses tested.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Each LEGEND-T2DM aim will represent evidence synthesis from a large number of bespoke studies across multiple data sources. Addressing questions one bespoke study at a time is prone to errors arising from multiple testing, random variation in effect estimates and publication bias. LEGEND-T2DM is designed to avoid these concerns through methodologic best practices [119] with full study diagnostics and external replication.

Through open science, LEGEND-T2DM will allow any interested investigators to engage as partners in our work at many levels. We will publicly develop all protocols and analytic code. This invites additional data custodians to participate in LEGEND-T2DM and enables others to modify and reuse our approach for other investigations. We will also host real-time access to all study result artifacts for outside analysis and interpretation. Such an open science framework ensures a feed-forward effect on other scientific contributions in the community. Collectively, LEGEND-T2DM will generate patient-centered, high quality, generalizable evidence that will transform the clinical management of T2DM through our active collaboration with patients, clinicians, and national medical societies. LEGEND-T2DM will spur scientific innovation through the generation of open-source resources in data science.

5.2 Limitations

Even though many potential confounders will be included in these studies, there may be residual bias due to unmeasured or misspecified confounders, such as confounding by indication, differences in physician characteristics that may be associated with drug choice, concomitant use of other drugs started after the index date, and informative censoring at the end of the on-treatment periods. To minimize this risk, we will use methods to detect residual bias through a large number of negative and positive controls.

Ideal negative controls carry identical confounding between exposures and the outcome of interest [120]. The true confounding structure, however, is unknowable. Instead of attempting to find the elusive perfect negative control, we will rely on a large sample of controls that represent a wide range of confounding structures. If a study comparison proves to be unbiased for all negative controls, we can feel confident that it will also be

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

unbiased for the outcome of interest. In our previous studies [22,25,121], using the active comparator, new-user cohort design we will employ here, we have observed minimal residual bias using negative controls. This stands in stark contrast to other designs such as the (nested) case-control that tends to show large residual bias because of incomparable exposure cohorts implied by the design [122].

Observed follow-up times are limited and variable, potentially reducing power to detect differences in effectiveness and safety and, further, misclassification of study variables is unavoidable in secondary use of health data, so it is possible to misclassify treatments, covariates, and outcomes. Based on our previous successful studies on antihypertensives, we do not expect differential misclassification, and therefore bias will most likely be towards the null. Finally, the electronic health record databases may be missing care episodes for patients due to care outside the respective health systems. Such bias, however, will also most likely be towards the null.

6 Protection of Human Subjects

LEGEND-T2DM does not involve human subjects research. The project does, however, use human data collected during routine healthcare provision. Most often the data are de-identified within data source. All data partners executing the LEGEND-T2DM studies within their data sources will have received institutional review board (IRB) approval or waiver for participation in accordance to their institutional governance prior to execution (see Table 4). LEGEND-T2DM executes across a federated and distributed data network, where analysis code is sent to participating data partners and only aggregate summary statistics are returned, with no sharing of patient-level data between organizations.

7 Management and Reporting of Adverse Events and Adverse Reactions

LEGEND-T2DM uses coded data that already exist in electronic databases. In these types of databases, it is not usually possible to link (i.e., identify a potential causal association

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

between) a particular product and medical event for any specific individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product and event) are not available and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important findings.

8 Patient and Public Involvement

No patient was involved in the study.

9 Plans for Disseminating and Communicating Study Results

Open science aims to make scientific research, including its data process and software, and its dissemination, through publication and presentation, accessible to all levels of an inquiring society, amateur or professional [123] and is a governing principle of LEGEND-T2DM. Open science delivers reproducible, transparent and reliable evidence. All aspects of LEGEND-T2DM (except private patient data) will be open and we will actively encourage other interested researchers, clinicians and patients to participate. This differs fundamentally from traditional studies that rarely open their analytic tools or share all result artifacts, and inform the community about hard-to-verify conclusions at completion.

9.1 Transparent and re-usable research tools

We will publicly register this protocol and announce its availability for feedback from stakeholders, the OHDSI community and within clinical professional societies. This protocol will link to open source code for all steps to generating diagnostics, effect estimates, figures and tables. Such transparency is possible because we will construct our studies on top of the OHDSI toolstack of open source software tools that are community developed and rigorously tested [25]. We will publicly host LEGEND-T2DM source code at (https://github.com/ohdsi-studies/LegendT2dm), allowing public contribution and review, and free re-use for anyone's future research.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

9.2 Continuous sharing of results

LEGEND-T2DM embodies a new approach to generating evidence from healthcare data that overcome weaknesses in the current process of answering and publishing (or not) one question at a time. Generating evidence for thousands of research and control questions using a systematic process enables us to not only evaluate that process and the coherence and consistency of the evidence, but also to avoid *p*-hacking and publication bias [35]. We will store and openly communicate all of these results as they become available using a user-friendly web-based app that serves up all descriptive statistics, study diagnostics and effect estimates for each cohort comparison and outcome. Open access to this app will be through a general public facing LEGEND-T2DM webpage.

9.3 Scientific meetings and publications

We will deliver multiple presentations annually at scientific venues including the annual meetings of the American Diabetes Association, American College of Cardiology, American Heart Association and American Medical Informatics Association. We will also prepare multiple scientific publications for clinical, informatics and statistical journals.

9.4 General public

We believe in sharing our findings that will guide clinical care with the general public. LEGEND-T2DM will use social-media (Twitter) to facilitate this. With dedicated support from the OHDSI communications specialist, we will deliver regular press releases at key project stages, distributed via the extensive media networks of UCLA, Columbia and Yale.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Acknowledgements

Author contributions:

RK and **MAS** conceived the research and drafted the proposal in consultation with **MJS**, **YL**, **AO**, **RC**, **GH**, **PBR**, and **HMK**, who provided critical feedback on the research proposal.

Funding Statement:

The proposal was partially funded through the National Institutes of Health grants K23 HL153775 and R01 LM006910 and an Intergovernmental Personnel Act agreement with the US Department of Veterans Affairs.
The funders had no role in the design and conduct of the proposal; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interest statement

This study is undertaken within Observational Health Data Sciences and Informatics (OHDSI), an open collaboration. **RK** is a founder of Evidence2Health, and receives grant funding from the US National Institutes of Health. **MJS** and **PBR** are employees of Janssen Research and Development and shareholders in John & Johnson. **GH** receives grant funding from the US National Institutes of Health and the US Food & Drug Administration and contracts from Janssen Research and Development. **HMK** receives grants from the US Food & Drug Administration, Medtronics and Janssen Research and Development, is co-founder of HugoHealth and chairs the Cardiac Scientific Advisory Board for UnitedHealth. **MAS** receives grant funding from the US National Institutes of Health, the US Department of Veterans Affairs and the US Food & Drug Administration and contracts from Janssen Research and Development and IQVIA.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

References

1 Lo C, Toyama T, Wang Y *et al.* Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane database of systematic reviews* 2018.

2 North EJ, Newman JD. Review of cardiovascular outcomes trials of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Current opinion in cardiology* 2019;**34**:687–92.

3 Zinman B, Wanner C, Lachin JM *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England journal of medicine* 2015;**373**:2117–28.

4 Neal B, Perkovic V, Mahaffey KW *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *The New England journal of medicine* 2017;**377**:644–57.

5 Marso SP, Daniels GH, Brown-Frandsen K *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *The New England journal of medicine* 2016;**375**:311–22.

6 Marso SP, Bain SC, Consoli A *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *The New England journal of medicine* 2016;**375**:1834–44.

7 Scirica BM, Bhatt DL, Braunwald E *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *The New England journal of medicine* 2013;**369**:1317–26.

8 White WB, Cannon CP, Heller SR *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *The New England journal of medicine* 2013;**369**:1327–35.

9 Green JB, Bethel MA, Armstrong PW *et al.* Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *The New England journal of medicine* 2015;**373**:232–42.

10 Rosenstock J, Kahn SE, Johansen OE *et al.* Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA randomized clinical trial. *JAMA: the journal of the American Medical Association* 2019.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

11 Cefalu WT, Kaul S, Gerstein HC *et al.* Cardiovascular outcomes trials in type 2 diabetes: Where do we go from here? Reflections from aDiabetes CareEditors' expert forum. Diabetes Care. 2018;**41**:14–31.

12 Palmer SC, Tendal B, Mustafa RA *et al.* Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: Systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;**372**:m4573.

13 Qiu M, Ding L-L, Wei X-B *et al.* Comparative efficacy of glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular events in type 2 diabetes: A network meta-analysis. *Journal of cardiovascular pharmacology* 2021;**77**:34–7.

14 Yamada T, Wakabayashi M, Bhalla A *et al.* Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and network meta-analysis. *Cardiovascular diabetology* 2021;**20**:14.

15 Puhan MA, Schünemann HJ, Murad MH *et al.* A GRADE working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630.

16 Brignardello-Petersen R, Izcovich A, Rochwerg B *et al.* GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. *BMJ* 2020;**371**:m3907.

17 McCoy RG, Dykhoff HJ, Sangaralingham L *et al.* Adoption of new Glucose-Lowering medications in the U.S.-The case of SGLT2 inhibitors: Nationwide cohort study. *Diabetes technology & therapeutics* 2019;**21**:702–12.

18 Curtis HJ, Dennis JM, Shields BM *et al.* Time trends and geographical variation in prescribing of drugs for diabetes in england from 1998 to 2017. *Diabetes, obesity & metabolism* 2018;**20**:2159–68.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

19 Arnold SV, Inzucchi SE, Tang F *et al.* Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR research to practice project. *European journal of preventive cardiology* 2017;**24**:1637–45.

20 Dave CV, Schneeweiss S, Wexler DJ *et al.* Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013-2018. *Diabetes care* 2020;**43**:921–4.

21 Le P, Chaitoff A, Misra-Hebert AD *et al.* Use of antihyperglycemic medications in U.S. Adults: An analysis of the national health and nutrition examination survey. *Diabetes care* 2020;**43**:1227–33.

22 Suchard MA, Schuemie MJ, Krumholz HM *et al.* Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: A systematic, multinational, large-scale analysis. *The Lancet* 2019;**394**:1816–26.

23 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nature reviews Rheumatology* 2015;**11**:437–41.

24 Ryan PB, Schuemie MJ, Gruber S *et al.* Empirical performance of a new user cohort method: Lessons for developing a risk identification and analysis system. *Drug safety: an international journal of medical toxicology and drug experience* 2013;**36 Suppl 1**:S59–72.

25 Schuemie MJ, Cepeda MS, Suchard MA *et al.* How confident are we about observational findings in health care: A benchmark study. *Harvard Data Science Review* 2020;**2**.

26 Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiology and drug safety* 2010;**19**:858–68.

27 Gagne JJ, Fireman B, Ryan PB *et al.* Design considerations in an active medical product safety monitoring system. *Pharmacoepidemiology and drug safety* 2012;**21 Suppl 1**:32–40.

28 Johnson ES, Bartman BA, Briesacher BA *et al.* The incident user design in comparative effectiveness research. *Pharmacoepidemiology and drug safety* 2013;**22**:1–6.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

29 Schneeweiss S, Patrick AR, Stürmer T *et al.* Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Medical care* 2007;**45**:S131–42.

30 Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and Drug Safety. 2017;**26**:459–68.

31 Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *International journal of epidemiology* 2018;**47**:2005–14.

32 Schuemie MJ, Ryan PB, DuMouchel W *et al.* Interpreting observational studies: Why empirical calibration is needed to correct p-values. *Statistics in Medicine* 2014;**33**:209–18.

33 Schuemie MJ, Hripcsak G, Ryan PB *et al.* Robust empirical calibration of p -values using observational data. Statistics in Medicine. 2016;**35**:3883–8.

34 Schuemie MJ, Hripcsak G, Ryan PB *et al.* Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proceedings of the National Academy of Sciences of the United States of America* 2018;**115**:2571–7.

35 Schuemie MJ, Ryan PB, Hripcsak G *et al.* Improving reproducibility by using high-throughput observational studies with empirical calibration. *Philosophical transactions Series A, Mathematical, physical, and engineering sciences* 2018;**376**.

36 Graham DJ, Ouellet-Hellstrom R, MaCurdy TE *et al.* Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. *JAMA: the journal of the American Medical Association* 2010;**304**:411–8.

37 Turner RM, Kwok CS, Chen-Turner C *et al.* Thiazolidinediones and associated risk of bladder cancer: A systematic review and meta-analysis. *British journal of clinical pharmacology* 2014;**78**:258–73.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

38 Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *American Journal of Epidemiology* 2016;**183**:758–64.

39 Hernán, Miguel. Antihyperglycemic therapy and cardiovascular risk: Design and emulation of a target trial using healthcare databases. Patient-Centered Outcomes Research Institute 2019.

40 American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2018. *Diabetes care* 2018;**41**:S73–85.

41 Nathan DM, Buse JB, Kahn SE *et al.* Rationale and design of the glycemia reduction approaches in diabetes: A comparative effectiveness study (GRADE). *Diabetes care* 2013;**36**:2254–61.

42 Association AD, American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2020. Diabetes Care. 2020;**43**:S98–S110.

43 Schuemie MJ, Ryan PB, Pratt N *et al.* Large-Scale evidence generation and evaluation across a network of databases (LEGEND): Assessing validity using hypertension as a case study. *Journal of the American Medical Informatics Association*;**ocaa124**.

44 Ryan PB, Buse JB, Schuemie MJ *et al.* Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes, obesity & metabolism* 2018;**20**:2585–2597. doi: 10.1111/dom.13424. Epub 2018 Jun 25.

45 You SC, Rho Y, Bikdeli B *et al.* Association of ticagrelor versus clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention in clinical practice. *Journal of the American Medical Association*;in press.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

46 Wang Y, Desai M, Ryan PB *et al.* Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes research and clinical practice* 2017;**128**:83–90.

47 Weinstein RB, Ryan PB, Berlin JA *et al.* Channeling bias in the analysis of risk of myocardial infarction, stroke, gastrointestinal bleeding, and acute renal failure with the use of paracetamol compared with ibuprofen. *Drug safety: an international journal of medical toxicology and drug experience* 2020.

48 Yuan Z, DeFalco FJ, Ryan PB *et al.* Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study. *Diabetes, obesity & metabolism* 2018;**20**:582–9.

49 Ammann EM, Schweizer ML, Robinson JG *et al.* Chart validation of inpatient ICD-9-CM administrative diagnosis codes for acute myocardial infarction (AMI) among intravenous immune globulin (IGIV) users in the sentinel distributed database. *Pharmacoepidemiology and drug safety* 2018;**27**:398–404. doi: 10.1002/pds.4398. Epub 2018 Feb 15.

50 Floyd JS, Blondon M, Moore KP *et al.* Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of veterans with diabetes. *Pharmacoepidemiology and drug safety* 2016;**25**:467–71. doi: 10.1002/pds.3921. Epub 2015 Nov 11.

51 Rubbo B, Fitzpatrick NK, Denaxas S *et al.* Use of electronic health records to ascertain, validate and phenotype acute myocardial infarction: A systematic review and recommendations. *International journal of cardiology* 2015;**187:705-11.**:10.1016/j.ijcard.2015.03.075. Epub 2015 Mar 5.

52 Singh S, Fouayzi H, Anzuoni K *et al.* Diagnostic algorithms for cardiovascular death in administrative claims databases: A systematic review. *Drug safety: an international journal of medical toxicology and drug experience* 2018;**23**:018–0754.

53 Wahl PM, Rodgers K, Schneeweiss S *et al.* Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

commercially-insured population. *Pharmacoepidemiology and drug safety* 2010;**19**:596–603. doi: 10.1002/pds.1924.

54 Normand SL, Morris CN, Fung KS *et al.* Development and validation of a claims based index for adjusting for risk of mortality: The case of acute myocardial infarction. *Journal of clinical epidemiology* 1995;**48**:229–43.

55 Andrade SE, Harrold LR, Tjia J *et al.* A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiology and drug safety* 2012;**21**:100–28. doi: 10.1002/pds.2312.

56 Park TH, Choi JC. Validation of stroke and thrombolytic therapy in korean national health insurance claim data. *Journal of clinical neurology* 2016;**12**:42–8. doi: 10.3988/jcn.2016.12.1.42. Epub 2015 Sep 11.

57 Gon Y, Kabata D, Yamamoto K *et al.* Validation of an algorithm that determines stroke diagnostic code accuracy in a japanese hospital-based cancer registry using electronic medical records. *BMC medical informatics and decision making* 2017;**17**:157. doi: 10.1186/s12911–017–0554–x.

58 Sung SF, Hsieh CY, Lin HJ *et al.* Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. *International journal of cardiology* 2016;**215:277-82.**:10.1016/j.ijcard.2016.04.069. Epub 2016 Apr 14.

59 Tu K, Wang M, Young J *et al.* Validity of administrative data for identifying patients who have had a stroke or transient ischemic attack using EMRALD as a reference standard. *The Canadian journal of cardiology* 2013;**29**:1388–94. doi: 10.1016/j.cjca.2013.07.676. Epub 2013 Sep 26.

60 Yuan Z, Voss EA, DeFalco FJ *et al.* Risk prediction for ischemic stroke and transient ischemic attack in patients without atrial fibrillation: A retrospective cohort study. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association* 2017;**26**:1721–1731. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.036. Epub 2017 Apr 6.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

61 Hennessy S, Leonard CE, Freeman CP *et al.* Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in medicaid and medicare claims data. *Pharmacoepidemiology and drug safety* 2010;**19**:555–62. doi: 10.1002/pds.1869.

62 Kaspar M, Fette G, Guder G *et al.* Underestimated prevalence of heart failure in hospital inpatients: A comparison of ICD codes and discharge letter information. *Clinical research in cardiology: official journal of the German Cardiac Society* 2018;**107**:778–787. doi: 10.1007/s00392–018–1245–z.Epub 2018 Apr 17.

63 Feder SL, Redeker NS, Jeon S *et al.* Validation of the ICD-9 diagnostic code for palliative care in patients hospitalized with heart failure within the veterans health administration. *The American journal of hospice & palliative care* 2018;**35**:959–965. doi: 10.1177/1049909117747519. Epub 2017 Dec 18.

64 Rosenman M, He J, Martin J *et al.* Database queries for hospitalizations for acute congestive heart failure: Flexible methods and validation based on set theory. *Journal of the American Medical Informatics Association: JAMIA* 2014;**21**:345–52. doi: 10.1136/amiajnl–2013–001942.Epub 2013 Oct 10.

65 Voors AA, Ouwerkerk W, Zannad F *et al.* Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *European journal of heart failure* 2017;**19**:627–634. doi: 10.1002/ejhf.785. Epub 2017 Mar 1.

66 Floyd JS, Wellman R, Fuller S *et al.* Use of electronic health data to estimate heart failure events in a Population-Based cohort with CKD. *Clinical journal of the American Society of Nephrology: CJASN* 2016;**11**:1954–1961. doi: 10.2215/CJN.03900416. Epub 2016 Aug 9.

67 Gini R, Schuemie MJ, Mazzaglia G *et al.* Automatic identification of type 2 diabetes, hypertension, ischaemic heart disease, heart failure and their levels of severity from italian general practitioners' electronic medical records: A validation study. *BMJ open* 2016;**6**:e012413. doi: 10.1136/bmjopen–2016–012413.

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

68 Afzal Z, Schuemie MJ, Blijderveen JC van *et al.* Improving sensitivity of machine learning methods for automated case identification from free-text electronic medical records. *BMC medical informatics and decision making* 2013;**13:30.**:10.1186/1472–6947–13–30.

69 Lenihan CR, Montez-Rath ME, Mora Mangano CT *et al.* Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. *The Annals of thoracic surgery* 2013;**95**:20–8. doi: 10.1016/j.athoracsur.2012.05.131. Epub 2012 Dec 25.

70 Winkelmayer WC, Schneeweiss S, Mogun H *et al.* Identification of individuals with CKD from medicare claims data: A validation study. *American journal of kidney diseases: the official journal of the National Kidney Foundation* 2005;**46**:225–32. doi: 10.1053/j.ajkd.2005.04.029.

71 Grams ME, Waikar SS, MacMahon B *et al.* Performance and limitations of administrative data in the identification of AKI. *Clinical journal of the American Society of Nephrology: CJASN* 2014;**9**:682–9. doi: 10.2215/CJN.07650713. Epub 2014 Jan 23.

72 Arnold J, Ng KP, Sims D *et al.* Incidence and impact on outcomes of acute kidney injury after a stroke: A systematic review and meta-analysis. *BMC nephrology* 2018;**19**:283. doi: 10.1186/s12882–018–1085–0.

73 Sutherland SM, Byrnes JJ, Kothari M *et al.* AKI in hospitalized children: Comparing the pRIFLE, AKIN, and KDIGO definitions. *Clinical journal of the American Society of Nephrology: CJASN* 2015;**10**:554–61. doi: 10.2215/CJN.01900214. Epub 2015 Feb 3.

74 Waikar SS, Wald R, Chertow GM *et al.* Validity of international classification of diseases, ninth revision, clinical modification codes for acute renal failure. *Journal of the American Society of Nephrology: JASN* 2006;**17**:1688–94. doi: 10.1681/ASN.2006010073. Epub 2006 Apr 26.

75 Rhee C, Murphy MV, Li L *et al.* Improving documentation and coding for acute organ dysfunction biases estimates of changing sepsis severity and burden: A retrospective study. *Critical care / the Society of Critical Care Medicine* 2015;**19:338.**:10.1186/s13054–015–1048–9.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

76 Vashisht R, Jung K, Schuler A *et al.* Association of hemoglobin a1c levels with use of sulfonylureas, dipeptidyl peptidase 4 inhibitors, and thiazolidinediones in patients with type 2 diabetes treated with metformin: Analysis from the observational health data sciences and informatics initiative. *JAMA network open* 2018;**1**:e181755–5.

77 Broder MS, Chang E, Cherepanov D *et al.* Identification of potential markers for cushing disease. *Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2016;**22**:567–74. doi: 10.4158/EP15914.OR. Epub 2016 Jan 20.

78 Williams BA. The clinical epidemiology of fatigue in newly diagnosed heart failure. *BMC cardiovascular disorders* 2017;**17**:122. doi: 10.1186/s12872–017–0555–9.

79 Yabe D, Kuwata H, Kaneko M *et al.* Use of the japanese health insurance claims database to assess the risk of acute pancreatitis in patients with diabetes: Comparison of DPP-4 inhibitors with other oral antidiabetic drugs. *Diabetes, obesity & metabolism* 2015;**17**:430–4. doi: 10.1111/dom.12381. Epub 2014 Sep 17.

80 Dore DD, Hussein M, Hoffman C *et al.* A pooled analysis of exenatide use and risk of acute pancreatitis. *Current medical research and opinion* 2013;**29**:1577–86. doi: 10.1185/03007995.2013.838550. Epub 2013 Sep 13.

81 Dore DD, Chaudhry S, Hoffman C *et al.* Stratum-specific positive predictive values of claims for acute pancreatitis among commercial health insurance plan enrollees with diabetes mellitus. *Pharmacoepidemiology and drug safety* 2011;**20**:209–13. doi: 10.1002/pds.2077. Epub 2010 Dec 23.

82 Chen HJ, Wang JJ, Tsay WI *et al.* Epidemiology and outcome of acute pancreatitis in end-stage renal disease dialysis patients: A 10-year national cohort study. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association* 2017;**32**:1731–1736. doi: 10.1093/ndt/gfw400.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

83 Ooba N, Setoguchi S, Ando T *et al.* Claims-based definition of death in japanese claims database: Validity and implications. *PLoS One* 2013;**8**:e66116. doi: 10.1371/journal.pone.0066116. Print 2013.

84 Robinson TE, Elley CR, Kenealy T *et al.* Development and validation of a predictive risk model for all-cause mortality in type 2 diabetes. *Diabetes Res Clin Pract* 2015;**108**:482–8. doi: 10.1016/j.diabres.2015.02.015. Epub 2015 Mar 16.

85 Wang L, Voss EA, Weaver J *et al.* Diabetic ketoacidosis in patients with type 2 diabetes treated with sodium glucose co-transporter 2 inhibitors versus other antihyperglycemic agents: An observational study of four us administrative claims databases. *Pharmacoepidemiology and Drug Safety* 2019;**28**:1620–8.

86 Buono JL, Mathur K, Averitt AJ *et al.* Economic burden of irritable bowel syndrome with diarrhea: Retrospective analysis of a U.S. Commercially insured population. *J Manag Care Spec Pharm* 2017;**23**:453–460. doi: 10.18553/jmcp.2016.16138. Epub 2016 Nov 21.

87 Krishnarajah G, Duh MS, Korves C *et al.* Public health impact of complete and incomplete rotavirus vaccination among commercially and medicaid insured children in the united states. *PloS one* 2016;**11**:e0145977. doi: 10.1371/journal.pone.0145977. eCollection 2016.

88 Panozzo CA, Becker-Dreps S, Pate V *et al.* Direct, indirect, total, and overall effectiveness of the rotavirus vaccines for the prevention of gastroenteritis hospitalizations in privately insured US children, 2007-2010. *American Journal of Epidemiology* 2014;**179**:895–909. doi: 10.1093/aje/kwu001. Epub 2014 Feb 26.

89 Nichols GA, Brodovicz KG, Kimes TM *et al.* Prevalence and incidence of urinary tract and genital infections among patients with and without type 2 diabetes. *Journal of diabetes and its complications* 2017;**31**:1587–91.

90 Abbas S, Ihle P, Harder S *et al.* Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: A population- and insurance-based cohort. *Pharmacoepidemiol Drug Saf* 2015;**24**:406–13. doi: 10.1002/pds.3748. Epub 2015 Feb 12.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

91 Betts KA, Woolley JM, Mu F *et al.* The prevalence of hyperkalemia in the united states. *Curr Med Res Opin* 2018;**34**:971–978. doi: 10.1080/03007995.2018.1433141. Epub 2018 Feb 21.

92 Fitch K, Woolley JM, Engel T *et al.* The clinical and economic burden of hyperkalemia on medicare and commercial payers. *Am Health Drug Benefits* 2017;**10**:202–210.

93 Leonard CE, Han X, Brensinger CM *et al.* Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. *Pharmacoepidemiology and Drug Safety* 2018;**27**:9–18.

94 Chrischilles E, Rubenstein L, Chao J *et al.* Initiation of nonselective alpha1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: A retrospective cohort study. *Clinical therapeutics* 2001;**23**:727–43.

95 Goldstein JL, Zhao SZ, Burke TA *et al.* Incidence of outpatient physician claims for upper gastrointestinal symptoms among new users of celecoxib, ibuprofen, and naproxen in an insured population in the united states. *The American journal of gastroenterology* 2003;**98**:2627–34. doi: 10.1111/j.1572–0241.2003.08722.x.

96 Donga PZ, Bilir SP, Little G *et al.* Comparative treatment-related adverse event cost burden in immune thrombocytopenic purpura. *Journal of medical economics* 2017;**20**:1200–1206. doi: 10.1080/13696998.2017.1370425. Epub 2017 Sep 8.

97 Marrett E, Kwong WJ, Frech F *et al.* Health care utilization and costs associated with nausea and vomiting in patients receiving oral Immediate-Release opioids for outpatient acute pain management. *Pain Ther* 2016;**5**:215–226. doi: 10.1007/s40122–016–0057–y.Epub 2016 Oct 4.

98 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;**21**:154–62. doi: 10.1002/pds.2341.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

99 Burwen DR, Wu C, Cirillo D *et al.* Venous thromboembolism incidence, recurrence, and mortality based on women's health initiative data and medicare claims. *Thromb Res* 2017;**150:78-85.**:10.1016/j.thromres.2016.11.015. Epub 2016 Nov 15.

100 Coleman CI, Peacock WF, Fermann GJ *et al.* External validation of a multivariable claims-based rule for predicting in-hospital mortality and 30-day post-pulmonary embolism complications. *BMC Health Serv Res* 2016;**16**:610. doi: 10.1186/s12913–016–1855–y.

101 Ammann EM, Cuker A, Carnahan RM *et al.* Chart validation of inpatient international classification of diseases, ninth revision, clinical modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the sentinel distributed database. *Medicine* 2018;**97**:e9960. doi: 10.1097/MD.0000000000009960.

102 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.

103 Schneeweiss S, Rassen JA, Glynn RJ *et al.* High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;**20**:512.

104 Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clinical trials* 2012;**9**:48–55.

105 Murray EJ, Caniglia EC, Swanson SA *et al.* Patients and investigators prefer measures of absolute risk in subgroups for pragmatic randomized trials. *Journal of Clinical Epidemiology* 2018;**103**:10–21.

106 Hernán MA, Robins JM. Per-Protocol analyses of pragmatic trials. *The New England journal of medicine* 2017;**377**:1391–8.

107 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;**7**:177–88.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

108 Gronsbell J, Hong C, Nie L *et al.* Exact inference for the random-effect model for meta-analyses with rare events. *Statistics in Medicine* 2020;**39**:252–64.

109 Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society Series A,* 2009;**172**:137–59.

110 Schuemie MJ, Chen Y, Madigan D *et al.* Combining cox regressions across a heterogeneous distributed research network facing small and zero counts. 2021.http://arxiv.org/abs/2101.01551

111 Varin C, Reid N, Firth D. An overview of composite likelihood methods. *Statistica Sinica* 2011.

112 Voss EA, Boyce RD, Ryan PB *et al.* Accuracy of an automated knowledge base for identifying drug adverse reactions. *Journal of Biomedical Informatics* 2017;**66**:72–81.

113 Dukes O, Martinussen T, Tchetgen Tchetgen EJ *et al.* On doubly robust estimation of the hazard difference. *Biometrics* 2019;**75**:100–9.

114 Funk MJ, Westreich D, Wiesen C *et al.* Doubly robust estimation of causal effects. *American Journal of Epidemiology* 2011;**173**:761–7.

115 Martinussen T, Vansteelandt S, Gerster M *et al.* Estimation of direct effects for survival data by using the aalen additive hazards model. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2011;**73**:773–88.

116 Aalen OO. A linear regression model for the analysis of life times. *Statistics in Medicine* 1989;**8**:907–25.

117 Wang Y, Lee M, Liu P *et al.* Doubly robust additive hazards models to estimate effects of a continuous exposure on survival. *Epidemiology (Cambridge, Mass)* 2017;**28**:771.

118 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine* 2009;**28**:3083–107.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

119 Schuemie MJ, Ryan PB, Pratt N *et al.* Large-Scale evidence generation and evaluation across a network of databases (LEGEND): Principles and methods. *Journal of the American Medical Informatics Association*;**ocaa103**.

120 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;**21**:383–8.

121 Hripcsak G, Suchard MA, Shea S *et al.* Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension. *JAMA internal medicine* 2020.

122 Schuemie MJ, Ryan PB, Man KKC *et al.* A plea to stop using the case-control design in retrospective database studies. *Statistics in Medicine* 2019;**38**:4199–208.

123 Woelfle M, Olliaro P, Todd MH. Open science is a research accelerator. *Nature Chemistry* 2011;**3**:745–8.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

FIGURE LEGENDS

Figure 1: *Schematic of LEGEND-T2DM new-user cohort design for the Class-vs-Class, Drug-vs-Drug and Heterogeneity studies.*

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 1: *T2DM drug classes and individual agents within each class*

DPP4 inhibitors	GLP1 receptor antagonists	SGLT2 inhibitors	Sulfonylureas
alogliptin	albiglutide	canagliflozin	chlorpropamide
linagliptin	dulaglutide	dapagliflozin	glimepiride
saxagliptin	exenatide	empagliflozin	glipizide
sitagliptin	liraglutide	ertugliflozin	gliquidone
vildagliptin	lixisenatide		glyburide
	semaglutide		tolazamide
			tolbutamide

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 2: *Committed LEGEND-T2DM data sources and the populations they cover.*

Data source	Population	Patients	History	Data capture process and short description
IBM MarketScan Commercial Claims and Encounters (CCAE)	Commercially insured, < 65 years	142M	2000 –	Adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents.
IBM MarketScan Medicare Supplemental Database (MDCR)	Commercially insured, 65 + years	10M	2000 –	Adjudicated health insurance claims of retirees with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans.
IBM MarketScan Multi-State Medicaid Database (MDCD)	Medicaid enrollees, racially diverse	26M	2006 –	Adjudicated health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims.
IQVIA Open Claims (IOC)	General	160M	2010 –	Pre-adjudicated claims at the anonymized patient-level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.
Japan Medical Data Center (JMDC)	Japan, general	5.5M	2005 –	Data from 60 society-managed health insurance plans covering workers aged 18 to 65 and their dependents.
Korea National Health Insurance Service (NHIS)	2% random sample of South Korea	1M	2002 –	National administrative claims database covering the South Korean population.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Optum Clinformatics Data Mart (Optum)	Commercially or Medicare insured	85M	2000 –	Inpatient and outpatient healthcare insurance claims.
Columbia University Irving Medical Center (CIUMC)	Academic medical center patients, racially diverse	6M	1989 –	General practice, specialists and inpatient hospital services from the New York-Presbyterian hospital and affiliated academic physician practices in New York.
Department of Veterans Affairs (VA)	Veterans, older, racially diverse	12M	2000 –	National VA health care system, the largest integrated provider of medical services in the US, provided at 170 VA medical centers and 1,063 outpatient sites.
Information System for Research in Primary Care (SIDIAP)	80% of all Catalonia (Spain)	7.7M	2006 –	Primary care partially linked to inpatient data with pharmacy dispensations and primary care laboratories. Healthcare is universal and taxpayer funded in the region, and PCPs are gatekeeps for all care and responsible for repeat prescriptions.
IQVIA Disease Analyzer Germany (DAG)	Germany, general	37M	1992 –	Collection from patient management software used by general practitioners and selected specialists to document patients' medical records within their office-based practice during a visit.
Optum Electronic Health Records (OptumEHR)	US, general	93M	2006 –	Clinical information, prescriptions, lab results, vital signs, body measurements, diagnoses and procedures derived from clinical notes using natural language processing.
Yale New Haven Health System (YNHHS)	Academic medical center patients	2M	2013 –	General practice, specialists and inpatient hospital services from the YNHHS in Connecticut.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 3: *LEGEND-T2DM study outcomes*

Phenotype	Brief logical description	Prior development
3-point MACE	Condition record of acute myocardial infarction, hemorrhagic or ischemic stroke or sudden cardiac death during an inpatient or ER visit	[49–61]
4-point MACE	3-Point MACE + inpatient or ER visit (hospitalization) with heart failure condition record	[44,49–67]
Acute myocardial infarction	Condition record of acute myocardial infarction during an inpatient or ER vist	[49–54]
Acute renal failure	Condition record of acute renal failure during an inpatient or ER visit	[47,68–75]
Glycemic control	First hemoglobin A1c measurement with value $\leq$ 7%	[76]
Hospitalization with heart failure	Inpatient or ER visit with heart failure condition record	[44,62–67]
Measured renal dysfunction	First creatinine measurement with value > 3 mg/dL	[75]
Revascularization	Procedure record of percutaneous coronary intervention or coronary artery bypass grafting during an inpatient or ER visit	[45]
Stroke	Condition record of hemorrhagic or ischemic stroke during an inpatient or ER visit	[55–60]
Sudden cardiac death	Condition record of sudden cardiac death during an inpatient or ER visit	[52,61]
Abnormal weight gain	Abnormal weight gain record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[77]
Abnormal weight loss	Abnormal weight loss record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[78]
Acute pancreatitis	Condition record of acute pancreatitis during an inpatient or ER visit	[79–82]
All-cause mortality	Death record of any type	[52,83,84]
Bladder cancer	Malignant tumor of urinary bladder condition record of any type; limited to earliest event per person	

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Bone fracture	Bone fracture condition record of any type; successive records with > 90 day gap are considered independent episodes	
Breast cancer	Malignant tumor of breast condition record of any type; limited to earliest event per person	
Diabetic ketoacidosis	Diabetic ketoacidosis condition record during an inpatient or ER visit	[46,85]
Diarrhea	Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes	[86–88]
Genitourinary infection	Condition record of any type of genital or urinary tract infection during an outpatient or ER vists	[89]
Hyperkalemia	Condition record for hyperkalemia or potassium measurements > 5.6 mmol/L; successive records with >90 day gap are considered independent episodes	[90–92]
Hypoglycemia	Hypoglycemia condition record of any type; successive records with > 90 day gap are considered independent episodes	[93]
Hypotension	Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes	[94]
Joint pain	Joint pain condition record of any type; successive records with > 90 days gap are considered independent episodes	
Lower extremity amputation	Procedure record of below knee lower extremity amputation during inpatient or outpatient visit	[44,48]
Nausea	Nausea condition record of any type; successive records with > 30 day gap are considered independent episodes	[95–97]
Peripheral edema	Edema condition record of any type; successive records with > 180 day gap are considered independent episodes	
Photosensitivity	Condition record of drug-induced photosensitivity during any type of visit	
Renal cancer	Primary malignant neoplasm of kidney condition record of any type; limited to earliest event per person	
Thyroid tumor	Neoplasm of thyroid gland condition record of any type; limited to earliest event per person	

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Venous thromboembolism	Venous thromboembolism condition record of any type; successive records with > 180 day gap are considered independent episodes	[98–101]
Vomiting	Vomiting condition record of any type; successive records with > 30 day gap are considered independent episodes	[95–97]

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 4: *IRB approval or waiver statement from partners.*

Data source	Statement
IBM MarketScan Commercial Claims and Encounters (CCAE)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Medicare Supplemental Database (MDCR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Multi-State Medicaid Database (MDCD)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IQVIA Open Claims (IOC)	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI network studies.
Japan Medical Data Center (JMDC)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Korea National Health Insurance Service (NHIS)	Ajou University Institutional Review Board (AJIRB-MED-EXP-17-054 for LEGEND-HTN) and approval expected shortly for LEGEND-T2DM.
Optum Clinformatics Data Mart (Optum)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Columbia University Irving Medical Center (CIUMC)	Use of the CUIMC data source was approved by the Columbia University Institutional Review Board as an OHDSI network study (IRB# AAAO7805).
Department of Veterans Affairs (VA)	Use of the VA-OMOP data source was reviewed by the Department of Veterans Affairs Central Institutional Review Board (IRB) and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization.
Information System for Research in Primary Care (SIDIAP)	Use of the SIDIAP data source was approved by the Clinical Research Ethics Committee of IDIAPJGol (project code: 20/070-PCV)
IQVIA Disease Analyzer Germany (DAG)	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI network studies.
Optum Electronic Health Records (OptumEHR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

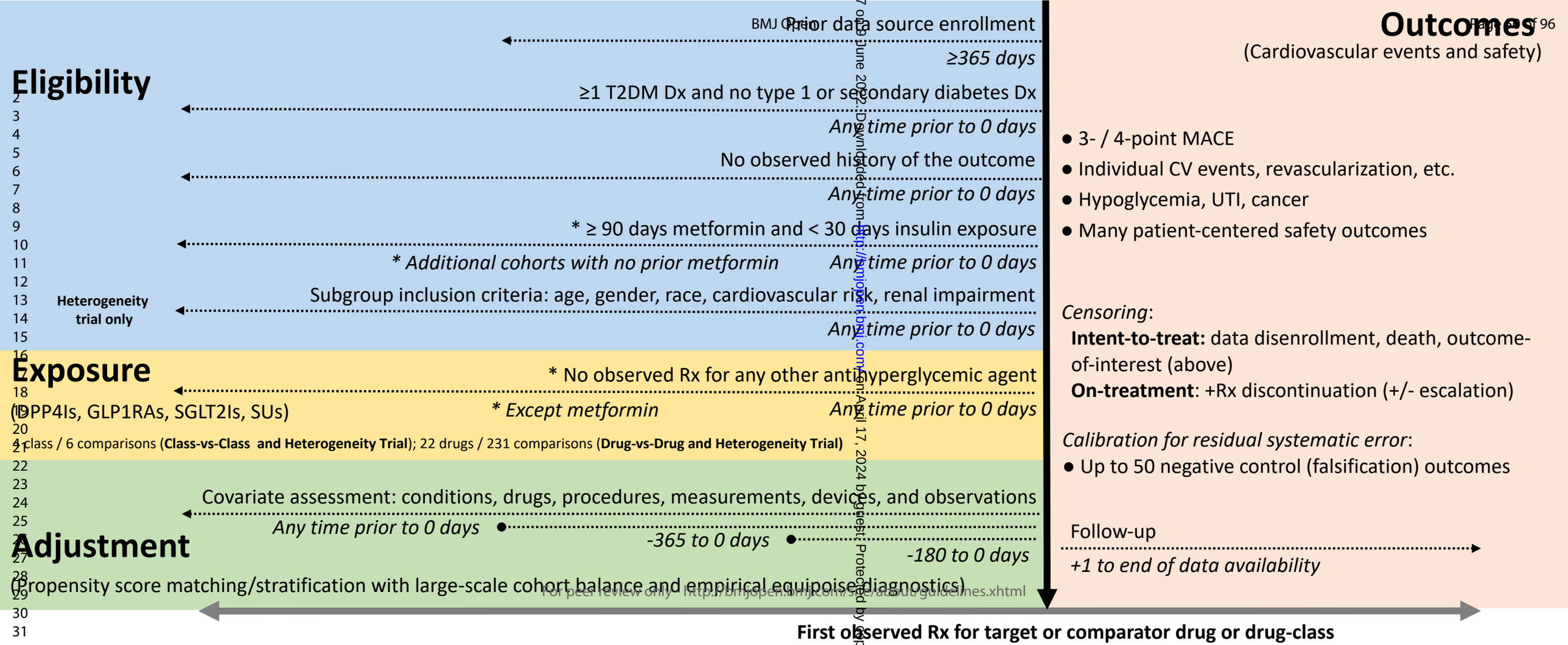
For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Yale New Haven Health System (YNHHS)	Use of the YNHHS EHR data source was approved by the Yale University Institutional Review Board as an OHDSI network study (IRB# pending).

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
http://bmjopen.bmj.com/ on April 17, 2024 by guest.
Downloaded from
7 obs. 8 June 2022.

Appendix

A Exposure Cohort Definitions

A.1 Class-vs-Class Exposure (DPP4 New-User) Cohort / OT1

A.1.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'DPP4 inhibitors' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.

A.1.2 Additional Inclusion Criteria

- No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SU exposure

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Entry events having no drug exposures of 'Sulfonylureas', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior other anti-diabetic exposure

Entry events having no drug exposures of 'Other anti-diabetics', starting anytime on or before cohort entry start date; allow events outside observation period.

- Prior metformin use

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin', starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events with all of the following criteria:

1. having no drug eras of 'Insulin', starting anytime up to 30 days before cohort entry start date; allow events outside observation period; with era length > 30 days.
2. having no drug eras of 'Insulin', starting between 30 days before and 0 days after cohort entry start date; allow events outside observation period.

A.1.3 Cohort Exit

The cohort end date will be based on a continuous exposure to 'DPP4 inhibitors': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

A.1.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.1.5 Concept: DPP4 inhibitors

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

A.1.6 Concept: GLP-1 receptor agonists

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
40170911	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO

A.1.7 Concept: SGLT2 inhibitors

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO

A.1.8 Concept: Sulfonylureas

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
19097821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

A.1.9 Concept: Other anti-diabetics

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1529331	acarbose	16681	RxNorm	NO	YES	NO
1530014	acetohexamide	173	RxNorm	NO	YES	NO
730548	bromocriptine	1760	RxNorm	NO	YES	NO
19033498	carbutamide	2068	RxNorm	NO	YES	NO
19001409	glibornuride	102846	RxNorm	NO	YES	NO
19059796	gliclazide	4816	RxNorm	NO	YES	NO
19001441	glymidine	102848	RxNorm	NO	YES	NO
1510202	miglitol	30009	RxNorm	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1502826	nateglinide	274332	RxNorm	NO	YES	NO
1525215	pioglitazone	33738	RxNorm	NO	YES	NO
1516766	repaglinide	73044	RxNorm	NO	YES	NO
1547504	rosiglitazone	84108	RxNorm	NO	YES	NO
1515249	troglitazone	72610	RxNorm	NO	YES	NO

A.1.10 Concept: Insulin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1596977	insulin, regular, human	253182	RxNorm	NO	YES	NO
1550023	insulin lispro	86009	RxNorm	NO	YES	NO
1567198	insulin aspart, human	51428	RxNorm	NO	YES	NO
1502905	insulin glargine	274783	RxNorm	NO	YES	NO
1513876	insulin lispro protamine, human	314684	RxNorm	NO	YES	NO
1531601	insulin aspart protamine, human	352385	RxNorm	NO	YES	NO
1586346	insulin, regular, pork	221109	RxNorm	NO	YES	NO
1544838	insulin glulisine, human	400008	RxNorm	NO	YES	NO
1516976	insulin detemir	139825	RxNorm	NO	YES	NO
1590165	insulin, regular, beef-pork	235275	RxNorm	NO	YES	NO
1513849	lente insulin, human	314683	RxNorm	NO	YES	NO
1562586	lente insulin, pork	93108	RxNorm	NO	YES	NO
1588986	insulin human, rDNA origin	631657	RxNorm	NO	YES	NO
1513843	lente insulin, beef-pork	314682	RxNorm	NO	YES	NO
1586369	ultralente insulin, human	221110	RxNorm	NO	YES	NO
35605670	insulin argine	1740938	RxNorm	NO	YES	NO
35602717	insulin degludec	1670007	RxNorm	NO	YES	NO
21600713	INSULINS AND ANALOGUES	A10A	ATC	NO	YES	NO
19078608	insulin, protamine zinc, beef-pork 100 UNT/ML Injectable Suspension	311053	RxNorm	NO	YES	NO

A.1.11 Concept: Metformin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1503297	metformin	6809	RxNorm	NO	YES	NO

A.1.12 Concept: Secondary diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
195771	Secondary diabetes mellitus	8801005	SNOMED	NO	YES	NO

A.1.13 Concept: Type 1 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201254	Type 1 diabetes mellitus	46635009	SNOMED	NO	YES	NO
435216	Disorder due to type 1 diabetes mellitus	420868002	SNOMED	NO	YES	NO
200687	Renal disorder due to type 1 diabetes mellitus	421893009	SNOMED	NO	YES	NO
377821	Disorder of nervous system due to type 1 diabetes mellitus	421468001	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

318712	Peripheral circulatory disorder due to type 1 diabetes mellitus	421365002	SNOMED	NO	YES	NO

A.1.14 Concept: Type 2 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201826	Type 2 diabetes mellitus	44054006	SNOMED	NO	YES	NO
443734	Ketoacidosis due to type 2 diabetes mellitus	421750000	SNOMED	NO	YES	NO
443767	Disorder of eye due to diabetes mellitus	25093002	SNOMED	NO	YES	NO
192279	Disorder of kidney due to diabetes mellitus	127013003	SNOMED	NO	YES	NO
443735	Coma due to diabetes mellitus	420662003	SNOMED	NO	YES	NO
376065	Disorder of nervous system due to type 2 diabetes mellitus	421326000	SNOMED	NO	YES	NO
443729	Peripheral circulatory disorder due to type 2 diabetes mellitus	422166005	SNOMED	NO	YES	NO
443732	Disorder due to type 2 diabetes mellitus	422014003	SNOMED	NO	YES	NO

A.2 Metformin Use Modifier

A.2.1 No prior metformin use

Entry events having no drug eras of 'Metformin', starting anytime on or before cohort entry start date; allow events outside observation period.

A.3 Escalation Exit Criteria

The cohort end date will be based on a continuous exposure to 'DPP4 inhibitors': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

The person also exists the cohort when encountering any of the following events:

1. drug exposures of 'All alternative target exposures'.
2. drug exposures of 'Other anti-diabetics'.
3. drug eras of 'Insulin', with era length > 30 days.

A.3.1 Concept: All alternative target exposures

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
19097821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
40170911	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

A.4 Heterogenity Study Inclusion Criteria

A.4.1 Lower age group

Entry events with the following event criteria: who are < 45 years old.

A.4.2 Middle age group

Entry events with all of the following criteria:

1. with the following event criteria: who are >= 45 years old.
2. with the following event criteria: who are < 65 years old.

A.4.3 Older age group

Entry events with the following event criteria: who are >= 65 years old.

A.4.4 Female stratum

Entry events with the following event criteria: who are female.

A.4.5 Male stratum

Entry events with the following event criteria: who are male.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.4.6 Race stratum

Entry events with the following event criteria: race is: “black or african american”, “black”, “african american”, “african”, “bahamian”, “barbadian”, “dominican”, “dominica islander”, “haitian”, “jamaican”, “tobagoan”, “trinidadian” or “west indian”.

A.4.7 Low cardiovascular risk

Entry events with all of the following criteria:

1. having no condition occurrences of ‘Conditions indicating established cardiovascular disease’, starting anytime on or before cohort entry start date; allow events outside observation period.
2. having no procedure occurrences of ‘Procedures indicating established cardiovascular disease’, starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.8 Higher cardiovascular risk

Entry events with any of the following criteria:

1. having at least 1 condition occurrence of ‘Conditions indicating established cardiovascular disease’, starting anytime on or before cohort entry start date; allow events outside observation period.
2. having at least 1 procedure occurrence of ‘Procedures indicating established cardiovascular disease’, starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.9 Concept: Conditions indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
319844	Acute ischemic heart disease	413439005	SNOMED	NO	YES	NO
321318	Angina pectoris	194828000	SNOMED	NO	YES	NO
4124841	Aortic bifurcation syndrome	233972005	SNOMED	YES	YES	NO
312337	Arterial embolus and thrombosis	266262004	SNOMED	NO	YES	NO
4278217	Arterial thrombosis	65198009	SNOMED	NO	YES	NO
40484167	Arteriosclerosis of artery of extremity	443971004	SNOMED	NO	YES	NO
318443	Arteriosclerotic vascular disease	72092001	SNOMED	NO	YES	NO
314659	Arteritis	52089001	SNOMED	NO	NO	NO
40479625	Atherosclerosis of artery	441574008	SNOMED	NO	YES	NO
40484541	Atherosclerosis of autologous vein bypass graft of limb	442693003	SNOMED	YES	YES	NO
312902	Benign intracranial hypertension	68267002	SNOMED	YES	YES	NO
4288310	Carotid artery obstruction	69798007	SNOMED	YES	YES	NO
372924	Cerebral artery occlusion	20059004	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

376713	Cerebral hemorrhage	274100004	SNOMED	NO	YES	NO
381591	Cerebrovascular disease	62914000	SNOMED	NO	YES	NO
316494	Cerebrovascular disorder in the puerperium	6594005	SNOMED	YES	YES	NO
315286	Chronic ischemic heart disease	413838009	SNOMED	NO	YES	NO
44782819	Chronic occlusion of artery of extremity	698816006	SNOMED	NO	YES	NO
4313767	Chronic peripheral venous hypertension	423674003	SNOMED	YES	YES	NO
372721	Congenital anomaly of cerebrovascular system	65587001	SNOMED	YES	YES	NO
316995	Coronary occlusion	63739005	SNOMED	NO	YES	NO
134057	Disorder of cardiovascular system	49601007	SNOMED	NO	NO	NO
40480453	Disorder of vein of lower extremity	441739009	SNOMED	YES	YES	NO
46272492	Dissection of artery	710864009	SNOMED	YES	YES	NO
4324690	Fracture of skull	71642004	SNOMED	YES	YES	NO
441246	Hemangioma of intracranial structure	93468003	SNOMED	YES	YES	NO
380113	Hemorrhage in optic nerve sheaths	14460007	SNOMED	YES	YES	NO
192763	Injury of blood vessel	57662003	SNOMED	YES	YES	NO
4275428	Injury of vein	64583005	SNOMED	YES	YES	NO
442774	Intermittent claudication	63491006	SNOMED	NO	YES	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	YES	NO
434056	Late effects of cerebrovascular disease	195239002	SNOMED	NO	YES	NO
4146311	Leriche's syndrome	307816004	SNOMED	NO	YES	NO
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4296029	Periarteritis	76805007	SNOMED	NO	YES	NO
260841	Perinatal subarachnoid hemorrhage	21202004	SNOMED	YES	YES	NO
317309	Peripheral arterial occlusive disease	399957001	SNOMED	NO	YES	NO
321822	Peripheral vascular disorder due to diabetes mellitus	421895002	SNOMED	NO	YES	NO
313928	Peripheral vascular complication	10596002	SNOMED	NO	YES	NO
321052	Peripheral vascular disease	400047006	SNOMED	NO	NO	NO
44782775	Peripheral vascular disease associated with another disorder	34881000119105	SNOMED	NO	YES	NO
318137	Phlebitis and thrombophlebitis of intracranial sinuses	192753009	SNOMED	YES	YES	NO
441039	Phlebitis of lower limb vein	312588002	SNOMED	NO	YES	NO
4067424	Polyarteritis	20258000	SNOMED	NO	YES	NO
320749	Polyarteritis nodosa	155441006	SNOMED	YES	YES	NO
443239	Precerebral arterial occlusion	266253001	SNOMED	NO	YES	NO
440417	Pulmonary embolism	59282003	SNOMED	YES	YES	NO
4318842	Renal vasculitis	95578000	SNOMED	NO	YES	NO
380943	Rupture of syphilitic cerebral aneurysm	186893003	SNOMED	YES	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO
320741	Thrombophlebitis	64156001	SNOMED	YES	YES	NO
4141106	Thrombosis of arteries of the extremities	33591000	SNOMED	NO	YES	NO
4132546	Traumatic brain injury	127295002	SNOMED	YES	YES	NO
4194610	Trunk arterial embolus	312593004	SNOMED	NO	YES	NO
318169	Varicose veins of lower extremity	72866009	SNOMED	YES	YES	NO
4189293	Vascular disorder of lower extremity	373408007	SNOMED	NO	YES	NO
443752	Ventricular hemorrhage	23276006	SNOMED	YES	YES	NO
432346	Dissection of vertebral artery	230730001	SNOMED	YES	YES	NO

A.4.10 Concept: Procedures indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4150819	Operative procedure on coronary artery	31413008	SNOMED	NO	YES	NO
4331725	Operative procedure on artery of extremity	22701007	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.4.11 Without renal impairment

Entry events having no condition occurrences of 'Renal impairment', starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.12 Renal impairment

Entry events having at least 1 condition occurrence of 'Renal impairment', starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.13 Concept: Renal impairment

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4030518	Renal impairment	236423003	SNOMED	NO	YES	NO

A.5 Drug-vs-Drug Exposure (Alogliptin New-User) Cohort / OT1

A.5.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'alogliptin' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus', starting anytime on or before cohort entry start date; allow events outside observation period.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.5.2 Additional Inclusion Criteria

- No prior with-in class exposure

Entry events having no drug exposures of 'DPP4 inhibitors excluding alogliptin', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SU exposure

Entry events having no drug exposures of 'Sulfonylureas', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior other anti-diabetic exposure

Entry events having no drug exposures of 'Other anti-diabetics', starting anytime on or before cohort entry start date; allow events outside observation period.

- Prior metformin use

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin', starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin', starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events having no drug eras of 'Insulin', starting anytime on or before cohort entry start date; allow events outside observation period; with era length > 30 days.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.5.3 Cohort Exit

The cohort end date will be based on a continuous exposure to 'alogliptin': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

A.5.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.5.5 Concept: alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO

A.5.6 Concept: DPP4 inhibitors excluding alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

B Outcome Cohort Definitions

B.1 3-point MACE

B.1.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction'.
2. condition occurrences of 'Sudden cardiac death'.
3. condition occurrences of 'Ischemic stroke'.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4. condition occurrences of ' Intracranial bleed Hemorrhagic stroke'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.1.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.1.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.1.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.1.5 Concept: Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.1.6 Concept: Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

B.1.7 Concept: Ischemic stroke

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO

B.1.8 Concept: Intracranial bleed Hemorrhagic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO
43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.1.9 Concept: Heart Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

B.2 4-point MACE

B.2.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Acute myocardial Infarction’.
2. condition occurrences of ‘Sudden cardiac death’.
3. condition occurrences of ‘Ischemic stroke’.
4. condition occurrences of ‘lintracranial bleed Hemorrhagic stroke’.
5. condition occurrences of ‘Heart Failure’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.2.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.2.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.2.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.2.5 Concept: Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.2.6 Concept: Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

B.2.7 Concept: Ischemic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO

B.2.8 Concept: Iintracranial bleed Hemorrhagic stroke

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO
43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.2.9 Concept: Heart Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

B.3 Acute myocardial infarction

B.3.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND-T2DM] Acute myocardial Infarction'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.3.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.3.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

B.3.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.3.5 Concept: [LEGEND-T2DM] Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.4 Acute renal failure

B.4.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Acute Renal Failure’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or ER visit’, starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.4.2 Cohort Exit

The cohort end date will be offset from index event’s start date plus 30 days.

B.4.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

B.4.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.4.5 Concept: Acute Renal Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
197320	Acute renal failure syndrome	14669001	SNOMED	NO	YES	NO
432961	Acute renal papillary necrosis with renal failure	298015003	SNOMED	NO	YES	NO
444044	Acute tubular necrosis	35455006	SNOMED	NO	YES	NO

B.5 Glycemic control

B.5.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. measurements of 'HbA1c_v2', numeric value <= 7; unit: "percent".
2. measurements of 'HbA1c_v2', numeric value <= 53; unit: "millimole per mole".

Limit qualifying entry events to the earliest event per person.

B.5.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.5.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.5.4 Concept: HbA1c_v2

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
3004410	Hemoglobin A1c (Glycated)	4548-4	LOINC	NO	YES	NO
3007263	Hemoglobin A1c/Hemoglobin.total in Blood by calculation	17855-8	LOINC	NO	YES	NO
3003309	Hemoglobin A1c/Hemoglobin.total in Blood by Electrophoresis	4549-2	LOINC	NO	YES	NO
3005673	Hemoglobin A1c/Hemoglobin.total in Blood by HPLC	17856-6	LOINC	NO	YES	NO
40762352	Hemoglobin A1c/Hemoglobin.total in Blood by IFCC protocol	59261-8	LOINC	NO	YES	NO
40758583	Hemoglobin A1c in Blood	55454-3	LOINC	NO	YES	NO
3034639	Hemoglobin A1c [Mass/volume] in Blood	41995-2	LOINC	NO	YES	NO

B.6 Hospitalization with heart failure

B.6.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. visit occurrences of 'Inpatient or ER visit'; having at least 1 condition occurrence of '[LEGEND-T2DM] Heart Failure', starting between 0 days before and all days after 'Inpatient or ER visit' start date and starting anytime on or before 'Inpatient or ER visit' end date.

B.6.2 Cohort Exit

The cohort end date will be offset from index event's end date plus 0 days.

B.6.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 7 days of each other.

B.6.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.6.5 Concept: [LEGEND-T2DM] Heart Failure

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

B.7 Measured renal dysfunction

B.7.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. measurements of 'Creatinine measurement', numeric value > 3; unit: "milligram per deciliter".
2. measurements of 'Creatinine measurement', numeric value > 265; unit: "micro-mole/liter".
3. measurements of 'Creatinine measurement', numeric value > 0.265; unit: "millimole per liter".
4. measurements of 'Creatinine measurement', numeric value > 3; unit: "milligram".

Limit cohort entry events to the earliest event per person.

B.7.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.7.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.7.4 Concept: Creatinine measurement

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
3016723	Creatinine [Mass/volume] in Serum or Plasma	2160-0	LOINC	NO	YES	NO
3022243	Creatinine [Mass/volume] in Serum or Plasma –pre dialysis	11042-9	LOINC	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3020564	Creatinine [Moles/volume] in Serum or Plasma	14682-9	LOINC	NO	YES	NO

B.8 Revascularization

B.8.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. procedure occurrences of 'PCI'.
2. procedure occurrences of 'CABG'.

B.8.2 Additional Inclusion Criteria

- Hospitalization

Entry events having at least 1 visit occurrence of 'Hospitalization', starting between 0 days before and 0 days after cohort entry start date.

B.8.3 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.8.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.8.5 Concept: PCI

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4006788	Percutaneous transluminal coronary angioplasty	11101003	SNOMED	NO	YES	NO
4264285	Percutaneous transluminal coronary angioplasty by rotoablation	397193006	SNOMED	NO	YES	NO
4265293	Percutaneous transluminal coronary angioplasty with rotoablation, single vessel	397431004	SNOMED	NO	YES	NO
4225903	Percutaneous transluminal coronary angioplasty, multiple vessels	85053006	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4283892	Placement of stent in coronary artery	36969009	SNOMED	NO	YES	NO
4337738	Percutaneous endarterectomy of coronary artery	232726007	SNOMED	NO	YES	NO
4139198	Percutaneous transluminal thrombolysis of artery	426485003	SNOMED	NO	YES	NO
44511532	Percutaneous transluminal thrombolysis of artery	L71.6	OPCS4	NO	YES	NO
45770795	Percutaneous transluminal balloon angioplasty and insertion of drug eluting stent into coronary artery	936451000000108	SNOMED	NO	YES	NO
44789455	Insertion of drug-eluting coronary artery stent	203741000000101	SNOMED	NO	NO	NO
44784573	Percutaneous transluminal atherectomy of coronary artery by rotary cutter using fluoroscopic guidance	698740005	SNOMED	NO	YES	NO
44512256	Percutaneous transluminal arterial thrombolysis and reconstruction	L66.1	OPCS4	NO	YES	NO
44511273	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	K75.9	OPCS4	NO	YES	NO
44511272	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	K75.8	OPCS4	NO	NO	NO
44511271	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC	K75.4	OPCS4	NO	YES	NO
44511269	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery	K75.2	OPCS4	NO	YES	NO
44511268	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery	K75.1	OPCS4	NO	YES	NO
44511133	Other specified transluminal balloon angioplasty of coronary artery	K49.8	OPCS4	NO	NO	NO
44511131	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	K49.3	OPCS4	NO	YES	NO
44511130	Percutaneous transluminal balloon angioplasty of multiple coronary arteries	K49.2	OPCS4	NO	YES	NO
43533353	Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	C9602	HCPCS	NO	YES	NO
43533352	Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	C9601	HCPCS	NO	NO	NO
43533248	Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	C9603	HCPCS	NO	YES	NO
43533247	Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	C9600	HCPCS	NO	NO	NO
43531440	Percutaneous transluminal insertion of metal stent into coronary artery using fluoroscopic guidance	609154002	SNOMED	NO	YES	NO
43531439	Percutaneous insertion of drug eluting stent into coronary artery using fluoroscopic guidance	609153008	SNOMED	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

43531438	Percutaneous insertion of stent into aneurysm of coronary artery using fluoroscopic guidance	609152003	SNOMED	NO	NO	NO
4329263	Placement of stent in circumflex branch of left coronary artery	429499003	SNOMED	NO	YES	NO
4328103	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty	75761004	SNOMED	NO	NO	NO
4264286	Percutaneous rotational coronary endarterectomy	397194000	SNOMED	NO	NO	NO
4238755	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty, single vessel	91338001	SNOMED	NO	NO	NO
4216356	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty, multiple vessels	80762004	SNOMED	NO	NO	NO
4214516	Insertion of drug coated stent	414509005	SNOMED	NO	NO	NO
4181025	Percutaneous transluminal balloon angioplasty with insertion of stent into coronary artery	429639007	SNOMED	NO	YES	NO
4178148	Placement of stent in anterior descending branch of left coronary artery	428488008	SNOMED	NO	YES	NO
4175997	Percutaneous transluminal thrombolysis and reconstruction of artery	428068004	SNOMED	NO	YES	NO
4171077	Fluoroscopic angiography of coronary artery and insertion of stent	418982001	SNOMED	NO	NO	NO
4020653	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	175066001	SNOMED	NO	YES	NO
2001506	Insertion of drug-eluting coronary artery stent(s)	36.07	ICD9Proc	NO	NO	NO
2001505	Insertion of non-drug-eluting coronary artery stent(s)	36.06	ICD9Proc	NO	NO	NO
2000064	Percutaneous transluminal coronary angioplasty [PTCA]	00.66	ICD9Proc	NO	YES	NO
2001500	Single vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy without mention of thrombolytic agent	36.01	ICD9Proc	NO	YES	NO
2001504	Multiple vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy performed during the same operation, with or without mention of thrombolytic agent	36.05	ICD9Proc	NO	NO	NO
2001501	Single vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy with mention of thrombolytic agent	36.02	ICD9Proc	NO	YES	NO

B.8.6 Concept: Hospitalization

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.8.7 Concept: CABG

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
2001516	Abdominal-coronary artery bypass	36.17	ICD9Proc	NO	YES	NO
4284104	Aortocoronary artery bypass graft	67166004.00	SNOMED	NO	YES	NO
4229433	Aortocoronary artery bypass graft with prosthesis	8876004.00	SNOMED	NO	YES	NO
4146972	Aortocoronary artery bypass graft with saphenous vein graft	3546002.00	SNOMED	NO	YES	NO
4228305	Aortocoronary artery bypass graft with three vein grafts	405599002.00	SNOMED	NO	YES	NO
4228304	Aortocoronary artery bypass graft with two vein grafts	405598005.00	SNOMED	NO	YES	NO
4063237	Aortocoronary artery bypass graft with vein graft	17073005.00	SNOMED	NO	YES	NO
4148030	Aortocoronary bypass grafting	309814006.00	SNOMED	NO	YES	NO
4008625	Aortocoronary bypass of four or more coronary arteries	10190003.00	SNOMED	NO	YES	NO
4106548	Aortocoronary bypass of one coronary artery	29819009.00	SNOMED	NO	YES	NO
4031996	Aortocoronary bypass of three coronary arteries	14323007.00	SNOMED	NO	YES	NO
4234990	Aortocoronary bypass of two coronary arteries	90487008.00	SNOMED	NO	YES	NO
45889469	Arterial Grafting for Coronary Artery Bypass	1006216.00	CPT4	NO	YES	NO
4240486	Carotid-subclavian artery bypass graft with vein	59012002.00	SNOMED	NO	YES	NO
4336464	Coronary artery bypass graft	232717009.00	SNOMED	NO	YES	NO
4337056	Coronary artery bypass graft x 1	232719007.00	SNOMED	NO	YES	NO
4000733	Coronary artery bypass graft, anastomosis of artery of thorax to coronary artery	119565001.00	SNOMED	NO	YES	NO
4336467	Coronary artery bypass grafts greater than 5	232724005.00	SNOMED	NO	YES	NO
4336465	Coronary artery bypass grafts x 2	232720001.00	SNOMED	NO	YES	NO
4339629	Coronary artery bypass grafts x 3	232721002.00	SNOMED	NO	YES	NO
4337737	Coronary artery bypass grafts x 4	232722009.00	SNOMED	NO	YES	NO
4336466	Coronary artery bypass grafts x 5	232723004.00	SNOMED	NO	YES	NO
4233421	Coronary artery bypass with autogenous graft of internal mammary artery, single graft	359601003.00	SNOMED	NO	YES	NO
4305509	Coronary artery bypass with autogenous graft, five grafts	82247006.00	SNOMED	NO	YES	NO
4309432	Coronary artery bypass with autogenous graft, four grafts	39202005.00	SNOMED	NO	YES	NO
4011931	Coronary artery bypass with autogenous graft, three grafts	10326007.00	SNOMED	NO	YES	NO
4253805	Coronary artery bypass with autogenous graft, two grafts	74371005.00	SNOMED	NO	YES	NO
45887879	Coronary artery bypass, using arterial graft(s)	1006217.00	CPT4	NO	YES	NO
2107242	Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	33534.00	CPT4	NO	YES	NO
2107243	Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	33535.00	CPT4	NO	YES	NO
2107244	Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	33536.00	CPT4	NO	YES	NO
2107231	Coronary artery bypass, using arterial graft(s); single arterial graft	33533.00	CPT4	NO	YES	NO
45889898	Coronary artery bypass, using venous graft(s) and arterial graft(s)	1006208.00	CPT4	NO	YES	NO
2107223	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (List separately in addition to code for primary procedure)	33518.00	CPT4	NO	YES	NO
2107224	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (List separately in addition to code for primary procedure)	33519.00	CPT4	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

2107226	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (List separately in addition to code for primary procedure)	33521.00	CPT4	NO	YES	NO
2107227	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (List separately in addition to code for primary procedure)	33522.00	CPT4	NO	YES	NO
2107228	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (List separately in addition to code for primary procedure)	33523.00	CPT4	NO	YES	NO
2107222	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (List separately in addition to code for primary procedure)	33517.00	CPT4	NO	YES	NO
45887862	Coronary artery bypass, vein only	1006200.00	CPT4	NO	YES	NO
2107217	Coronary artery bypass, vein only; 2 coronary venous grafts	33511.00	CPT4	NO	YES	NO
2107218	Coronary artery bypass, vein only; 3 coronary venous grafts	33512.00	CPT4	NO	YES	NO
2107219	Coronary artery bypass, vein only; 4 coronary venous grafts	33513.00	CPT4	NO	YES	NO
2107220	Coronary artery bypass, vein only; 5 coronary venous grafts	33514.00	CPT4	NO	YES	NO
2107221	Coronary artery bypass, vein only; 6 or more coronary venous grafts	33516.00	CPT4	NO	YES	NO
2107216	Coronary artery bypass, vein only; single coronary venous graft	33510.00	CPT4	NO	YES	NO
2001515	Double internal mammary-coronary artery bypass	36.16	ICD9Proc	NO	YES	NO
4000732	Internal mammary-coronary artery bypass graft	119564002.00	SNOMED	NO	YES	NO
2001514	Single internal mammary-coronary artery bypass	36.15	ICD9Proc	NO	YES	NO
4233420	Single internal mammary-coronary artery bypass	359597003.00	SNOMED	NO	YES	NO
45889467	Venous Grafting Only for Coronary Artery Bypass	1006199.00	CPT4	NO	YES	NO
4020216	Revision of bypass for coronary artery	175036008.00	SNOMED	NO	NO	NO
4305852	Off-pump coronary artery bypass	418824004.00	SNOMED	NO	NO	NO

B.9 Stroke

B.9.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND-T2DM] Stroke (ischemic or hemorrhagic)'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting between all days before and 1 days after cohort entry start date and ending between 0 days before and all days after cohort entry start date.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.9.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.9.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.9.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.9.5 Concept: [LEGEND-T2DM] Stroke (ischemic or hemorrhagic)

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO
43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.10 Sudden cardiac death

B.10.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Sudden cardiac death'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.10.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.10.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.10.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.10.5 Concept: [LEGEND HTN] Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

B.11 Abnormal weight gain

B.11.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. observations of '[LEGEND HTN] Abnormal weight gain'.

B.11.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.11.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.11.4 Concept: [LEGEND HTN] Abnormal weight gain

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
439141	Abnormal weight gain	161833006	SNOMED	NO	YES	NO

B.12 Abnormal weight loss

B.12.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. observations of '[LEGEND HTN] Abnormal weight loss'.

B.12.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.12.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.12.4 Concept: [LEGEND HTN] Abnormal weight loss

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
435928	Abnormal weight loss	267024001	SNOMED	NO	YES	NO
40303297	Weight loss (& abnormal)	139091004	SNOMED	NO	NO	NO

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.13 Acute pancreatitis

B.13.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Acute pancreatitis'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit', starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.13.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.13.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.13.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.13.5 Concept: [LEGEND HTN] Acute pancreatitis

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
199074	Acute pancreatitis	197456007	SNOMED	NO	YES	NO
2109394	Placement of drains, peripancreatic, for acute pancreatitis	48000	CPT4	NO	NO	NO
2109400	Resection or debridement of pancreas and peripancreatic tissue for acute necrotizing pancreatitis	48105	CPT4	NO	NO	NO
2109395	Placement of drains, peripancreatic, for acute pancreatitis; with cholecystostomy, gastrostomy, and jejunostomy	48001	CPT4	NO	NO	NO
42737025	Resection or debridement of pancreas and peripancreatic tissue for acute necrotizing pancreatitis (Deprecated)	48005	CPT4	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.14 All-cause mortality

B.14.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. death of any form.

Limit cohort entry events to the earliest event per person.

B.14.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.14.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.15 Bladder cancer

B.15.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of ‘Bladder cancer’ for the first time in the person’s history.

Limit cohort entry events to the earliest event per person.

B.15.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.15.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.15.4 Concept: Bladder cancer

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
197508	Malignant tumor of urinary bladder	399326009	SNOMED	NO	YES	NO

B.16 Bone fracture

B.16.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Bone fracture'.

B.16.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.16.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.16.4 Concept: Bone fracture

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
75053	Fracture of bone	125605004	SNOMED	NO	YES	NO
4071354	Open reduction of fracture with internal fixation	20701002	SNOMED	NO	YES	NO

B.17 Breast cancer

B.17.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1. condition occurrence of ‘Malignant tumor of breast’ for the first time in the person’s history.

Limit cohort entry events to the earliest event per person.

B.17.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.17.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.17.4 Concept: Malignant tumor of breast

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4112853	Malignant tumor of breast	254837009	SNOMED	NO	YES	NO

B.18 Diabetic ketoacidosis

B.18.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of ‘Diabetic ketoacidosis’.

Restrict entry events to having at least 1 visit occurrence of ‘Inpatient or ER visit’, starting between all days before and 1 days after cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.18.2 Cohort Exit

The cohort end date will be offset from index event’s start date plus 7 days.

B.18.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.18.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.18.5 Concept: Diabetic ketoacidosis

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
443727	Diabetic ketoacidosis	420422005	SNOMED	NO	YES	NO

B.19 Diarrhea

B.19.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN} Diarrhea'.

B.19.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.19.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.19.4 Concept: [LEGEND HTN} Diarrhea

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
196523	Diarrhea	62315008	SNOMED	NO	YES	NO
4134607	Diarrheal disorder	128333008	SNOMED	NO	YES	NO
201773	Enteritis of small intestine	64613007	SNOMED	NO	NO	NO
80141	Functional diarrhea	47812002	SNOMED	NO	YES	NO
4207688	Infectious enteritis	55184003	SNOMED	NO	NO	NO
4324838	Noninfectious enteritis	71207007	SNOMED	NO	NO	NO
197596	Toxic gastroenteritis	71583005	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

196620	Viral enteritis	78420004	SNOMED	NO	YES	NO

B.20 Genitourinary infection

B.20.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'UTI'.

Limit qualifying entry events to the earliest event per person.

B.20.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.20.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.20.4 Concept: UTI

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
81902	Urinary tract infectious disease	6.85660050e+07	SNOMED	NO	YES	NO
4167328	Pyuria	4.80000100e+06	SNOMED	NO	YES	NO
77340	Genitourinary tract infection in pregnancy	2.67204006e+08	SNOMED	NO	YES	NO
4265485	Bacteriuria	6.13730060e+07	SNOMED	NO	YES	NO
4126297	Chronic obstructive pyelonephritis	2.36379002e+08	SNOMED	NO	YES	NO
195588	Cystitis	3.88220070e+07	SNOMED	NO	YES	NO
198806	Abscess of prostate	8.72500500e+06	SNOMED	YES	YES	NO
4126267	Chronic radiation cystitis	2.36629009e+08	SNOMED	YES	YES	NO
194997	Prostatitis	9.71300200e+06	SNOMED	YES	NO	NO
4077499	Sterile pyuria	2.75742001e+08	SNOMED	YES	YES	NO
442345	Syphilis of kidney	5.95300010e+07	SNOMED	YES	YES	NO
4062493	Mumps nephritis	1.71210060e+07	SNOMED	YES	YES	NO
45757237	Diphtheria tubulointerstitial nephropathy	1.08607100e+15	SNOMED	YES	YES	NO
36714969	Asymptomatic bacteriuria	7.20406004e+08	SNOMED	YES	YES	NO
195743	Diphtheritic cystitis	4.82780010e+07	SNOMED	YES	YES	NO
201353	Irradiation cystitis	1.12510000e+07	SNOMED	YES	YES	NO
4047937	Neonatal urinary tract infection	1.23010090e+07	SNOMED	YES	YES	NO
201792	Nongonococcal urethritis	8.46190010e+07	SNOMED	YES	YES	NO
4128384	Non-infective cystitis	2.36623005e+08	SNOMED	YES	NO	NO
78357	Reactive arthritis triad	6.72240070e+07	SNOMED	YES	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

195313	Urethral abscess	6.72770020e+07	SNOMED	YES	YES	NO
197919	Urethral stricture due to infection	8.03750020e+07	SNOMED	YES	YES	NO
439349	Cystitis associated with another disorder	1.97845000e+08	SNOMED	YES	NO	NO
4227291	Hemorrhagic cystitis	8.76960040e+07	SNOMED	YES	NO	NO
4060312	Infections of urethra in pregnancy	1.99206009e+08	SNOMED	YES	NO	NO
4127564	Acute cystitis - culture-negative	2.36624004e+08	SNOMED	YES	YES	NO
4126141	Chronic cystitis - culture negative	2.36626002e+08	SNOMED	YES	NO	NO
4127565	Recurrent cystitis - culture-negative	2.36625003e+08	SNOMED	YES	YES	NO
4207186	Viral infection by site	3.12130009e+08	SNOMED	YES	YES	NO
4207190	Fungal infection by site	3.12146001e+08	SNOMED	YES	YES	NO
434557	Tuberculosis	5.67170010e+07	SNOMED	YES	YES	NO
432251	Disease caused by parasite	1.73220070e+07	SNOMED	YES	YES	NO
36102152	Protozoal infectious disorders	1.00370720e+07	MedDRA	YES	YES	NO
433417	Gonorrhea	1.56280030e+07	SNOMED	YES	YES	NO
36102938	Chlamydial infections	1.00085610e+07	MedDRA	YES	YES	NO

B.21 Hyperkalemia

B.21.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Hyperkalemia'.
2. measurements of '[LEGEND HTN] Potassium measurement', numeric value > 5.6; unit: "millimole per liter".

B.21.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.21.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.21.4 Concept: [LEGEND HTN] Hyperkalemia

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
434610	Hyperkalemia	14140009	SNOMED	NO	YES	NO

B.21.5 Concept: [LEGEND HTN] Potassium measurement

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40789890	Potassium	Bld-Ser-Plas	LP42189-8	LOINC	NO	YES
4245152	Potassium measurement	59573005	SNOMED	NO	YES	NO
4276440	Potassium level - finding	365760004	SNOMED	NO	YES	NO

B.22 Hypoglycemia

B.22.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Hypoglycemia'.

B.22.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.22.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.22.4 Concept: Hypoglycemia

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
380688	Hypoglycemic coma	267384006	SNOMED	NO	YES	NO
4048805	Non-diabetic hypoglycemic coma	230796005	SNOMED	YES	YES	NO
4226798	Hypoglycemic coma due to diabetes mellitus	421725003	SNOMED	NO	YES	NO
4228112	Hypoglycemic coma due to type 1 diabetes mellitus	421437000	SNOMED	YES	YES	NO
36714116	Hypoglycemic coma due to type 2 diabetes mellitus	719216001	SNOMED	NO	YES	NO
24609	Hypoglycemia	302866003	SNOMED	NO	YES	NO
23034	Neonatal hypoglycemia	52767006	SNOMED	YES	YES	NO
4029424	Non-diabetic hypoglycemia	237637005	SNOMED	YES	YES	NO
4029423	Hypoglycemia due to diabetes mellitus	237633009	SNOMED	NO	YES	NO
45769876	Hypoglycemia due to type 1 diabetes mellitus	84371000119108	SNOMED	YES	YES	NO
45757363	Hypoglycemia due to type 2 diabetes mellitus	120731000119103	SNOMED	NO	YES	NO
4096804	Drug-induced hypoglycemia without coma	190448007	SNOMED	NO	YES	NO

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

B.23 Hypotension

B.23.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Hypotension'.

B.23.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.23.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.23.4 Concept: [LEGEND HTN] Hypotension

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
313232	Hemodialysis-associated hypotension	408667000	SNOMED	YES	YES	NO
317002	Low blood pressure	45007003	SNOMED	NO	YES	NO
314432	Maternal hypotension syndrome	88887003	SNOMED	YES	YES	NO

B.24 Joint pain

B.24.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Joint pain'.

B.24.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.24.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.24.4 Concept: Joint pain

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
77074	Joint pain	57676002	SNOMED	NO	NO	NO

B.25 Lower extremity amputation

B.25.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. procedure occurrences of 'below-knee amputations'.

Restrict entry events to having no procedure occurrences of 'below-knee amputations', starting in the 30 days prior to cohort entry start date.

B.25.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

B.25.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.25.4 Concept: below-knee amputations

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4264289	Amputation of ankle	397218006.00	SNOMED	NO	YES	NO
2006242	Amputation of ankle through malleoli of tibia and fibula	84.14	ICD9Proc	NO	YES	NO
2105446	Amputation, leg, through tibia and fibula	27880.00	CPT4	NO	YES	NO
2105804	Amputation, foot; midtarsal (eg, Chopart type procedure)	28800.00	CPT4	NO	YES	NO
2105805	Amputation, foot; transmetatarsal	28805.00	CPT4	NO	YES	NO
2105806	Amputation, metatarsal, with toe, single	28810.00	CPT4	NO	YES	NO
2105807	Amputation, toe; metatarsophalangeal joint	28820.00	CPT4	NO	YES	NO
2105808	Amputation, toe; interphalangeal joint	28825.00	CPT4	NO	YES	NO
2105451	Amputation, ankle, through malleoli of tibia and fibula (eg, Syme, Pirogoff type procedures), with plastic closure and resection of nerves	27888.00	CPT4	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

2105447	Amputation, leg, through tibia and fibula; with immediate fitting technique including application of first cast	27881.00	CPT4	NO	YES	NO
4338257	Amputation of leg through tibia and fibula	88312006.00	SNOMED	NO	YES	NO
2105448	Amputation, leg, through tibia and fibula; open, circular (guillotine)	27882.00	CPT4	NO	YES	NO
4108565	Amputation of the foot	180030006.00	SNOMED	NO	YES	NO
2006229	Amputation of toe	84.11	ICD9Proc	NO	YES	NO
4159766	Amputation of toe	371186005.00	SNOMED	NO	YES	NO
4054983	Amputation through foot	211570009.00	SNOMED	NO	YES	NO
2006230	Amputation through foot	84.12	ICD9Proc	NO	YES	NO
4143797	Amputation through metatarsal bones	265739006.00	SNOMED	NO	YES	NO
2105450	Amputation, leg, through tibia and fibula; re-amputation	27886.00	CPT4	NO	YES	NO
2006231	Disarticulation of ankle	84.13	ICD9Proc	NO	YES	NO
2006244	Disarticulation of knee	84.16	ICD9Proc	NO	YES	NO
4018719	Midtarsal amputation of foot	209724005.00	SNOMED	NO	YES	NO
2006243	Other amputation below knee	84.15	ICD9Proc	NO	YES	NO
2105449	Amputation, leg, through tibia and fibula; secondary closure or scar revision	27884.00	CPT4	YES	YES	NO
4219032	Amputation of lower limb	397117006.00	SNOMED	NO	YES	NO

B.26 Nausea

B.26.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Nausea'.

B.26.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.26.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.26.4 Concept: [LEGEND HTN] Nausea

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
30284	Motion sickness	37031009	SNOMED	YES	YES	NO
31967	Nausea	422587007	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.27 Peripheral edema

B.27.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Edema'.

B.27.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.27.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.27.4 Concept: Edema

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
433595	Edema	267038008	SNOMED	NO	YES	NO
133299	Swelling of limb	80068009	SNOMED	NO	YES	NO

B.28 Photosensitivity

B.28.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Photosensitivity'.

B.28.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.28.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.28.4 Concept: Photosensitivity

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4300445	Acantholytic actinic keratosis	403199007	SNOMED	YES	NO	NO
4263325	Actinic cheilitis	46795000	SNOMED	YES	NO	NO
4031007	Actinic folliculitis	238529007	SNOMED	YES	NO	NO
442179	Actinic granuloma	79144000	SNOMED	YES	NO	NO
37312586	Actinic intraepidermal squamous cell carcinoma	789051005	SNOMED	YES	NO	NO
138825	Actinic keratosis	201101007	SNOMED	YES	NO	NO
4304266	Actinic keratosis of eyelid	418686001	SNOMED	YES	NO	NO
4064057	Actinic lichen planus	200999007	SNOMED	YES	NO	NO
141374	Actinic prurigo	201015007	SNOMED	YES	NO	NO
4031006	Actinic reaction	238528004	SNOMED	YES	NO	NO
439096	Actinic reticuloid	52636001	SNOMED	YES	NO	NO
4070156	Acute actinic otitis externa	21543000	SNOMED	YES	NO	NO
4290728	Acute effect of ultraviolet radiation on normal skin	402165001	SNOMED	YES	NO	NO
4241471	Acute phytophotodermatitis	58306008	SNOMED	YES	NO	NO
36674412	Ataxia, photosensitivity, short stature syndrome	773769008	SNOMED	YES	NO	NO
4293437	Atrophic actinic keratosis	403200005	SNOMED	YES	NO	NO
4066470	Berloque dermatitis	200836002	SNOMED	YES	NO	NO
4119822	Bowenoid actinic keratosis	304524009	SNOMED	YES	NO	NO
4033832	Brachioradial summer pruritus	109252001	SNOMED	YES	NO	NO
37116482	Burn of skin caused by exposure to artificial source of ultraviolet radiation	733209003	SNOMED	YES	NO	NO
37116483	Burn of skin caused by ultraviolet radiation due to ultraviolet light therapy	733210008	SNOMED	YES	NO	NO
4290729	Chronic effect of ultraviolet radiation on normal skin (photo-aging)	402166000	SNOMED	YES	NO	NO
4239682	Chronic phototoxic dermatitis	69231004	SNOMED	YES	NO	NO
4242265	Chronic phytophotodermatitis	58419006	SNOMED	YES	NO	NO
36715275	Cutaneous photosensitivity and lethal colitis syndrome	720820000	SNOMED	YES	NO	NO
4230340	Cutis rhomboidalis nuchae	89019003	SNOMED	YES	NO	NO
4300796	Diffuse actinic hyperkeratosis	403208003	SNOMED	YES	NO	NO
141650	Disseminated superficial actinic porokeratosis	41495000	SNOMED	YES	NO	NO
4301164	Drug-induced pellagra	403626007	SNOMED	YES	NO	NO
4299673	Familial actinic prurigo of lip	403210001	SNOMED	YES	NO	NO
4234867	Food-induced photosensitivity	90386003	SNOMED	YES	NO	NO
36715367	Hair defect with photosensitivity and intellectual disability syndrome	721007005	SNOMED	YES	NO	NO
4308081	Hydroa vacciniforme	200837006	SNOMED	YES	NO	NO
42709861	Hyperkeratotic actinic keratosis	449733007	SNOMED	YES	NO	NO
4112749	Hypertrophic solar keratosis	254667001	SNOMED	YES	NO	NO
4300444	Idiopathic photo-onycholysis	403196000	SNOMED	YES	NO	NO
4031005	Juvenile spring eruption	238526000	SNOMED	YES	NO	NO
4116197	Lentigo maligna	302836005	SNOMED	YES	NO	NO
4299672	Lichenoid actinic keratosis	403198004	SNOMED	YES	NO	NO
4080922	Light - exacerbated acne	238530002	SNOMED	YES	NO	NO
4293560	Multiple actinic keratoses	403202002	SNOMED	YES	NO	NO
4293562	Multiple actinic keratoses involving face	403204001	SNOMED	YES	NO	NO
4300794	Multiple actinic keratoses involving forehead and temples	403205000	SNOMED	YES	NO	NO
4300795	Multiple actinic keratoses involving hands	403206004	SNOMED	YES	NO	NO
4293563	Multiple actinic keratoses involving legs	403207008	SNOMED	YES	NO	NO
4293561	Multiple actinic keratoses involving scalp	403203007	SNOMED	YES	NO	NO
37110331	Neonatal burn due to phototherapy caused by ultraviolet radiation	724551009	SNOMED	YES	NO	NO
4006157	Nodular elastosis with cysts and comedones	111200005	SNOMED	YES	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

37110590	Occupational phototoxic reaction to skin contact with exogenous photoactive agent	724873006	SNOMED	YES	NO	NO
4292224	Photoaggravated psoriasis	402318000	SNOMED	YES	NO	NO
4293593	Photoaggravated rosacea	403365004	SNOMED	YES	NO	NO
4290732	Photoaggravation of disorder	402179009	SNOMED	YES	NO	NO
42537710	Photodermatitis co-occurrent and due to autoimmune disease	737249005	SNOMED	YES	NO	NO
4318376	Photoonycholysis	95342006	SNOMED	YES	NO	NO
4234104	Photosensitivity	90128006	SNOMED	NO	YES	NO
42537712	Phototoxic reaction of skin caused by cosmetic	737251009	SNOMED	YES	NO	NO
42537711	Phototoxic reaction of skin caused by fragrance	737250005	SNOMED	YES	NO	NO
4290730	Phototoxic reaction to dye	402174004	SNOMED	YES	NO	NO
4298594	Phototoxic reaction to tar or derivative	402175003	SNOMED	YES	NO	NO
4298593	Phototoxic reaction to topical chemical	402173005	SNOMED	YES	NO	NO
4270722	Phototoxic reaction to topically applied medicament	402176002	SNOMED	YES	NO	NO
42539382	Pigmentation of skin caused by artificial ultraviolet light	762664003	SNOMED	YES	NO	NO
42709860	Pigmented actinic keratosis	449732002	SNOMED	YES	NO	NO
4080921	Polymorphous light eruption	238525001	SNOMED	YES	NO	NO
4176424	Polymorphous light eruption, diffuse erythematous type	51048002	SNOMED	YES	NO	NO
4223992	Polymorphous light eruption, eczematous type	84036008	SNOMED	YES	NO	NO
4204365	Polymorphous light eruption, papular type	54116000	SNOMED	YES	NO	NO
4195589	Polymorphous light eruption, papulovesicular type	79372000	SNOMED	YES	NO	NO
4278846	Polymorphous light eruption, plaque type	6618004	SNOMED	YES	NO	NO
4297664	Porphyria-induced phototoxic burn	402480004	SNOMED	YES	NO	NO
4296207	Proliferative actinic keratosis	403201009	SNOMED	YES	NO	NO
4066838	Pruritus estivalis	201024003	SNOMED	YES	NO	NO
4031625	Solar comedone	238518008	SNOMED	YES	NO	NO
4185267	Solar degeneration	43982006	SNOMED	YES	NO	NO
4031162	Solar lentiginosis	238712007	SNOMED	YES	NO	NO
4217502	Solar lentigo	72100002	SNOMED	YES	NO	NO
4296189	Solar pruritus	402177006	SNOMED	YES	NO	NO
4033831	Solar pruritus of elbows	109251008	SNOMED	YES	NO	NO
4031004	Strimmer dermatitis	238522003	SNOMED	YES	NO	NO
4296206	Sun-induced wrinkles	403197009	SNOMED	YES	NO	NO

B.29 Renal cancer

B.29.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of ‘Primary malignant neoplasm of kidney’ for the first time in the person’s history.

Limit cohort entry events to the earliest event per person.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.29.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.29.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.29.4 Concept: Primary malignant neoplasm of kidney

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
198985	Primary malignant neoplasm of kidney	93849006	SNOMED	NO	YES	NO
4215373	Renal cell carcinoma	41607009	SNOMED	NO	NO	NO

B.30 Thyroid tumor

B.30.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of ‘Neoplasm of thyroid gland’ for the first time in the person’s history.

Limit cohort entry events to the earliest event per person.

B.30.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.30.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.30.4 Concept: Neoplasm of thyroid gland

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4131909	Neoplasm of thyroid gland	127018007	SNOMED	NO	YES	NO

B.31 Venous thromboembolism

B.31.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Venous thromboembolism (pulmonary embolism and deep vein thrombosis)'.

B.31.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.31.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.31.4 Concept: [LEGEND HTN] Venous thromboembolism (pulmonary embolism and deep vein thrombosis)

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
435616	Amniotic fluid embolism	17263003.0	SNOMED	YES	YES	NO
435887	Antepartum deep vein thrombosis	49956009.0	SNOMED	YES	YES	NO
196715	Budd-Chiari syndrome	82385007.0	SNOMED	YES	YES	NO
4062269	Cerebral venous thrombosis in pregnancy	200259003.0	SNOMED	YES	YES	NO
442055	Obstetric air pulmonary embolism	200286003.0	SNOMED	YES	YES	NO
433832	Obstetric blood-clot pulmonary embolism	200299000.0	SNOMED	YES	YES	NO
435026	Obstetric pulmonary embolism	200284000.0	SNOMED	YES	YES	NO
440477	Obstetric pyemic and septic pulmonary embolism	267284008.0	SNOMED	YES	YES	NO
318137	Phlebitis and thrombophlebitis of intracranial sinuses	192753009.0	SNOMED	YES	YES	NO
199837	Portal vein thrombosis	17920008.0	SNOMED	YES	YES	NO
438820	Postpartum deep phlebothrombosis	56272000.0	SNOMED	YES	YES	NO
440417	Pulmonary embolism	59282003.0	SNOMED	NO	YES	NO
254662	Pulmonary infarction	64662007.0	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4235812	Septic thrombophlebitis	439731006.0	SNOMED	YES	YES	NO
195294	Thrombosed hemorrhoids	75955007.0	SNOMED	YES	YES	NO
4187790	Thrombosis of retinal vein	46085004.0	SNOMED	YES	YES	NO
444247	Venous thrombosis	111293003.0	SNOMED	NO	YES	NO
44834756	Acute venous embolism and thrombosis of other specified veins	453.8	ICD9CM	NO	NO	NO

B.32 Vomiting

B.32.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Vomiting'.

B.32.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.32.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.32.4 Concept: [LEGEND HTN] Vomiting

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40480290	Hyperemesis	444673007	SNOMED	YES	YES	NO
4216862	Postoperative vomiting	72245005	SNOMED	YES	YES	NO
441408	Vomiting	422400008	SNOMED	NO	YES	NO
440785	Vomiting of pregnancy	90325002	SNOMED	YES	YES	NO

C Negative Control Concepts

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 68: Negative outcome controls specified through condition occurrences that map to (a descendent of) the indicated concept ID

	Concept ID
Abnormal posture	439935
Abnormal pupil	436409
Abrasion and/or friction burn of multiple sites	443585
Abrasion and/or friction burn of trunk without infection	199192
Absence of breast	4088290
Absent kidney	4092879
Acquired hallux valgus	75911
Acquired keratoderma	137951
Anal and rectal polyp	73241
Anomaly of jaw size	45757682
Benign paroxysmal positional vertigo	81878
Bizarre personal appearance	4216219
Burn of forearm	133655
Cachexia	134765
Calcaneal spur	73560
Cannabis abuse	434327
Changes in skin texture	140842
Chondromalacia of patella	81378
Cocaine abuse	432303
Colostomy present	4201390
Complication due to Crohn's disease	46269889
Complication of gastrostomy	434675
Contact dermatitis	134438
Contusion of knee	78619
Crohn's disease	201606
Derangement of knee	76786
Developmental delay	436077
Deviated nasal septum	377910
Difficulty sleeping	4115402
Disproportion of reconstructed breast	45757370
Effects of hunger	433111
Endometriosis	433527
Epidermoid cyst	4170770
Exhaustion due to excessive exertion	437448
Feces contents abnormal	4092896
Feces contents abnormal	4092896
Foreign body in ear	374801
Foreign body in orifice	259995
Foreskin deficient	4096540
Galactosemia	439788
Ganglion cyst	40481632
Ganglion cyst	40481632
Genetic disorder carrier	4168318
Hammer toe	433577
Hereditary thrombophilia	4231770
High risk sexual behavior	4012570
Homocystinuria	4012934
Impacted cerumen	374375
Impacted cerumen	374375
Impingement syndrome of shoulder region	4344500
Inadequate sleep hygiene	40481897
Ingrowing nail	139099
Injury of knee	444132
Jellyfish poisoning	4265896
Kwashiorkor	432593
Lagophthalmos	381021
Late effect of contusion	434203

(Continued on Next Page...)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 68: Negative outcome controls specified through condition occurrences that map to (a descendent of) the indicated concept ID *(continued)*

	Concept ID
Late effect of motor vehicle accident	438329
Lipid storage disease	4027782
Lymphangioma	433997
Macular drusen	4083487
Malingering	4051630
Marfan's syndrome	258540
Mechanical complication of internal orthopedic device, implant AND/OR graft	432798
Melena	4103703
Minimal cognitive impairment	439795
Nicotine dependence	4209423
Nicotine dependence	4209423
Noise effects on inner ear	377572
Non-toxic multinodular goiter	136368
Nonspecific tuberculin test reaction	40480893
Nonspecific tuberculin test reaction	40480893
Opioid abuse	438130
Opioid abuse	438130
Opioid intoxication	4299094
Passing flatus	4091513
Physiological development failure	437092
Poisoning by tranquilizer	433951
Postviral fatigue syndrome	4202045
Presbyopia	373478
Psychalgia	439790
Ptotic breast	81634
Regular astigmatism	380706
Senile hyperkeratosis	141932
Social exclusion	4019836
Somatic dysfunction of lumbar region	36713918
Splinter of face without major open wound	443172
Sprain of ankle	81151
Strain of rotator cuff capsule	72748
Symbolic dysfunction	432436
Tear film insufficiency	378427
Tobacco dependence syndrome	437264
Tooth loss	433244
Toxic effect of lead compound	436876
Toxic effect of tobacco and nicotine	440612
Tracheostomy present	4201387
Unsatisfactory tooth restoration	45757285
Verruca vulgaris	140641
Wrist joint pain	4115367
Wristdrop	440193

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open

Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): Protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057977.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Apr-2022
Complete List of Authors:	Khera, Rohan; Yale School of Medicine, Internal Medicine/Cardiology; Yale University School of Medicine, Schuemie, Martijn; Observational Health Data Sciences and Informatics, Epidemiology Analytics; University of California, Los Angeles, Department of Biostatistics Lu, Yuan; Yale University School of Medicine, Internal Medicine; Yale University Ostropolets, Anna; Columbia University Chen, RuiJun; Geisinger Hripcsak, George; Columbia University Ryan, Patrick; Janssen Research and Development LLC, Observational Health Data Analytics; Columbia University Irving Medical Center, Department of Biomedical Informatics Krumholz, Harlan; Yale School of Medicine, Suchard, MA; University of California Los Angeles,
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice, Pharmacology and therapeutics
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, DIABETES & ENDOCRINOLOGY, Cardiology < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): Protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies

Rohan Khera MD MS[1,2], Martijn J Schuemie PhD[3,4], Yuan Lu ScD[1,2] Anna Ostropolets MD[5], Ruijun Chen MD[6], George Hripcsak MD MS [5,7], Patrick B Ryan PhD[3,5], Harlan M Krumholz MD SM [1,2], Marc A Suchard MD PhD [4,8,9,10]

1. Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT
2. Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT
3. Epidemiology Analytics, Janssen Research and Development, Titusville, NJ
4. Department of Biostatistics, UCLA Fielding School of Public Health, University of California, Los Angeles, CA
5. Department of Biomedical Informatics, Columbia University Medical Center, New York, NY
6. Department of Translational Data Science and Informatics, Geisinger, Danville, PA
7. New York-Presbyterian Hospital, New York, NY
8. Department of Biomathematics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA
9. Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA
10. VA Informatics and Computing Infrastructure, US Department of Veterans Affairs, Salt Lake City, UT

Corresponding author:
Marc A Suchard, MD PhD
6558 Gonda Building, 695 Charles E. Young Drive
South Los Angeles, CA 90095-1766
Email: msuchard@ucla.edu
Tel (310) 825-7442; Fax (310) 825-8685

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Abstract

Introduction: Therapeutic options for type 2 diabetes mellitus (T2DM) have expanded over the last decade with the emergence of cardioprotective novel agents, but without such data for older drugs, leaving a critical gap in our understanding of the relative effects of T2DM agents on cardiovascular risk.

Methods and Analysis: The Large-Scale Evidence Generations Across a Network of Databases for T2DM (LEGEND-T2DM) initiative is a series of systematic, large-scale, multinational, real-world comparative cardiovascular effectiveness and safety studies of all 4 major second-line anti-hyperglycemic agents including SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor and sulfonylureas. LEGEND-T2DM will leverage the Observational Health Data Sciences and Informatics (OHDSI) community that provides access to a global network of administrative claims and electronic health record (EHR) data sources, representing 190 million patients in the US and about 50 million internationally. LEGEND-T2DM will identify all adult, T2DM patients who newly initiate a traditionally second-line T2DM agent. Using an active comparator, new-user cohort design, LEGEND-T2DM will execute all pairwise class-vs-class and drug-vs-drug comparisons in each data source, producing extensive study diagnostics that assess reliability and generalizability through cohort balance and equipoise to examine the relative risk of cardiovascular and safety outcomes. The primary cardiovascular outcomes include a composite of major adverse cardiovascular events and a series of safety outcomes. The study will pursue data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias.

Ethics and Dissemination: The study ensures data safety through a federated analytic approach and follows research best practices, including prespecification and full disclosure of results. LEGEND-T2DM is dedicated to open science and transparency and will publicly share all analytic code from reproducible cohort definitions through turn-key software, enabling other research groups to leverage our methods, data, and results to verify and extend our findings.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Strengths and limitations of this study

- The proposal seeks to use health information encompassing millions of patients with type 2 diabetes mellitus (T2DM) in the multinational Observational Health Data Science and Informatics (OHDSI) community to determine real-world comparative effectiveness and safety of traditionally second-line T2DM agents.
- The proposed set of studies will be comprehensive, with a systematic pairwise comparisons of all SGLT2 inhibitor, GLP1 receptor agonist, DPP4 inhibitor and sulfonylurea agents at the drug-, class- and population subgroup-level.
- The studies will focus on a broad set of outcomes including comprehensive measures of adverse cardiovascular events as well as secondary effectiveness and safety outcomes.
- The studies use robust methods an observational, active-comparator, new-user cohort design with a systematic framework to address residual confounding, publication bias, and p-hacking using data-driven, large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, prespecification and full disclosure of hypotheses tested and their results. These approaches capitalize on mature OHDSI open-source resources and a large body of clinical and quantitative research that the LEGEND-T2DM investigators originated and continue to drive.
- The study will focus on drug effectiveness rather than safety without the ability to systematically track the adherence to individual agents across cohorts.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1 Rationale and Background

The landscape of therapeutic options for type 2 diabetes mellitus (T2DM) has been dramatically transformed over the last decade [1]. The emergence of drugs targeting the sodium-glucose co-transporter-2 (SGLT2) and the glucagon-like peptide-1 (GLP1) receptor has expanded the role of T2DM agents from lowering blood glucose to directly reducing cardiovascular risk [2]. A series of large randomized clinical trials designed to evaluate the cardiovascular safety of SGLT2 inhibitors and GLP1 receptor agonists found that use of many of these agents led to a reduction in major adverse cardiovascular events, including myocardial infarction, hospitalization for heart failure, and cardiovascular mortality [3–6]. However, other T2DM drugs widely used before the introduction of these novel agents, such as sulfonylureas, did not undergo similarly comprehensive trials to evaluate their cardiovascular efficacy or safety. Moreover, direct comparisons of newer agents with dipeptidyl peptidase-4 (DPP4) inhibitors, with neutral effects on major cardiovascular outcomes [7–10], have not been conducted. Nevertheless, DPP4 inhibitors and sulfonylureas continue to be used in clinical practice and are recommended as second-line T2DM agents in national clinical practice guidelines.

Several challenges remain in formulating T2DM treatment recommendations based on existing evidence [11]. First, trials of novel agents did not pursue head-to-head comparisons to older agents and were instead designed as additive treatments on the background of commonly used T2DM agents. Therefore, the relative cardiovascular efficacy and safety of novel compared with older agents is not known, and indirect estimates have relied on summary-level data restricted to common comparators [12–14] and are less reliable [15,16]. Second, trials of novel agents have tested individual drugs against placebo, but have not directly compared SGLT2 inhibitors with GLP1 receptor agonists in reducing adverse cardiovascular event risk. Moreover, there is no evidence to guide the use of individual drugs within each class and across different drug classes, particularly among patients at lower cardiovascular risk than recruited in clinical trials. Third, randomized trials focused on cardiovascular efficacy and safety, but were not powered to adequately assess the safety of these agents across a spectrum of non-cardiovascular outcomes.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Finally, restricted enrollment across regions, and subgroups of age, sex, and race further limits the efficacy and safety assessment that may guide individual patients' treatment.

Evidence gaps from these trials also pose a challenge in designing treatment algorithms, which rely on comparative effectiveness and safety of drugs. Perhaps, as a result, there is large variation in clinical practice guidelines and in clinical practice with regard to these medications, with many patients initiated on the newer therapies and many others treated with older regimens [17–21]. Among the second-line options, there is much variation with respect to the order of drugs used. This lack of consensus about the best approach provides an opportunity for systematic, large-scale observational studies.

2 Study Objectives

To inform critical decisions facing patients with diabetes, their caregivers, clinicians, policymakers and healthcare system leaders, we have launched the Large-Scale Evidence Generation and Evaluation across a Network of Databases for Diabetes (LEGEND-T2DM) initiative to execute a series of comprehensive observational studies to compare cardiovascular outcome rates and safety of second-line T2DM glucose-lowering agents. Specifically, these studies aim

1. To determine, through systematic evaluation, the comparative effectiveness of traditionally second-line T2DM agents, SGLT2 inhibitors and GLP1 receptor agonists, with each other and with DPP4 inhibitors and sulfonylureas, for cardiovascular outcomes.
2. To determine, through systematic evaluation, the comparative safety of traditionally second-line T2DM agents among patients with T2DM.
3. To assess heterogeneity in effectiveness and safety of traditionally second-line T2DM agents among key patient subgroups: Using stratified patient cohorts, we will quantify differential effectiveness and safety across subgroups of patients based on age, sex, race, renal impairment, and baseline cardiovascular risk.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3 Research Methods

LEGEND-T2DM will execute three systematic, large-scale observational studies of second-line T2DM agents to estimate the relative risks of cardiovascular effectiveness and safety outcomes.

1. The **Class-vs-Class Study** will provide all pairwise comparisons between the four major T2DM agent classes to evaluate their comparative effects on cardiovascular risk (Objective 1) and patient-centered safety outcomes (Objective 2);
2. The **Drug-vs-Drug Study** will furnish head-to-head pairwise comparisons between individual agents within and across classes (both Objectives 1 and 2); and
3. The **Heterogeneity Study** will refine these comparisons for T2DM patients for important subgroups (Objective 3). In contrast to a single comparison approach, LEGEND-T2DM will provide a comprehensive view of the findings and their consistency across populations, drugs, and outcomes. We will model each study on our successful collaborative research evaluating the comparative effectiveness of antihypertensives recently published in *The Lancet* [22].

Table 1 list the four major T2DM agent classes and the individual agents licensed in the U.S. within each class. We will examine all $\binom{4}{2} = 6$ class-wise comparisons and all $\binom{5+6+4+7}{2} = 231$ ingredient-wise comparisons.

For each comparison, we are interested in the relative risk of each of the cardiovascular and safety outcomes described in the Outcomes Section.

3.1 Study Design

For each study, we will employ an active comparator, new-user cohort design [23–25]. New-user cohort design is advocated as the primary design to be considered for comparative effectiveness and drug safety [26–28]. By identifying patients who start a new treatment course and using therapy initiation as the start of follow-up, the new-user design

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

models an randomized controlled trial (RCT) where treatment commences at the index study visit. Exploiting such an index date allows a clear separation of baseline patient characteristics that occur prior to index date and are usable as covariates in the analysis without concern of inadvertently introducing mediator variables that arise between exposure and outcome [29]. Excluding prevalent users as those without a sufficient washout period prior to first exposure occurrence further reduces bias due to balancing mediators on the causal pathway, time-varying hazards, and depletion of susceptibles [28,30]. Our systematic framework across studies further will address residual confounding, publication bias, and p-hacking using data-driven, large-scale propensity adjustment for measured confounding [31], a large set of negative control outcome experiments to address unmeasured and systematic bias [32–34], and full disclosure of hypotheses tested [35]. Figure 1 illustrates our design for all studies that the following sections describe in more detail.

3.2 Data Sources

We will execute LEGEND-T2DM as a series of OHDSI network studies. All data partners within OHDSI are encouraged to participate voluntarily and can do so conveniently, because of the community's shared Observational Medical Outcomes Partnership (OMOP) common data model (CDM) and OHDSI tool-stack. Many OHDSI community data partners have already committed to participate and we will recruit further data partners through OHDSI's standard recruitment process, which includes protocol publication on OHDSI's GitHub, an announcement in OHDSI's research forum, presentation at the weekly OHDSI all-hands-on meeting and direct requests to data holders.

Table 2 lists the 13 already committed data sources for LEGEND-T2DM; these sources encompass a large variety of practice types and populations. For each data source, we report a brief description and size of the population it represents and its patient capture process and start date. While the earliest patient capture begins in 1989 (CUIMC), the vast majority come from the mid-2000s to today, providing almost two decades of T2DM treatment coverage. US populations include those commercially and publicly insured,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

enriched for older individuals (MDCR, VA), lower socioeconomic status (MDCD), and racially diverse (VA >20% Black or African American, CUIMC 8%). The US data sources may capture the same patients across multiple sources. Different views of the same patients are an advantage in capturing the diversity of real-world health events that patients experience. Across CCAE (commercially insured), MCDR (Medicare) and MCDC (Medicaid), we expect little overlap in terms of the same observations recorded at the same time for a patient; patients can flow between sources (e.g., a CCAE patient who retires can opt-in to become an MDCR patient), but the enrollment time periods stand distinct. On the other hand, Optum, PanTher, OpenClaims, CUIMC and YNHHS may overlap in time with the other US data sources. While it remains against licensing agreements to attempt to link patients between most data sources, Optum reports <20% overlap between their claims and EHR data sources that is reassuringly small. All data sources will receive institutional review board approval or exemption for their participation before executing LEGEND-T2DM.

3.3 Study Population

We will include all subjects in a data source who meet inclusion criteria for one or more traditionally second-line T2DM agent exposure cohorts. Broadly, these cohorts will consist of T2DM patients either with or without prior metformin monotherapy who initiate treatment with one of the 22 drug ingredients that comprise the DPP4 inhibitor, GLP1 receptor agonist, SGT2 inhibitor and sulfonylurea drug classes (Table 1). We do not consider thiazolidinediones given their known association with a risk of heart failure and bladder cancer [36,37]. We describe specific definitions for exposure cohorts for each study in the following sections.

3.4 Exposure Comparators

3.4.1 Class-vs-Class Study comparisons

The **Class-vs-Class** Study will construct four exposure cohorts for new-users of any drug ingredient within the four traditionally second-line drug classes in Table 1. Cohort entry

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

(index date) for each patient is their first observed exposure to any drug ingredient for the four second-line drug classes. Consistent with an idealized target trial for T2DM therapy and cardiovascular risk [38,39], inclusion criteria for patients based on the index date will include:

- T2DM diagnosis and no Type 1 or secondary diabetes mellitus diagnosis before the index date;
- At least 1 year of observation time before the index date (to improve new-user sensitivity); and
- No prior drug exposure to a comparator second-line or other antihyperglycemic agent (i.e. thiazolidinediones, acarbose, acetohexamide, bromocriptine, glibornuride, miglitol and nateglinide) or $>$ 30 days insulin exposure before index date.

We will construct and compare separately cohorts patients either with

- At least 3 months of metformin use before the index date,

or

- No prior metformin use before the index date.

In the first case, three months of metformin is consistent with ADA guidelines [40]. In the second case, we are interested in relative effectiveness and safety of these traditionally second-line agents in patients who initiate their treatments without first using metformin. We purposefully do not automatically exclude or restrict to patients with a history of myocardial infarction, stroke or other major cardiovascular events, which will allow us to report relative effectiveness and safety for individuals with both low or moderate and high cardiovascular risk. Likewise, we do not automatically exclude or restrict to individuals with severe renal impairment [41]. We will use cohort diagnostics, such as achieving covariate balance and clinical empirical equipoise between exposure cohorts (Section 4) and stakeholder input to guide the possible need to exclude other prior diagnoses, such as congestive heart failure, pancreatitis or cancer [41].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Appendix A.1 reports the complete OHDSI ATLAS cohort description for new-users of DDP4 inhibitors with prior metformin use. This description lists complete specification of cohort entry events, additional inclusion criteria, cohort exit events, and all associated standard OMOP CDM concept code sets used in the definition. We generate programmatically equivalent cohort definitions for new-others of each drug class with and without prior metformin use. ATLAS then automatically translates these definitions into network-deployable SQL source code. Appendix A.2 lists the inclusion criteria modifier for no prior metformin use.

Of note, the inclusion criteria do not directly incorporate quantitative measures of poor glycemic control, such as one or more elevated serum HbA1c measurements; such laboratory values are irregularly captured in large claims and even EHR data sources. Older ADA guidelines (but not since 2020 for patients with cardiovascular disease [42]) advise escalating to a second-line agent only when glycemic control is not met with metformin monotherapy, nicely mirroring our cohort design for our historical data. We will conduct sensitivity analyses involving available HbA1c measurements to demonstrate their balance between exposure cohorts (described later in Section 4). In the unlikely event that balance is not met, we will consider an inclusion criterion of at least two HbA1c measurements $\geq$ 7% within 6 months before the index [39]. We will also conduct sensitivity analyses to assess prior insulin use exclusions, bearing in mind difficulties in assessing insulin use end-dates.

For each data source, we will then execute all $2 \times \binom{4}{2} = 6$ pairwise class comparisons for which the data source yields $\geq$ 1,000 patients in each arm. Significantly fewer numbers of patients strongly suggest data source-specific differences in prescribing practices that may introduce residual bias and sufficient samples sizes are required to construct effective propensity score models [43].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.4.2 Drug-vs-Drug Study comparisons

The **Drug-vs-Drug Study** will construct 2×22 exposure cohorts for new-users of each drug ingredient in Table 1. We will apply the same cohort definition, inclusion criteria and patient count minimum as described in Section 3.4.1.

For each data source, we will then execute all $2 \times \binom{22}{2} = 462$ pairwise drug comparisons. While we will publicly report studies results for all pairwise comparisons, we will focus primary clinical interpretation and scientific publishing to the $2 \times \binom{5}{2}$ [within DPP4Is] $+2 \times \binom{6}{2}$ [within GLPR1RAs] $+2 \times \binom{4}{2}$ [within SGLT2Is] $+2 \times \binom{7}{2}$ [within SUs] $= 104$ comparisons that pit drugs within the same class against each other, as well as across-class comparisons that stakeholders deem pertinent given their experiences.

Appendix A.3 reports the complete OHDSI ATLAS cohort description for new-users of aloglipitin with prior metformin use. Again, we programmatically construct all new-user drug-level cohort and automatically translate into SQL.

3.4.3 Heterogeneity Study comparisons

The **Heterogeneity Study** will further stratify all 237 class- and drug-level exposure cohorts in Sections 3.4.1 and 3.4.2 by clinically important patient characteristics that modify cardiovascular risk or relative treatment heterogeneity to provide patient-focused treatment recommendations. These factors will include:

- Age (18 - 44 / 45 - 64 / $\geq$ 65 at the index date)
- Gender (women / men)
- Race (African American or black)
- Cardiovascular risk (low or moderate/high, defined by established cardiovascular disease at the index date)
- Renal impairment (at the index date)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

We will define patients at high cardiovascular risk as those who fulfill at index date an established cardiovascular disease (CVD) definition that has been previously developed and validated for risk stratification among new-users of second-line T2DM agents [44]. Under this definition, established CVD means having at least 1 diagnosis code for a condition indicating cardiovascular disease, such as atherosclerotic vascular disease, cerebrovascular disease, ischemic heart disease or peripheral vascular disease, or having undergone at least 1 procedure indicating cardiovascular disease, such as percutaneous coronary intervention, coronary artery bypass graft or revascularization, any time on or prior to the exposure start. Likewise, we will define renal impairment through diagnosis codes for chronic kidney disease and end-stage renal disease, dialysis procedures, and laboratory measurements of estimated glomerular filtration rate, serum creatinine and urine albumin.

Appendix A.4 presents complete OHDSI `ATLAS` specifications for these subgroups, including all standard OMOP CDM concept codes defining cardiovascular risk and renal disease.

3.4.4 Validation

We will validate exposure cohorts and aggregate drug utilization using comprehensive cohort characterization tools against both claims and EHR data sources. Chief among these tools stands OHDSI's `CohortDiagnostic` package (github). For any cohort and data source mapped to OMOP CDM, this package systematically generates incidence new-user rates (stratified by age, gender, and calendar year), cohort characteristics (all comorbidities, drug use, procedures, health utilization) and the actual codes found in the data triggering the various rules in the cohort definitions. This can allow researchers and stakeholders to understand the heterogeneity of source coding for exposures and health outcomes as well as the impact of various inclusion criteria on overall cohort counts (details described in Section 4).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.5 Outcomes

Across all data sources and pairwise exposure cohorts, we will assess relative risks of 32 cardiovascular and patient-centered outcomes (Table 3). Primary outcomes of interest are:

- 3-point major adverse cardiovascular events (MACE), including acute myocardial infarction, stroke, and sudden cardiac death, and
- 4-point MACE that additionally includes heart failure hospitalization.

Secondary outcomes include:

- individual MACE components,
- acute renal failure,
- coronary revascularization

In data sources with laboratory measurements, secondary outcomes further include:

- glycemic control, and
- measured renal dysfunction

We will also study second-line T2DM drug side-effects and safety concerns highlighted in the 2018 ADA guidelines [40] and from RCTs, including:

- abnormal weight change,
- genitourinary (GU) infection,
- various cancers, and
- hypoglycemia.

We will employ the same level of systematic rigor in studying outcomes regardless of their primary or secondary label (Appendix B).

A majority of outcome definitions have been previously implemented and validated in our own work [22,44–48] based heavily on prior development by others (see references in Table 3 [44–101]). To assess across-source consistency and general clinical validity, we will characterize outcome incidence, stratified by age, sex and index year for each data source.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.6 Analysis

3.6.1 Contemporary utilization of drug classes and individual agents

For all cohorts in the three studies, we will describe overall utilization as well as temporal trends in the use of each drug class and agents within the class. Further, we will evaluate these trends in patient groups by age (18-44 / 45-64 / ≥ 65 years), gender, race and geographic regions. Since the emergence of novel medications in the management of type 2 DM in 2014, there has been a rapid expansion in both the number of drug classes and individual agents. These data will provide insight into the current patterns of use and possible disparities. These data are critical to guide the real-world application of treatment decision pathways for the treatment of T2DM patients.

Specifically, we will calculate and validate aggregate drug utilization using the OHDSI's CohortDiagnostic package against both claims and EHR data sources. The CohortDiagnostics package works in two steps: 1) Generate the utilization results and diagnostics against a data source and 2) Explore the generated utilization and diagnostics in a user-friendly graphical interface R-Shiny app. Through the interface, one can explore patient profiles of a random sample of subjects in a cohort. These diagnostics provide a consistent methodology to evaluate cohort definitions/phenotype algorithms across a variety of observational databases. This will enable researchers and stakeholders to become informed on the appropriateness of including specific data sources within analyses, exposing potential risks related to heterogeneity and variability in patient care delivery that, when not addressed in the design, could result in errors such as highly correlated covariates in propensity score matching of a target and a comparator cohort. Thus, the added value of this approach is two-fold in terms of exposing data quality for a study question and ensuring face validity checks are performed on proposed covariates to be used for balancing propensity scores.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

3.6.2 Relative risk of cardiovascular and patient-centered outcomes

For all three studies, we will execute a systematic process to estimate the relative risk of cardiovascular and patient-centered outcomes between new-users of second-line T2DM agents. The process will adjust for measured confounding, control from further residual (unmeasured) bias and accommodate important design choices to best emulate the nearly impossible to execute, idealized RCT that our stakeholders envision across data source populations, comparators, outcomes and subgroups.

To adjust for potential measured confounding and improve the balance between cohorts, we will build large-scale propensity score (PS) models [102] for each pairwise comparison and data source using a consistent data-driven process through regularized regression [31]. This process engineers a large set of predefined baseline patient characteristics, including age, gender, race, index month/year and other demographics and prior conditions, drug exposures, procedures, laboratory measurements and health service utilization behaviors, to provide the most accurate prediction of treatment and balance patient cohorts across many characteristics. Construction of condition, drug, procedures and observations include occurrences within 365, 180 and 30 days prior to index date and are aggregated at several SNOMED (conditions) and ingredient/ATC class (drugs) levels. Other demographic measures include comorbidity risk scores (Charlson, DCSI, CHADS2, CHAD2VASc). From prior work, feature counts have ranged in the 1,000s - 10,000s, and these large-scale PS models have outperformed hdPS [103] in simulation and real-world examples [31]. Given the subcutaneous route of administration of GLP1RAs compared with other drugs administered orally, device codes that represent needles and associated health management encounters will be excluded from propensity score construction.

We will:

- Exclude patients who have experienced the outcome prior to their index date,
- Stratify and variable-ratio match patients by PS, and
- Use Cox proportional hazards models

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

to estimate hazard ratios (HRs) between alternative target and comparator treatments for the risk of each outcome in each data source. In addition, we will perform a sensitivity analysis that does not exclude individuals who previously experienced a glycemic control outcome before the index date. The regression will condition on the PS strata/matching-unit with treatment allocation as the sole explanatory variable and censor patients at the end of their time-at-risk (TAR) or data source observation period. We will prefer stratification over matching if both sufficiently balance patients (see Section 4), as the former optimizes patient inclusions and thus generalizability.

We will execute each comparison using three different TAR definitions, reflecting different and important causal contrasts:

- Intent-to-treat (TAR: index + 1 → end of observation) captures both direct treatment effects and (long-term) behavioral/treatment changes that initial assignment triggers [104];
- On-treatment-1 (TAR: index + 1 → treatment discontinuation) is more patient-centered [105] and captures direct treatment effect while allowing for escalation with additional T2DM agents; and
- On-treatment-2 (TAR: index + 1 → discontinuation or escalation with T2DM agents) carries the least possible confounding with other concurrent T2DM agents.

Our "on-treatment" is often called "per-protocol" [106]. Systematically executing with multiple causal contrasts enables us to identify potential biases that missing prescription data, treatment escalation and behavioral changes introduce, while preserving the ease of intent-to-treat interpretation and power if the data demonstrate them as unbiased. Appendix A.5 reports the modified cohort exit rule for the on-treatment-2 TAR.

We will aggregate HR estimates across non-overlapping data sources to produce meta-analytic estimates using a random-effects meta-analysis [107]. This classic meta-analysis assumes that per-data source likelihoods are approximately normally distributed [108]. This assumption fails when outcomes are rare as we expect for some safety events. Here, our recent research shows that as the number of data sources increases, the non-normality effect increases to where coverage of 95% confidence intervals (CIs) can be as low as 5%.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

To counter this, we will also apply a Bayesian meta-analysis model [109,110] that neither assumes normality nor requires patient-level data sharing by building on composite likelihood methods [111] and enables us to introduce appropriate overlap weights between data sources.

Residual study bias from unmeasured and systematic sources often remains in observational studies even after controlling for measured confounding through PS-adjustment [32,33]. For each comparison-outcome effect, we will conduct negative control (falsification) outcome experiments, where the null hypothesis of no effect is believed to be true, using approximately 100 controls. We identified these controls through a data-rich algorithm [112] that identifies prevalent OMOP condition concept occurrences that lack evidence of association with exposures in published literature, drug-product labeling and spontaneous reports, and were then adjudicated by clinical review. We previously validated 60 of the controls in LEGEND-HTN [22]. Appendix C lists these negative controls and their OMOP condition concept IDs.

Using the empirical null distributions from these experiments, we will calibrate each study effect HR estimate, its 95% CI and the p-value to reject the null hypothesis of no differential effect [34]. We will declare an HR as significantly different from no effect when its calibrated $p < 0.05$ without correcting for multiple testing. Finally, blinded to all trial results, study investigators will evaluate study diagnostics for all comparisons to assess if they were likely to yield unbiased estimates (Section 4).

3.6.3 Sensitivity analyses and missingness

Because of the potential confounding effect of glycemic control at baseline between treatment choice and outcomes and to better understand the impact of limited glucose level measurements on effectiveness and safety estimation that arises in administrative claims and some EHR data, we will perform pre-specified sensitivity analyses for all studies within data sources that contain reliable glucose or hemoglobin A1c measurements. Within a study, for each exposure pair, we will first rebuild PS models where we additionally include baseline glucose or hemoglobin A1c measurements as patient characteristics,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

stratify or match patients under the new PS models that directly adjust for potential confounding by glycemic control and then estimate effectiveness and safety HRs.

A limitation of the Cox model is that no doubly robust procedure is believed to exist for estimating HRs, due to their non-collapsibility [113]. Doubly robust procedures combine baseline patient characteristic-adjusted outcome and PS models to control for confounding and, in theory, remain unbiased when either (but not necessarily both) model is correctly specified [114]. Doubly robust procedures do exist for hazard differences [115] and we will validate the appropriateness of our univariable Cox modeling by comparing estimate differences under an additive hazards model [116] with and without doubly robust-adjustment [117]. In practice, however, neither the outcome nor PS model is correctly specified, leading to systematic error in the observational setting.

Missing data of potential concern are patient demographics (gender, age, race) for our inclusion criteria. We will include only individuals whose baseline eligibility can be characterized that will most notably influence race subgroup assessments in the **Heterogeneity Study**. No further missing data can arise in our large-scale PS models because all features, with the exception of demographics, simply indicate the presence or absence of health records in a given time-period. Finally, we limit the impact of missing data, such as prescription information, relating to exposure time-at-risk by entertaining multiple definitions [29]. In all reports, we will clearly tabulate numbers of missing observations and patient attrition.

4 Sample Size and Study Power

Within each data source, we will execute all comparisons with $\geq$ 1,000 eligible patients per arm. Blinded to effect estimates, investigators and stakeholders will evaluate extensive study diagnostics for each comparison to assess reliability and generalizability, and only report risk estimates that pass [25,35]. These diagnostics will include

1. Minimum detectable risk ratio (MDRR) as a typical proxy for power,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

2. Preference score distributions to evaluate empirical equipoise10 and population generalizability,
3. Extensive patient characteristics to evaluate cohort balance before and after PS-adjustment,
4. Negative control calibration plots to assess residual bias, and
5. Kaplan-Meier plots to examine hazard ratio proportionality assumptions.

We will define cohorts to stand in empirical equipoise if the majority of patients carry preference scores between 0.3 and 0.7 and to achieve balance if all after-adjustment characteristics return absolute standardized mean differences < 0.1 [118].

5 Strengths and Limitations

5.1 Strengths

LEGEND-T2DM is, to our knowledge, the largest and most comprehensive study to provide evidence about the comparative effectiveness and safety of second-line T2DM agents. The LEGEND-T2DM studies will encompass over 1 million patients initiating second-line T2DM agents across at least 13 databases from 5 countries and will examine all pairwise comparisons between the four second-line drug classes against a panel of TODO health outcomes. Through an international network, LEGEND-T2DM seeks to take advantage of disparate health databases drawn from different sources and across a range of countries and practice settings. These large-scale and unfiltered populations better represent real-world practice than the restricted study populations in prescribed treatment and follow-up settings from RCTs. Our use of the OMOP CDM allows extension of the LEGEND-T2DM experiment to future databases and allows replication of these results on licensable databases that were used in this experiment, while still maintaining patient privacy on patient-level data.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

LEGEND-T2DM further advances the statistically rigorous and empirically validated methods we have developed in OHDSI that specifically address bias inherent in observational studies and allow for reliable causal inference. Patient characteristics and their treatment choices are likely to confound comparative effectiveness and safety estimates. Our approach combines active comparator new-user designs that emulate randomized clinical trials with large-scale propensity adjustment for measured confounding, a large set of negative control outcome experiments to address unmeasured and systematic bias, and full disclosure of hypotheses tested.

Each LEGEND-T2DM aim will represent evidence synthesis from a large number of bespoke studies across multiple data sources. Addressing questions one bespoke study at a time is prone to errors arising from multiple testing, random variation in effect estimates and publication bias. LEGEND-T2DM is designed to avoid these concerns through methodologic best practices [119] with full study diagnostics and external replication.

Through open science, LEGEND-T2DM will allow any interested investigators to engage as partners in our work at many levels. We will publicly develop all protocols and analytic code. This invites additional data custodians to participate in LEGEND-T2DM and enables others to modify and reuse our approach for other investigations. We will also host real-time access to all study result artifacts for outside analysis and interpretation. Such an open science framework ensures a feed-forward effect on other scientific contributions in the community. Collectively, LEGEND-T2DM will generate patient-centered, high quality, generalizable evidence that will transform the clinical management of T2DM through our active collaboration with patients, clinicians, and national medical societies. LEGEND-T2DM will spur scientific innovation through the generation of open-source resources in data science.

5.2 Limitations

Even though many potential confounders will be included in these studies, there may be residual bias due to unmeasured or misspecified confounders, such as confounding by indication, differences in physician characteristics that may be associated with drug choice,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

concomitant use of other drugs started after the index date, and informative censoring at the end of the on-treatment periods. To minimize this risk, we will use methods to detect residual bias through a large number of negative and positive controls.

Ideal negative controls carry identical confounding between exposures and the outcome of interest [120]. The true confounding structure, however, is unknowable. Instead of attempting to find the elusive perfect negative control, we will rely on a large sample of controls that represent a wide range of confounding structures. If a study comparison proves to be unbiased for all negative controls, we can feel confident that it will also be unbiased for the outcome of interest. In our previous studies [22,25,121], using the active comparator, new-user cohort design we will employ here, we have observed minimal residual bias using negative controls. This stands in stark contrast to other designs such as the (nested) case-control that tends to show large residual bias because of incomparable exposure cohorts implied by the design [122].

Observed follow-up times are limited and variable, potentially reducing power to detect differences in effectiveness and safety and, further, misclassification of study variables is unavoidable in secondary use of health data, so it is possible to misclassify treatments, covariates, and outcomes. Based on our previous successful studies on antihypertensives, we do not expect differential misclassification, and therefore bias will most likely be towards the null. Finally, the electronic health record databases may be missing care episodes for patients due to care outside the respective health systems. Such bias, however, will also most likely be towards the null.

Finally, since our studies focus on healthcare datasets, as opposed to vital statistics datasets, the cause of the death among those suffering sudden cardiac death in the outpatient setting will not be identified as such.

6 Ethics and Dissemination

LEGEND-T2DM does not involve human subjects research. The project does, however, use human data collected during routine healthcare provision. Most often the data are de-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

identified within data source. All data partners executing the LEGEND-T2DM studies within their data sources will have received institutional review board (IRB) approval or waiver for participation in accordance with their institutional governance prior to execution (see Table 4). LEGEND-T2DM executes across a federated and distributed data network, where analysis code is sent to participating data partners and only aggregate summary statistics are returned, with no sharing of patient-level data between organizations.

6.1 Management and Reporting of Adverse Events and Adverse Reactions

LEGEND-T2DM uses coded data that already exist in electronic databases. In these types of databases, it is not usually possible to link (i.e., identify a potential causal association between) a particular product and medical event for any specific individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product and event) are not available and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important findings.

6.2 Plans for Disseminating and Communicating Study Results

Open science aims to make scientific research, including its data process and software, and its dissemination, through publication and presentation, accessible to all levels of an inquiring society, amateur or professional [123] and is a governing principle of LEGEND-T2DM. Open science delivers reproducible, transparent and reliable evidence. All aspects of LEGEND-T2DM (except private patient data) will be open and we will actively encourage

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

other interested researchers, clinicians and patients to participate. This differs fundamentally from traditional studies that rarely open their analytic tools or share all result artifacts, and inform the community about hard-to-verify conclusions at completion.

6.3 Transparent and re-usable research tools

We will publicly register this protocol and announce its availability for feedback from stakeholders, the OHDSI community and within clinical professional societies. This protocol will link to open-source code for all steps to generating diagnostics, effect estimates, figures and tables. Such transparency is possible because we will construct our studies on top of the OHDSI toolstack of open-source software tools that are community developed and rigorously tested [25]. We will publicly host LEGEND-T2DM source code at (https://github.com/ohdsi-studies/LegendT2dm), allowing public contribution and review, and free re-use for anyone's future research.

6.4 Continuous sharing of results

LEGEND-T2DM embodies a new approach to generating evidence from healthcare data that overcome weaknesses in the current process of answering and publishing (or not) one question at a time. Generating evidence for thousands of research and control questions using a systematic process enables us to not only evaluate that process and the coherence and consistency of the evidence, but also to avoid *p*-hacking and publication bias [35]. We will store and openly communicate all these results as they become available using a user-friendly web-based app that serves up all descriptive statistics, study diagnostics and effect estimates for each cohort comparison and outcome. Open access to this app will be through a public facing LEGEND-T2DM webpage.

6.5 Dissemination through scientific meetings and publications

We will deliver multiple presentations annually at scientific venues including the annual meetings of the American Diabetes Association, American College of Cardiology, American

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Heart Association and American Medical Informatics Association. We will also prepare multiple scientific publications for clinical, informatics and statistical journals.

6.6 Dissemination to general public

We believe in sharing our findings that will guide clinical care with the public. LEGEND-T2DM will use social-media (Twitter) to facilitate this. With dedicated support from the OHDSI communications specialist, we will deliver regular press releases at key project stages, distributed via the extensive media networks of UCLA, Columbia, and Yale.

7 Patient and Public Involvement

No patients were involved in the design of our studies.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Acknowledgements

Author contributions:

RK and **MAS** conceived the research and drafted the proposal in consultation with **MJS**, **YL**, **AO**, **RC**, **GH**, **PBR**, and **HMK**, who provided critical feedback on the research proposal.

Funding Statement:

This protocol was partially funded through the National Institutes of Health grants K23 HL153775, R01 LM006910 and R01 HG006139 and an Intergovernmental Personnel Act agreement with the US Department of Veterans Affairs.
The funders had no role in the design and conduct of the protocol; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interest statement

This protocol is undertaken within Observational Health Data Sciences and Informatics (OHDSI), an open collaboration. **RK** is a founder of Evidence2Health, and receives grant funding from the US National Institutes of Health. **MJS** and **PBR** are employees of Janssen Research and Development and shareholders in John & Johnson. **GH** receives grant funding from the US National Institutes of Health and the US Food & Drug Administration and contracts from Janssen Research and Development. **HMK** receives grants from the US Food & Drug Administration, Medtronics and Janssen Research and Development, is co-founder of HugoHealth and chairs the Cardiac Scientific Advisory Board for UnitedHealth. **MAS** receives grant funding from the US National Institutes of Health, the US Department of Veterans Affairs and the US Food & Drug Administration and contracts from Janssen Research and Development and IQVIA.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

References

1 Lo C, Toyama T, Wang Y *et al.* Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane database of systematic reviews* 2018.

2 North EJ, Newman JD. Review of cardiovascular outcomes trials of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists. *Current opinion in cardiology* 2019;**34**:687–92.

3 Zinman B, Wanner C, Lachin JM *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England journal of medicine* 2015;**373**:2117–28.

4 Neal B, Perkovic V, Mahaffey KW *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *The New England journal of medicine* 2017;**377**:644–57.

5 Marso SP, Daniels GH, Brown-Frandsen K *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *The New England journal of medicine* 2016;**375**:311–22.

6 Marso SP, Bain SC, Consoli A *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *The New England journal of medicine* 2016;**375**:1834–44.

7 Scirica BM, Bhatt DL, Braunwald E *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *The New England journal of medicine* 2013;**369**:1317–26.

8 White WB, Cannon CP, Heller SR *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *The New England journal of medicine* 2013;**369**:1327–35.

9 Green JB, Bethel MA, Armstrong PW *et al.* Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *The New England journal of medicine* 2015;**373**:232–42.

10 Rosenstock J, Kahn SE, Johansen OE *et al.* Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: The CAROLINA randomized clinical trial. *JAMA: the journal of the American Medical Association* 2019.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11 Cefalu WT, Kaul S, Gerstein HC *et al.* Cardiovascular outcomes trials in type 2 diabetes: Where do we go from here? Reflections from aDiabetes CareEditors' expert forum. Diabetes Care. 2018;**41**:14–31.

12 Palmer SC, Tendal B, Mustafa RA *et al.* Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: Systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;**372**:m4573.

13 Qiu M, Ding L-L, Wei X-B *et al.* Comparative efficacy of glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular events in type 2 diabetes: A network meta-analysis. *Journal of cardiovascular pharmacology* 2021;**77**:34–7.

14 Yamada T, Wakabayashi M, Bhalla A *et al.* Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and network meta-analysis. *Cardiovascular diabetology* 2021;**20**:14.

15 Puhan MA, Schünemann HJ, Murad MH *et al.* A GRADE working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630.

16 Brignardello-Petersen R, Izcovich A, Rochwerg B *et al.* GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. *BMJ* 2020;**371**:m3907.

17 McCoy RG, Dykhoff HJ, Sangaralingham L *et al.* Adoption of new Glucose-Lowering medications in the U.S.-The case of SGLT2 inhibitors: Nationwide cohort study. *Diabetes technology & therapeutics* 2019;**21**:702–12.

18 Curtis HJ, Dennis JM, Shields BM *et al.* Time trends and geographical variation in prescribing of drugs for diabetes in england from 1998 to 2017. *Diabetes, obesity & metabolism* 2018;**20**:2159–68.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

19 Arnold SV, Inzucchi SE, Tang F *et al.* Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR research to practice project. *European journal of preventive cardiology* 2017;**24**:1637–45.

20 Dave CV, Schneeweiss S, Wexler DJ *et al.* Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013-2018. *Diabetes care* 2020;**43**:921–4.

21 Le P, Chaitoff A, Misra-Hebert AD *et al.* Use of antihyperglycemic medications in U.S. Adults: An analysis of the national health and nutrition examination survey. *Diabetes care* 2020;**43**:1227–33.

22 Suchard MA, Schuemie MJ, Krumholz HM *et al.* Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: A systematic, multinational, large-scale analysis. *The Lancet* 2019;**394**:1816–26.

23 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nature reviews Rheumatology* 2015;**11**:437–41.

24 Ryan PB, Schuemie MJ, Gruber S *et al.* Empirical performance of a new user cohort method: Lessons for developing a risk identification and analysis system. *Drug safety: an international journal of medical toxicology and drug experience* 2013;**36 Suppl 1**:S59–72.

25 Schuemie MJ, Cepeda MS, Suchard MA *et al.* How confident are we about observational findings in health care: A benchmark study. *Harvard Data Science Review* 2020;**2**.

26 Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiology and drug safety* 2010;**19**:858–68.

27 Gagne JJ, Fireman B, Ryan PB *et al.* Design considerations in an active medical product safety monitoring system. *Pharmacoepidemiology and drug safety* 2012;**21 Suppl 1**:32–40.

28 Johnson ES, Bartman BA, Briesacher BA *et al.* The incident user design in comparative effectiveness research. *Pharmacoepidemiology and drug safety* 2013;**22**:1–6.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

29 Schneeweiss S, Patrick AR, Stürmer T *et al.* Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Medical care* 2007;**45**:S131–42.

30 Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and Drug Safety. 2017;**26**:459–68.

31 Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *International journal of epidemiology* 2018;**47**:2005–14.

32 Schuemie MJ, Ryan PB, DuMouchel W *et al.* Interpreting observational studies: Why empirical calibration is needed to correct p-values. *Statistics in Medicine* 2014;**33**:209–18.

33 Schuemie MJ, Hripcsak G, Ryan PB *et al.* Robust empirical calibration of p -values using observational data. Statistics in Medicine. 2016;**35**:3883–8.

34 Schuemie MJ, Hripcsak G, Ryan PB *et al.* Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proceedings of the National Academy of Sciences of the United States of America* 2018;**115**:2571–7.

35 Schuemie MJ, Ryan PB, Hripcsak G *et al.* Improving reproducibility by using high-throughput observational studies with empirical calibration. *Philosophical transactions Series A, Mathematical, physical, and engineering sciences* 2018;**376**.

36 Graham DJ, Ouellet-Hellstrom R, MaCurdy TE *et al.* Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. *JAMA: the journal of the American Medical Association* 2010;**304**:411–8.

37 Turner RM, Kwok CS, Chen-Turner C *et al.* Thiazolidinediones and associated risk of bladder cancer: A systematic review and meta-analysis. *British journal of clinical pharmacology* 2014;**78**:258–73.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

38 Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *American Journal of Epidemiology* 2016;**183**:758–64.

39 Hernán, Miguel. Antihyperglycemic therapy and cardiovascular risk: Design and emulation of a target trial using healthcare databases. Patient-Centered Outcomes Research Institute 2019.

40 American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2018. *Diabetes care* 2018;**41**:S73–85.

41 Nathan DM, Buse JB, Kahn SE *et al.* Rationale and design of the glycemia reduction approaches in diabetes: A comparative effectiveness study (GRADE). *Diabetes care* 2013;**36**:2254–61.

42 Association AD, American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2020. Diabetes Care. 2020;**43**:S98–S110.

43 Schuemie MJ, Ryan PB, Pratt N *et al.* Large-Scale evidence generation and evaluation across a network of databases (LEGEND): Assessing validity using hypertension as a case study. *Journal of the American Medical Informatics Association*;**ocaa124**.

44 Ryan PB, Buse JB, Schuemie MJ *et al.* Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes, obesity & metabolism* 2018;**20**:2585–2597. doi: 10.1111/dom.13424. Epub 2018 Jun 25.

45 You SC, Rho Y, Bikdeli B *et al.* Association of ticagrelor versus clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention in clinical practice. *Journal of the American Medical Association*;in press.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

46 Wang Y, Desai M, Ryan PB *et al.* Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes research and clinical practice* 2017;**128**:83–90.

47 Weinstein RB, Ryan PB, Berlin JA *et al.* Channeling bias in the analysis of risk of myocardial infarction, stroke, gastrointestinal bleeding, and acute renal failure with the use of paracetamol compared with ibuprofen. *Drug safety: an international journal of medical toxicology and drug experience* 2020.

48 Yuan Z, DeFalco FJ, Ryan PB *et al.* Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA: A retrospective cohort study. *Diabetes, obesity & metabolism* 2018;**20**:582–9.

49 Ammann EM, Schweizer ML, Robinson JG *et al.* Chart validation of inpatient ICD-9-CM administrative diagnosis codes for acute myocardial infarction (AMI) among intravenous immune globulin (IGIV) users in the sentinel distributed database. *Pharmacoepidemiology and drug safety* 2018;**27**:398–404. doi: 10.1002/pds.4398. Epub 2018 Feb 15.

50 Floyd JS, Blondon M, Moore KP *et al.* Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of veterans with diabetes. *Pharmacoepidemiology and drug safety* 2016;**25**:467–71. doi: 10.1002/pds.3921. Epub 2015 Nov 11.

51 Rubbo B, Fitzpatrick NK, Denaxas S *et al.* Use of electronic health records to ascertain, validate and phenotype acute myocardial infarction: A systematic review and recommendations. *International journal of cardiology* 2015;**187:705-11.**:10.1016/j.ijcard.2015.03.075. Epub 2015 Mar 5.

52 Singh S, Fouayzi H, Anzuoni K *et al.* Diagnostic algorithms for cardiovascular death in administrative claims databases: A systematic review. *Drug safety: an international journal of medical toxicology and drug experience* 2018;**23**:018–0754.

53 Wahl PM, Rodgers K, Schneeweiss S *et al.* Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

commercially-insured population. *Pharmacoepidemiology and drug safety* 2010;**19**:596–603. doi: 10.1002/pds.1924.

54 Normand SL, Morris CN, Fung KS *et al.* Development and validation of a claims based index for adjusting for risk of mortality: The case of acute myocardial infarction. *Journal of clinical epidemiology* 1995;**48**:229–43.

55 Andrade SE, Harrold LR, Tjia J *et al.* A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiology and drug safety* 2012;**21**:100–28. doi: 10.1002/pds.2312.

56 Park TH, Choi JC. Validation of stroke and thrombolytic therapy in korean national health insurance claim data. *Journal of clinical neurology* 2016;**12**:42–8. doi: 10.3988/jcn.2016.12.1.42. Epub 2015 Sep 11.

57 Gon Y, Kabata D, Yamamoto K *et al.* Validation of an algorithm that determines stroke diagnostic code accuracy in a japanese hospital-based cancer registry using electronic medical records. *BMC medical informatics and decision making* 2017;**17**:157. doi: 10.1186/s12911–017–0554–x.

58 Sung SF, Hsieh CY, Lin HJ *et al.* Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. *International journal of cardiology* 2016;**215:277-82.**:10.1016/j.ijcard.2016.04.069. Epub 2016 Apr 14.

59 Tu K, Wang M, Young J *et al.* Validity of administrative data for identifying patients who have had a stroke or transient ischemic attack using EMRALD as a reference standard. *The Canadian journal of cardiology* 2013;**29**:1388–94. doi: 10.1016/j.cjca.2013.07.676. Epub 2013 Sep 26.

60 Yuan Z, Voss EA, DeFalco FJ *et al.* Risk prediction for ischemic stroke and transient ischemic attack in patients without atrial fibrillation: A retrospective cohort study. *Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association* 2017;**26**:1721–1731. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.036. Epub 2017 Apr 6.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

61 Hennessy S, Leonard CE, Freeman CP *et al.* Validation of diagnostic codes for outpatient-originating sudden cardiac death and ventricular arrhythmia in medicaid and medicare claims data. *Pharmacoepidemiology and drug safety* 2010;**19**:555–62. doi: 10.1002/pds.1869.

62 Kaspar M, Fette G, Guder G *et al.* Underestimated prevalence of heart failure in hospital inpatients: A comparison of ICD codes and discharge letter information. *Clinical research in cardiology: official journal of the German Cardiac Society* 2018;**107**:778–787. doi: 10.1007/s00392–018–1245–z.Epub 2018 Apr 17.

63 Feder SL, Redeker NS, Jeon S *et al.* Validation of the ICD-9 diagnostic code for palliative care in patients hospitalized with heart failure within the veterans health administration. *The American journal of hospice & palliative care* 2018;**35**:959–965. doi: 10.1177/1049909117747519. Epub 2017 Dec 18.

64 Rosenman M, He J, Martin J *et al.* Database queries for hospitalizations for acute congestive heart failure: Flexible methods and validation based on set theory. *Journal of the American Medical Informatics Association: JAMIA* 2014;**21**:345–52. doi: 10.1136/amiajnl–2013–001942.Epub 2013 Oct 10.

65 Voors AA, Ouwerkerk W, Zannad F *et al.* Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *European journal of heart failure* 2017;**19**:627–634. doi: 10.1002/ejhf.785. Epub 2017 Mar 1.

66 Floyd JS, Wellman R, Fuller S *et al.* Use of electronic health data to estimate heart failure events in a Population-Based cohort with CKD. *Clinical journal of the American Society of Nephrology: CJASN* 2016;**11**:1954–1961. doi: 10.2215/CJN.03900416. Epub 2016 Aug 9.

67 Gini R, Schuemie MJ, Mazzaglia G *et al.* Automatic identification of type 2 diabetes, hypertension, ischaemic heart disease, heart failure and their levels of severity from italian general practitioners' electronic medical records: A validation study. *BMJ open* 2016;**6**:e012413. doi: 10.1136/bmjopen–2016–012413.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

68 Afzal Z, Schuemie MJ, Blijderveen JC van *et al.* Improving sensitivity of machine learning methods for automated case identification from free-text electronic medical records. *BMC medical informatics and decision making* 2013;**13:30.**:10.1186/1472–6947–13–30.

69 Lenihan CR, Montez-Rath ME, Mora Mangano CT *et al.* Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. *The Annals of thoracic surgery* 2013;**95**:20–8. doi: 10.1016/j.athoracsur.2012.05.131. Epub 2012 Dec 25.

70 Winkelmayer WC, Schneeweiss S, Mogun H *et al.* Identification of individuals with CKD from medicare claims data: A validation study. *American journal of kidney diseases: the official journal of the National Kidney Foundation* 2005;**46**:225–32. doi: 10.1053/j.ajkd.2005.04.029.

71 Grams ME, Waikar SS, MacMahon B *et al.* Performance and limitations of administrative data in the identification of AKI. *Clinical journal of the American Society of Nephrology: CJASN* 2014;**9**:682–9. doi: 10.2215/CJN.07650713. Epub 2014 Jan 23.

72 Arnold J, Ng KP, Sims D *et al.* Incidence and impact on outcomes of acute kidney injury after a stroke: A systematic review and meta-analysis. *BMC nephrology* 2018;**19**:283. doi: 10.1186/s12882–018–1085–0.

73 Sutherland SM, Byrnes JJ, Kothari M *et al.* AKI in hospitalized children: Comparing the pRIFLE, AKIN, and KDIGO definitions. *Clinical journal of the American Society of Nephrology: CJASN* 2015;**10**:554–61. doi: 10.2215/CJN.01900214. Epub 2015 Feb 3.

74 Waikar SS, Wald R, Chertow GM *et al.* Validity of international classification of diseases, ninth revision, clinical modification codes for acute renal failure. *Journal of the American Society of Nephrology: JASN* 2006;**17**:1688–94. doi: 10.1681/ASN.2006010073. Epub 2006 Apr 26.

75 Rhee C, Murphy MV, Li L *et al.* Improving documentation and coding for acute organ dysfunction biases estimates of changing sepsis severity and burden: A retrospective study. *Critical care / the Society of Critical Care Medicine* 2015;**19:338.**:10.1186/s13054–015–1048–9.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

76 Vashisht R, Jung K, Schuler A *et al.* Association of hemoglobin a1c levels with use of sulfonylureas, dipeptidyl peptidase 4 inhibitors, and thiazolidinediones in patients with type 2 diabetes treated with metformin: Analysis from the observational health data sciences and informatics initiative. *JAMA network open* 2018;**1**:e181755–5.

77 Broder MS, Chang E, Cherepanov D *et al.* Identification of potential markers for cushing disease. *Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2016;**22**:567–74. doi: 10.4158/EP15914.OR. Epub 2016 Jan 20.

78 Williams BA. The clinical epidemiology of fatigue in newly diagnosed heart failure. *BMC cardiovascular disorders* 2017;**17**:122. doi: 10.1186/s12872–017–0555–9.

79 Yabe D, Kuwata H, Kaneko M *et al.* Use of the japanese health insurance claims database to assess the risk of acute pancreatitis in patients with diabetes: Comparison of DPP-4 inhibitors with other oral antidiabetic drugs. *Diabetes, obesity & metabolism* 2015;**17**:430–4. doi: 10.1111/dom.12381. Epub 2014 Sep 17.

80 Dore DD, Hussein M, Hoffman C *et al.* A pooled analysis of exenatide use and risk of acute pancreatitis. *Current medical research and opinion* 2013;**29**:1577–86. doi: 10.1185/03007995.2013.838550. Epub 2013 Sep 13.

81 Dore DD, Chaudhry S, Hoffman C *et al.* Stratum-specific positive predictive values of claims for acute pancreatitis among commercial health insurance plan enrollees with diabetes mellitus. *Pharmacoepidemiology and drug safety* 2011;**20**:209–13. doi: 10.1002/pds.2077. Epub 2010 Dec 23.

82 Chen HJ, Wang JJ, Tsay WI *et al.* Epidemiology and outcome of acute pancreatitis in end-stage renal disease dialysis patients: A 10-year national cohort study. *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association* 2017;**32**:1731–1736. doi: 10.1093/ndt/gfw400.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

83 Ooba N, Setoguchi S, Ando T *et al.* Claims-based definition of death in japanese claims database: Validity and implications. *PLoS One* 2013;**8**:e66116. doi: 10.1371/journal.pone.0066116. Print 2013.

84 Robinson TE, Elley CR, Kenealy T *et al.* Development and validation of a predictive risk model for all-cause mortality in type 2 diabetes. *Diabetes Res Clin Pract* 2015;**108**:482–8. doi: 10.1016/j.diabres.2015.02.015. Epub 2015 Mar 16.

85 Wang L, Voss EA, Weaver J *et al.* Diabetic ketoacidosis in patients with type 2 diabetes treated with sodium glucose co-transporter 2 inhibitors versus other antihyperglycemic agents: An observational study of four us administrative claims databases. *Pharmacoepidemiology and Drug Safety* 2019;**28**:1620–8.

86 Buono JL, Mathur K, Averitt AJ *et al.* Economic burden of irritable bowel syndrome with diarrhea: Retrospective analysis of a U.S. Commercially insured population. *J Manag Care Spec Pharm* 2017;**23**:453–460. doi: 10.18553/jmcp.2016.16138. Epub 2016 Nov 21.

87 Krishnarajah G, Duh MS, Korves C *et al.* Public health impact of complete and incomplete rotavirus vaccination among commercially and medicaid insured children in the united states. *PloS one* 2016;**11**:e0145977. doi: 10.1371/journal.pone.0145977. eCollection 2016.

88 Panozzo CA, Becker-Dreps S, Pate V *et al.* Direct, indirect, total, and overall effectiveness of the rotavirus vaccines for the prevention of gastroenteritis hospitalizations in privately insured US children, 2007-2010. *American Journal of Epidemiology* 2014;**179**:895–909. doi: 10.1093/aje/kwu001. Epub 2014 Feb 26.

89 Nichols GA, Brodovicz KG, Kimes TM *et al.* Prevalence and incidence of urinary tract and genital infections among patients with and without type 2 diabetes. *Journal of diabetes and its complications* 2017;**31**:1587–91.

90 Abbas S, Ihle P, Harder S *et al.* Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: A population- and insurance-based cohort. *Pharmacoepidemiol Drug Saf* 2015;**24**:406–13. doi: 10.1002/pds.3748. Epub 2015 Feb 12.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

91 Betts KA, Woolley JM, Mu F *et al.* The prevalence of hyperkalemia in the united states. *Curr Med Res Opin* 2018;**34**:971–978. doi: 10.1080/03007995.2018.1433141. Epub 2018 Feb 21.

92 Fitch K, Woolley JM, Engel T *et al.* The clinical and economic burden of hyperkalemia on medicare and commercial payers. *Am Health Drug Benefits* 2017;**10**:202–210.

93 Leonard CE, Han X, Brensinger CM *et al.* Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. *Pharmacoepidemiology and Drug Safety* 2018;**27**:9–18.

94 Chrischilles E, Rubenstein L, Chao J *et al.* Initiation of nonselective alpha1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: A retrospective cohort study. *Clinical therapeutics* 2001;**23**:727–43.

95 Goldstein JL, Zhao SZ, Burke TA *et al.* Incidence of outpatient physician claims for upper gastrointestinal symptoms among new users of celecoxib, ibuprofen, and naproxen in an insured population in the united states. *The American journal of gastroenterology* 2003;**98**:2627–34. doi: 10.1111/j.1572–0241.2003.08722.x.

96 Donga PZ, Bilir SP, Little G *et al.* Comparative treatment-related adverse event cost burden in immune thrombocytopenic purpura. *Journal of medical economics* 2017;**20**:1200–1206. doi: 10.1080/13696998.2017.1370425. Epub 2017 Sep 8.

97 Marrett E, Kwong WJ, Frech F *et al.* Health care utilization and costs associated with nausea and vomiting in patients receiving oral Immediate-Release opioids for outpatient acute pain management. *Pain Ther* 2016;**5**:215–226. doi: 10.1007/s40122–016–0057–y.Epub 2016 Oct 4.

98 Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;**21**:154–62. doi: 10.1002/pds.2341.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

99 Burwen DR, Wu C, Cirillo D *et al.* Venous thromboembolism incidence, recurrence, and mortality based on women's health initiative data and medicare claims. *Thromb Res* 2017;**150:78-85.**:10.1016/j.thromres.2016.11.015. Epub 2016 Nov 15.

100 Coleman CI, Peacock WF, Fermann GJ *et al.* External validation of a multivariable claims-based rule for predicting in-hospital mortality and 30-day post-pulmonary embolism complications. *BMC Health Serv Res* 2016;**16**:610. doi: 10.1186/s12913–016–1855–y.

101 Ammann EM, Cuker A, Carnahan RM *et al.* Chart validation of inpatient international classification of diseases, ninth revision, clinical modification (ICD-9-CM) administrative diagnosis codes for venous thromboembolism (VTE) among intravenous immune globulin (IGIV) users in the sentinel distributed database. *Medicine* 2018;**97**:e9960. doi: 10.1097/MD.0000000000009960.

102 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.

103 Schneeweiss S, Rassen JA, Glynn RJ *et al.* High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;**20**:512.

104 Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clinical trials* 2012;**9**:48–55.

105 Murray EJ, Caniglia EC, Swanson SA *et al.* Patients and investigators prefer measures of absolute risk in subgroups for pragmatic randomized trials. *Journal of Clinical Epidemiology* 2018;**103**:10–21.

106 Hernán MA, Robins JM. Per-Protocol analyses of pragmatic trials. *The New England journal of medicine* 2017;**377**:1391–8.

107 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;**7**:177–88.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

108 Gronsbell J, Hong C, Nie L *et al.* Exact inference for the random-effect model for meta-analyses with rare events. *Statistics in Medicine* 2020;**39**:252–64.

109 Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society Series A,* 2009;**172**:137–59.

110 Schuemie MJ, Chen Y, Madigan D *et al.* Combining cox regressions across a heterogeneous distributed research network facing small and zero counts. 2021.http://arxiv.org/abs/2101.01551

111 Varin C, Reid N, Firth D. An overview of composite likelihood methods. *Statistica Sinica* 2011.

112 Voss EA, Boyce RD, Ryan PB *et al.* Accuracy of an automated knowledge base for identifying drug adverse reactions. *Journal of Biomedical Informatics* 2017;**66**:72–81.

113 Dukes O, Martinussen T, Tchetgen Tchetgen EJ *et al.* On doubly robust estimation of the hazard difference. *Biometrics* 2019;**75**:100–9.

114 Funk MJ, Westreich D, Wiesen C *et al.* Doubly robust estimation of causal effects. *American Journal of Epidemiology* 2011;**173**:761–7.

115 Martinussen T, Vansteelandt S, Gerster M *et al.* Estimation of direct effects for survival data by using the aalen additive hazards model. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2011;**73**:773–88.

116 Aalen OO. A linear regression model for the analysis of life times. *Statistics in Medicine* 1989;**8**:907–25.

117 Wang Y, Lee M, Liu P *et al.* Doubly robust additive hazards models to estimate effects of a continuous exposure on survival. *Epidemiology (Cambridge, Mass)* 2017;**28**:771.

118 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine* 2009;**28**:3083–107.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

119 Schuemie MJ, Ryan PB, Pratt N *et al.* Large-Scale evidence generation and evaluation across a network of databases (LEGEND): Principles and methods. *Journal of the American Medical Informatics Association*;**ocaa103**.

120 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;**21**:383–8.

121 Hripcsak G, Suchard MA, Shea S *et al.* Comparison of cardiovascular and safety outcomes of chlorthalidone vs hydrochlorothiazide to treat hypertension. *JAMA internal medicine* 2020.

122 Schuemie MJ, Ryan PB, Man KKC *et al.* A plea to stop using the case-control design in retrospective database studies. *Statistics in Medicine* 2019;**38**:4199–208.

123 Woelfle M, Olliaro P, Todd MH. Open science is a research accelerator. *Nature Chemistry* 2011;**3**:745–8.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1: *Schematic of LEGEND-T2DM new-user cohort design for the Class-vs-Class, Drug-vs-Drug and Heterogeneity studies.*

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1: *T2DM drug classes and individual agents within each class*

DPP4 inhibitors	GLP1 receptor antagonists	SGLT2 inhibitors	Sulfonylureas
alogliptin	albiglutide	canagliflozin	chlorpropamide
linagliptin	dulaglutide	dapagliflozin	glimepiride
saxagliptin	exenatide	empagliflozin	glipizide
sitagliptin	liraglutide	ertugliflozin	gliquidone
vildagliptin	lixisenatide		glyburide
	semaglutide		tolazamide
			tolbutamide

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 2: *Committed LEGEND-T2DM data sources and the populations they cover.*

Data source	Population	Patients	History	Data capture process and short description
IBM MarketScan Commercial Claims and Encounters (CCAE)	Commercially insured, < 65 years	142M	2000 –	Adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) from large employers and health plans who provide private healthcare coverage to employees, their spouses and dependents.
IBM MarketScan Medicare Supplemental Database (MDCR)	Commercially insured, 65 + years	10M	2000 –	Adjudicated health insurance claims of retirees with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service or capitated health plans.
IBM MarketScan Multi-State Medicaid Database (MDCD)	Medicaid enrollees, racially diverse	26M	2006 –	Adjudicated health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims.
IQVIA Open Claims (IOC)	General	160M	2010 –	Pre-adjudicated claims at the anonymized patient-level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.
Japan Medical Data Center (JMDC)	Japan, general	5.5M	2005 –	Data from 60 society-managed health insurance plans covering workers aged 18 to 65 and their dependents.
Korea National Health Insurance Service (NHIS)	2% random sample of South Korea	1M	2002 –	National administrative claims database covering the South Korean population.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Optum Clinformatics Data Mart (Optum)	Commercially or Medicare insured	85M	2000 –	Inpatient and outpatient healthcare insurance claims.
Columbia University Irving Medical Center (CIUMC)	Academic medical center patients, racially diverse	6M	1989 –	General practice, specialists and inpatient hospital services from the New York-Presbyterian hospital and affiliated academic physician practices in New York.
Department of Veterans Affairs (VA)	Veterans, older, racially diverse	12M	2000 –	National VA health care system, the largest integrated provider of medical services in the US, provided at 170 VA medical centers and 1,063 outpatient sites.
Information System for Research in Primary Care (SIDIAP)	80% of all Catalonia (Spain)	7.7M	2006 –	Primary care partially linked to inpatient data with pharmacy dispensations and primary care laboratories. Healthcare is universal and taxpayer funded in the region, and PCPs are gatekeeps for all care and responsible for repeat prescriptions.
IQVIA Disease Analyzer Germany (DAG)	Germany, general	37M	1992 –	Collection from patient management software used by general practitioners and selected specialists to document patients' medical records within their office-based practice during a visit.
Optum Electronic Health Records (OptumEHR)	US, general	93M	2006 –	Clinical information, prescriptions, lab results, vital signs, body measurements, diagnoses and procedures derived from clinical notes using natural language processing.
Yale New Haven Health System (YNHHS)	Academic medical center patients	2M	2013 –	General practice, specialists and inpatient hospital services from the YNHHS in Connecticut.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Table 3: *LEGEND-T2DM study outcomes*

Phenotype	Brief logical description	Prior development
3-point MACE	Condition record of acute myocardial infarction, hemorrhagic or ischemic stroke or sudden cardiac death during an inpatient or ER visit	[49–61]
4-point MACE	3-Point MACE + inpatient or ER visit (hospitalization) with heart failure condition record	[44,49–67]
Acute myocardial infarction	Condition record of acute myocardial infarction during an inpatient or ER vist	[49–54]
Acute renal failure	Condition record of acute renal failure during an inpatient or ER visit	[47,68–75]
Glycemic control	First hemoglobin A1c measurement with value $\leq$ 7%	[76]
Hospitalization with heart failure	Inpatient or ER visit with heart failure condition record	[44,62–67]
Measured renal dysfunction	First creatinine measurement with value > 3 mg/dL	[75]
Coronary Revascularization	Procedure record of percutaneous coronary intervention or coronary artery bypass grafting during an inpatient or ER visit	[45]
Stroke	Condition record of hemorrhagic or ischemic stroke during an inpatient or ER visit	[55–60]
Sudden cardiac death	Condition record of sudden cardiac death during an inpatient or ER visit	[52,61]
Abnormal weight gain	Abnormal weight gain record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[77]
Abnormal weight loss	Abnormal weight loss record of any type; successive records with > 90 day gap are considered independent episodes; note, weight measurements not used	[78]
Acute pancreatitis	Condition record of acute pancreatitis during an inpatient or ER visit	[79–82]
All-cause mortality	Death record of any type	[52,83,84]
Bladder cancer	Malignant tumor of urinary bladder condition record of any type; limited to earliest event per person	

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Bone fracture	Bone fracture condition record of any type; successive records with > 90 day gap are considered independent episodes	
Breast cancer	Malignant tumor of breast condition record of any type; limited to earliest event per person	
Diabetic ketoacidosis	Diabetic ketoacidosis condition record during an inpatient or ER visit	[46,85]
Diarrhea	Diarrhea condition record of any type; successive records with > 30 day gap are considered independent episodes	[86–88]
Genitourinary infection	Condition record of any type of genital or urinary tract infection during an outpatient or ER vists	[89]
Hyperkalemia	Condition record for hyperkalemia or potassium measurements > 5.6 mmol/L; successive records with >90 day gap are considered independent episodes	[90–92]
Hypoglycemia	Hypoglycemia condition record of any type; successive records with > 90 day gap are considered independent episodes	[93]
Hypotension	Hypotension condition record of any type; successive records with > 90 day gap are considered independent episodes	[94]
Joint pain	Joint pain condition record of any type; successive records with > 90 days gap are considered independent episodes	
Lower extremity amputation	Procedure record of below knee lower extremity amputation during inpatient or outpatient visit	[44,48]
Nausea	Nausea condition record of any type; successive records with > 30 day gap are considered independent episodes	[95–97]
Peripheral edema	Edema condition record of any type; successive records with > 180 day gap are considered independent episodes	
Photosensitivity	Condition record of drug-induced photosensitivity during any type of visit	
Renal cancer	Primary malignant neoplasm of kidney condition record of any type; limited to earliest event per person	
Thyroid tumor	Neoplasm of thyroid gland condition record of any type; limited to earliest event per person	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Venous thromboembolism	Venous thromboembolism condition record of any type; successive records with > 180 day gap are considered independent episodes	[98–101]
Vomiting	Vomiting condition record of any type; successive records with > 30 day gap are considered independent episodes	[95–97]

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 4: *IRB approval or waiver statement from partners.*

Data source	Statement
IBM MarketScan Commercial Claims and Encounters (CCAE)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Medicare Supplemental Database (MDCR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IBM MarketScan Multi-State Medicaid Database (MDCD)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
IQVIA Open Claims (IOC)	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI network studies.
Japan Medical Data Center (JMDC)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Korea National Health Insurance Service (NHIS)	Ajou University Institutional Review Board (AJIRB-MED-EXP-17-054 for LEGEND-HTN) and approval expected shortly for LEGEND-T2DM.
Optum Clinformatics Data Mart (Optum)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Columbia University Irving Medical Center (CIUMC)	Use of the CUIMC data source was approved by the Columbia University Institutional Review Board as an OHDSI network study (IRB# AAAO7805).
Department of Veterans Affairs (VA)	Use of the VA-OMOP data source was reviewed by the Department of Veterans Affairs Central Institutional Review Board (IRB) and was determined to meet the criteria for exemption under Exemption Category 4(3) and approved the request for Waiver of HIPAA Authorization.
Information System for Research in Primary Care (SIDIAP)	Use of the SIDIAP data source was approved by the Clinical Research Ethics Committee of IDIAPJGol (project code: 20/070-PCV)
IQVIA Disease Analyzer Germany (DAG)	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI network studies.
Optum Electronic Health Records (OptumEHR)	New England Institutional Review Board and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

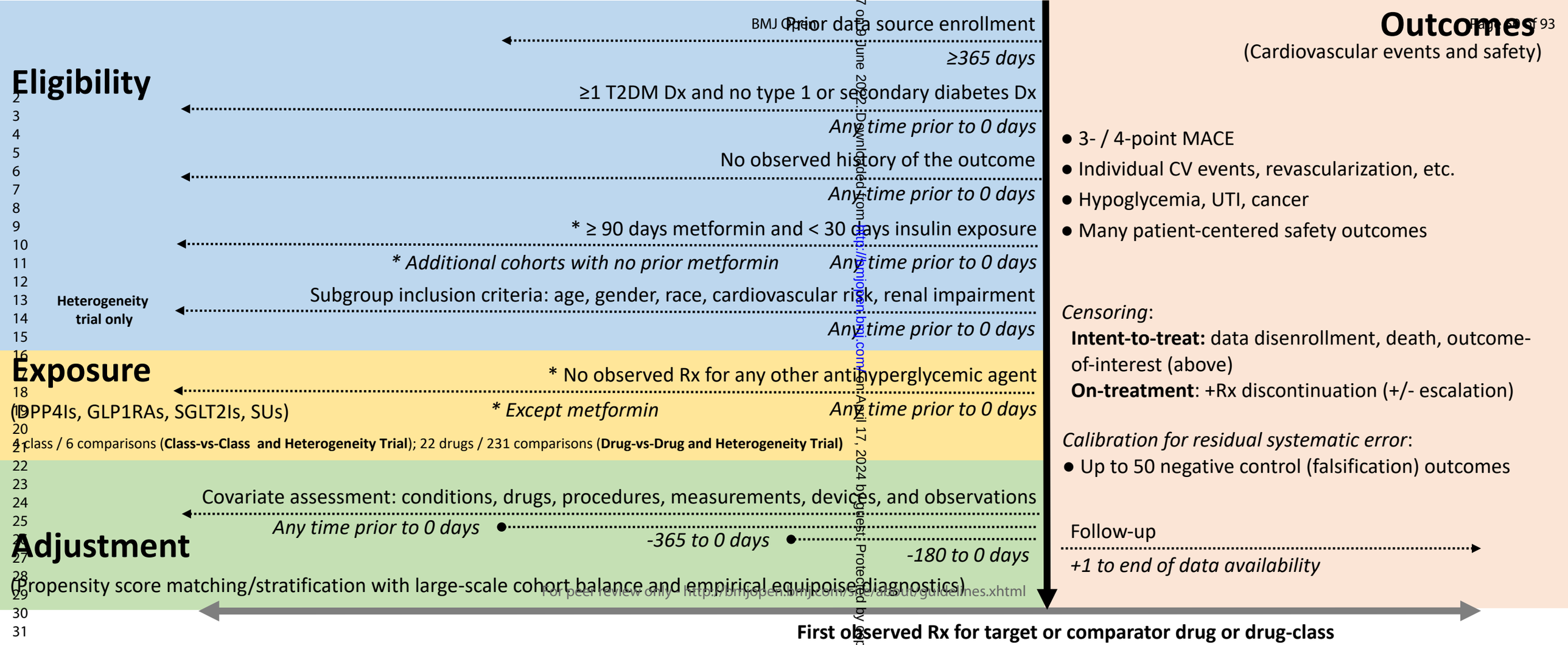
BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Yale New Haven Health System (YNHHS)	Use of the YNHHS EHR data source was approved by the Yale University Institutional Review Board as an OHDSI network study (IRB# pending).

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml



For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
http://bmjopen.bmj.com/ on April 17, 2024 by guest.
7 October 2022. Downloaded from

Appendix

A Exposure Cohort Definitions

A.1 Class-vs-Class Exposure (DPP4 New-User) Cohort / OT1

A.1.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'DPP4 inhibitors' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.

A.1.2 Additional Inclusion Criteria

- No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SU exposure

Entry events having no drug exposures of 'Sulfonylureas,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior other anti-diabetic exposure

Entry events having no drug exposures of 'Other anti-diabetics,' starting anytime on or before cohort entry start date; allow events outside observation period.

- Prior metformin use

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin,' starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events with all of the following criteria:

1. having no drug eras of 'Insulin,' starting anytime up to 30 days before cohort entry start date; allow events outside observation period; with era length > 30 days.
2. having no drug eras of 'Insulin,' starting between 30 days before and 0 days after cohort entry start date; allow events outside observation period.

A.1.3 Cohort Exit

The cohort end date will be based on a continuous exposure to 'DPP4 inhibitors': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

A.1.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.1.5 Concept: DPP4 inhibitors

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

A.1.6 Concept: GLP-1 receptor agonists

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
40170911	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO

A.1.7 Concept: SGLT2 inhibitors

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO

A.1.8 Concept: Sulfonylureas

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
19097821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

A.1.9 Concept: Other anti-diabetics

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1529331	acarbose	16681	RxNorm	NO	YES	NO
1530014	acetohexamide	173	RxNorm	NO	YES	NO
730548	bromocriptine	1760	RxNorm	NO	YES	NO
19033498	carbutamide	2068	RxNorm	NO	YES	NO
19001409	glibornuride	102846	RxNorm	NO	YES	NO
19059796	gliclazide	4816	RxNorm	NO	YES	NO
19001441	glymidine	102848	RxNorm	NO	YES	NO
1510202	miglitol	30009	RxNorm	NO	YES	NO
1502826	nateglinide	274332	RxNorm	NO	YES	NO
1525215	pioglitazone	33738	RxNorm	NO	YES	NO
1516766	repaglinide	73044	RxNorm	NO	YES	NO
1547504	rosiglitazone	84108	RxNorm	NO	YES	NO
1515249	troglitazone	72610	RxNorm	NO	YES	NO

A.1.10 Concept: Insulin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1596977	insulin, regular, human	253182	RxNorm	NO	YES	NO
1550023	insulin lispro	86009	RxNorm	NO	YES	NO
1567198	insulin aspart, human	51428	RxNorm	NO	YES	NO
1502905	insulin glargine	274783	RxNorm	NO	YES	NO
1513876	insulin lispro protamine, human	314684	RxNorm	NO	YES	NO
1531601	insulin aspart protamine, human	352385	RxNorm	NO	YES	NO
1586346	insulin, regular, pork	221109	RxNorm	NO	YES	NO
1544838	insulin glulisine, human	400008	RxNorm	NO	YES	NO
1516976	insulin detemir	139825	RxNorm	NO	YES	NO
1590165	insulin, regular, beef-pork	235275	RxNorm	NO	YES	NO
1513849	lente insulin, human	314683	RxNorm	NO	YES	NO
1562586	lente insulin, pork	93108	RxNorm	NO	YES	NO
1588986	insulin human, rDNA origin	631657	RxNorm	NO	YES	NO
1513843	lente insulin, beef-pork	314682	RxNorm	NO	YES	NO
1586369	ultralente insulin, human	221110	RxNorm	NO	YES	NO
35605670	insulin argine	1740938	RxNorm	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

35602717	insulin degludec	1670007	RxNorm	NO	YES	NO
21600713	INSULINS AND ANALOGUES	A10A	ATC	NO	YES	NO
19078608	insulin, protamine zinc, beef-pork 100 UNT/ML Injectable Suspension	311053	RxNorm	NO	YES	NO

A.1.11 Concept: Metformin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
1503297	metformin	6809	RxNorm	NO	YES	NO

A.1.12 Concept: Secondary diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
195771	Secondary diabetes mellitus	8801005	SNOMED	NO	YES	NO

A.1.13 Concept: Type 1 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201254	Type 1 diabetes mellitus	46635009	SNOMED	NO	YES	NO
435216	Disorder due to type 1 diabetes mellitus	420868002	SNOMED	NO	YES	NO
200687	Renal disorder due to type 1 diabetes mellitus	421893009	SNOMED	NO	YES	NO
377821	Disorder of nervous system due to type 1 diabetes mellitus	421468001	SNOMED	NO	YES	NO
318712	Peripheral circulatory disorder due to type 1 diabetes mellitus	421365002	SNOMED	NO	YES	NO

A.1.14 Concept: Type 2 diabetes mellitus

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
201826	Type 2 diabetes mellitus	44054006	SNOMED	NO	YES	NO
443734	Ketoacidosis due to type 2 diabetes mellitus	421750000	SNOMED	NO	YES	NO
443767	Disorder of eye due to diabetes mellitus	25093002	SNOMED	NO	YES	NO
192279	Disorder of kidney due to diabetes mellitus	127013003	SNOMED	NO	YES	NO
443735	Coma due to diabetes mellitus	420662003	SNOMED	NO	YES	NO
376065	Disorder of nervous system due to type 2 diabetes mellitus	421326000	SNOMED	NO	YES	NO
443729	Peripheral circulatory disorder due to type 2 diabetes mellitus	422166005	SNOMED	NO	YES	NO
443732	Disorder due to type 2 diabetes mellitus	422014003	SNOMED	NO	YES	NO

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.2 Metformin Use Modifier

A.2.1 No prior metformin use

Entry events having no drug eras of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

A.3 Drug-vs-Drug Exposure (Alogliptin New-User) Cohort / OT1

A.3.1 Cohort Entry Events

People with continuous observation of 365 days before event may enter the cohort when observing any of the following:

1. drug exposure of 'alogliptin' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

Restrict entry events to with all of the following criteria:

1. with the following event criteria: who are >= 18 years old.
2. having at least 1 condition occurrence of 'Type 2 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
3. having no condition occurrences of 'Type 1 diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.
4. having no condition occurrences of 'Secondary diabetes mellitus,' starting anytime on or before cohort entry start date; allow events outside observation period.

A.3.2 Additional Inclusion Criteria

- No prior with-in class exposure

Entry events having no drug exposures of 'DPP4 inhibitors excluding alogliptin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior GLP-1 receptor agonist exposure

Entry events having no drug exposures of 'GLP-1 receptor agonists,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SGLT-2 inhibitor exposure

Entry events having no drug exposures of 'SGLT2 inhibitors,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior SU exposure

Entry events having no drug exposures of 'Sulfonylureas,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior other anti-diabetic exposure

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Entry events having no drug exposures of 'Other anti-diabetics,' starting anytime on or before cohort entry start date; allow events outside observation period.

- Prior metformin use

Entry events with any of the following criteria:

1. having at least 1 drug era of 'Metformin,' starting anytime up to 90 days before cohort entry start date; allow events outside observation period; with era length >= 90 days.
2. having at least 3 drug exposures of 'Metformin,' starting anytime on or before cohort entry start date; allow events outside observation period.

- No prior insulin use or combo initiation: Proxy for < 30 days drug era anytime before index and no combination use on index

Entry events having no drug eras of 'Insulin,' starting anytime on or before cohort entry start date; allow events outside observation period; with era length > 30 days.

A.3.3 Cohort Exit

The cohort end date will be based on a continuous exposure to 'alogliptin': allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

A.3.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

A.3.5 Concept: alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
43013884	alogliptin	1368001	RxNorm	NO	YES	NO

A.3.6 Concept: DPP4 inhibitors excluding alogliptin

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40239216	linagliptin	1100699	RxNorm	NO	YES	NO
40166035	saxagliptin	857974	RxNorm	NO	YES	NO
1580747	sitagliptin	593411	RxNorm	NO	YES	NO
19122137	vildagliptin	596554	RxNorm	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

A.4 Heterogenity Study Inclusion Criteria

A.4.1 Lower age group

Entry events with the following event criteria: who are < 45 years old.

A.4.2 Middle age group

Entry events with all of the following criteria:

1. with the following event criteria: who are >= 45 years old.
2. with the following event criteria: who are < 65 years old.

A.4.3 Older age group

Entry events with the following event criteria: who are >= 65 years old.

A.4.4 Female stratum

Entry events with the following event criteria: who are female.

A.4.5 Male stratum

Entry events with the following event criteria: who are male.

A.4.6 Race stratum

Entry events with the following event criteria: race is: “black or african american,” “black,” “african american,” “african,” “bahamian,” “barbadian,” “dominican,” “dominica islander,” “haitian,” “jamaican,” “tobagoan,” “trinidadian” or “west indian.”

A.4.7 Low cardiovascular risk

Entry events with all of the following criteria:

1. having no condition occurrences of ‘Conditions indicating established cardiovascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.
2. having no procedure occurrences of ‘Procedures indicating established cardiovascular disease,’ starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.8 Higher cardiovascular risk

Entry events with any of the following criteria:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

1. having at least 1 condition occurrence of 'Conditions indicating established cardiovascular disease,' starting anytime on or before cohort entry start date; allow events outside observation period.
2. having at least 1 procedure occurrence of 'Procedures indicating established cardiovascular disease,' starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.9 Concept: Conditions indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
319844	Acute ischemic heart disease	413439005	SNOMED	NO	YES	NO
321318	Angina pectoris	194828000	SNOMED	NO	YES	NO
4124841	Aortic bifurcation syndrome	233972005	SNOMED	YES	YES	NO
312337	Arterial embolus and thrombosis	266262004	SNOMED	NO	YES	NO
4278217	Arterial thrombosis	65198009	SNOMED	NO	YES	NO
40484167	Arteriosclerosis of artery of extremity	443971004	SNOMED	NO	YES	NO
318443	Arteriosclerotic vascular disease	72092001	SNOMED	NO	YES	NO
314659	Arteritis	52089001	SNOMED	NO	NO	NO
40479625	Atherosclerosis of artery	441574008	SNOMED	NO	YES	NO
40484541	Atherosclerosis of autologous vein bypass graft of limb	442693003	SNOMED	YES	YES	NO
312902	Benign intracranial hypertension	68267002	SNOMED	YES	YES	NO
4288310	Carotid artery obstruction	69798007	SNOMED	YES	YES	NO
372924	Cerebral artery occlusion	20059004	SNOMED	NO	YES	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	YES	NO
381591	Cerebrovascular disease	62914000	SNOMED	NO	YES	NO
316494	Cerebrovascular disorder in the puerperium	6594005	SNOMED	YES	YES	NO
315286	Chronic ischemic heart disease	413838009	SNOMED	NO	YES	NO
44782819	Chronic occlusion of artery of extremity	698816006	SNOMED	NO	YES	NO
4313767	Chronic peripheral venous hypertension	423674003	SNOMED	YES	YES	NO
372721	Congenital anomaly of cerebrovascular system	65587001	SNOMED	YES	YES	NO
316995	Coronary occlusion	63739005	SNOMED	NO	YES	NO
134057	Disorder of cardiovascular system	49601007	SNOMED	NO	NO	NO
40480453	Disorder of vein of lower extremity	441739009	SNOMED	YES	YES	NO
46272492	Dissection of artery	710864009	SNOMED	YES	YES	NO
4324690	Fracture of skull	71642004	SNOMED	YES	YES	NO
441246	Hemangioma of intracranial structure	93468003	SNOMED	YES	YES	NO
380113	Hemorrhage in optic nerve sheaths	14460007	SNOMED	YES	YES	NO
192763	Injury of blood vessel	57662003	SNOMED	YES	YES	NO
4275428	Injury of vein	64583005	SNOMED	YES	YES	NO
442774	Intermittent claudication	63491006	SNOMED	NO	YES	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	YES	NO
434056	Late effects of cerebrovascular disease	195239002	SNOMED	NO	YES	NO
4146311	Leriche's syndrome	307816004	SNOMED	NO	YES	NO
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
4296029	Periarteritis	76805007	SNOMED	NO	YES	NO
260841	Perinatal subarachnoid hemorrhage	21202004	SNOMED	YES	YES	NO
317309	Peripheral arterial occlusive disease	399957001	SNOMED	NO	YES	NO
321822	Peripheral vascular disorder due to diabetes mellitus	421895002	SNOMED	NO	YES	NO
313928	Peripheral vascular complication	10596002	SNOMED	NO	YES	NO
321052	Peripheral vascular disease	400047006	SNOMED	NO	NO	NO
44782775	Peripheral vascular disease associated with another disorder	34881000119105	SNOMED	NO	YES	NO
318137	Phlebitis and thrombophlebitis of intracranial sinuses	192753009	SNOMED	YES	YES	NO
441039	Phlebitis of lower limb vein	312588002	SNOMED	NO	YES	NO
4067424	Polyarteritis	20258000	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

320749	Polyarteritis nodosa	155441006	SNOMED	YES	YES	NO
443239	Precerebral arterial occlusion	266253001	SNOMED	NO	YES	NO
440417	Pulmonary embolism	59282003	SNOMED	YES	YES	NO
4318842	Renal vasculitis	95578000	SNOMED	NO	YES	NO
380943	Rupture of syphilitic cerebral aneurysm	186893003	SNOMED	YES	YES	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	YES	NO
439040	Subdural hemorrhage	35486000	SNOMED	NO	YES	NO
320741	Thrombophlebitis	64156001	SNOMED	YES	YES	NO
4141106	Thrombosis of arteries of the extremities	33591000	SNOMED	NO	YES	NO
4132546	Traumatic brain injury	127295002	SNOMED	YES	YES	NO
4194610	Trunk arterial embolus	312593004	SNOMED	NO	YES	NO
318169	Varicose veins of lower extremity	72866009	SNOMED	YES	YES	NO
4189293	Vascular disorder of lower extremity	373408007	SNOMED	NO	YES	NO
443752	Ventricular hemorrhage	23276006	SNOMED	YES	YES	NO
432346	Dissection of vertebral artery	230730001	SNOMED	YES	YES	NO

A.4.10 Concept: Procedures indicating established cardiovascular disease

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4150819	Operative procedure on coronary artery	31413008	SNOMED	NO	YES	NO
4331725	Operative procedure on artery of extremity	22701007	SNOMED	NO	YES	NO

A.4.11 Without renal impairment

Entry events having no condition occurrences of ‘Renal impairment,’ starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.12 Renal impairment

Entry events having at least 1 condition occurrence of ‘Renal impairment,’ starting anytime on or before cohort entry start date; allow events outside observation period.

A.4.13 Concept: Renal impairment

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4030518	Renal impairment	236423003	SNOMED	NO	YES	NO

A.5 Escalation Exit Criteria

The cohort end date will be based on a continuous exposure to ‘DPP4 inhibitors’: allowing 30 days between exposures, adding 0 days after exposure ends, and using days supply and exposure end date for exposure duration.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

The person also exists the cohort when encountering any of the following events:

1. drug exposures of 'All alternative target exposures.'
2. drug exposures of 'Other anti-diabetics.'
3. drug eras of 'Insulin,' with era length > 30 days.

A.5.1 Concept: All alternative target exposures

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
44816332	albiglutide	1534763	RxNorm	NO	YES	NO
43526465	canagliflozin	1373458	RxNorm	NO	YES	NO
1594973	chlorpropamide	2404	RxNorm	NO	YES	NO
44785829	dapagliflozin	1488564	RxNorm	NO	YES	NO
45774435	dulaglutide	1551291	RxNorm	NO	YES	NO
45774751	empagliflozin	1545653	RxNorm	NO	YES	NO
793293	ertugliflozin	1992672	RxNorm	NO	YES	NO
1583722	exenatide	60548	RxNorm	NO	YES	NO
1597756	glimepiride	25789	RxNorm	NO	YES	NO
1560171	glipizide	4821	RxNorm	NO	YES	NO
19097821	gliquidone	25793	RxNorm	NO	YES	NO
1559684	glyburide	4815	RxNorm	NO	YES	NO
40170911	liraglutide	475968	RxNorm	NO	YES	NO
44506754	lixisenatide	1440051	RxNorm	NO	YES	NO
793143	semaglutide	1991302	RxNorm	NO	YES	NO
1502809	tolazamide	10633	RxNorm	NO	YES	NO
1502855	tolbutamide	10635	RxNorm	NO	YES	NO

B Outcome Cohort Definitions

B.1 3-point MACE

B.1.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction.'
2. condition occurrences of 'Sudden cardiac death.'
3. condition occurrences of 'Ischemic stroke.'
4. condition occurrences of ' Intracranial bleed Hemorrhagic stroke'.

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.1.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.1.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.1.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.1.5 Concept: Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.1.6 Concept: Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

B.1.7 Concept: Ischemic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO

B.1.8 Concept: Intracranial bleed Hemorrhagic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.1.9 Concept: Heart Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

B.2 4-point MACE

B.2.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute myocardial Infarction.'
2. condition occurrences of 'Sudden cardiac death.'
3. condition occurrences of 'Ischemic stroke.'
4. condition occurrences of 'Iintracranial bleed Hemorrhagic stroke.'
5. condition occurrences of 'Heart Failure.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.2.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.2.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.2.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

B.2.5 Concept: Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.2.6 Concept: Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

B.2.7 Concept: Ischemic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO

B.2.8 Concept: Iintracranial bleed Hemorrhagic stroke

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO
432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO
43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.2.9 Concept: Heart Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

B.3 Acute myocardial infarction

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.3.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND-T2DM] Acute myocardial Infarction.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.3.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.3.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.3.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.3.5 Concept: [LEGEND-T2DM] Acute myocardial Infarction

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4329847	Myocardial infarction	22298006	SNOMED	NO	YES	NO
314666	Old myocardial infarction	1755008	SNOMED	YES	YES	NO

B.4 Acute renal failure

B.4.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Acute Renal Failure.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.4.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 30 days.

B.4.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.4.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.4.5 Concept: Acute Renal Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
197320	Acute renal failure syndrome	14669001	SNOMED	NO	YES	NO
432961	Acute renal papillary necrosis with renal failure	298015003	SNOMED	NO	YES	NO
444044	Acute tubular necrosis	35455006	SNOMED	NO	YES	NO

B.5 Glycemic control

B.5.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. measurements of 'HbA1c_v2,' numeric value <= 7; unit: "percent."
2. measurements of 'HbA1c_v2,' numeric value <= 53; unit: "millimole per mole."

B.5.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.5.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.5.4 Concept: HbA1c_v2

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
3004410	Hemoglobin A1c (Glycated)	4548-4	LOINC	NO	YES	NO
3007263	Hemoglobin A1c/Hemoglobin.total in Blood by calculation	17855-8	LOINC	NO	YES	NO
3003309	Hemoglobin A1c/Hemoglobin.total in Blood by Electrophoresis	4549-2	LOINC	NO	YES	NO
3005673	Hemoglobin A1c/Hemoglobin.total in Blood by HPLC	17856-6	LOINC	NO	YES	NO
40762352	Hemoglobin A1c/Hemoglobin.total in Blood by IFCC protocol	59261-8	LOINC	NO	YES	NO
40758583	Hemoglobin A1c in Blood	55454-3	LOINC	NO	YES	NO
3034639	Hemoglobin A1c [Mass/volume] in Blood	41995-2	LOINC	NO	YES	NO

B.6 Hospitalization with heart failure

B.6.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. visit occurrences of 'Inpatient or ER visit'; having at least 1 condition occurrence of '[LEGEND-T2DM] Heart Failure,' starting between 0 days before and all days after 'Inpatient or ER visit' start date and starting anytime on or before 'Inpatient or ER visit' end date.

B.6.2 Cohort Exit

The cohort end date will be offset from index event's end date plus 0 days.

B.6.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 7 days of each other.

B.6.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.6.5 Concept: [LEGEND-T2DM] Heart Failure

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
315295	Congestive rheumatic heart failure	82523003	SNOMED	YES	YES	NO
316139	Heart failure	84114007	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

B.7 Measured renal dysfunction

B.7.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. measurements of 'Creatinine measurement,' numeric value > 3; unit: "milligram per deciliter."
2. measurements of 'Creatinine measurement,' numeric value > 265; unit: "micro-mole/liter."
3. measurements of 'Creatinine measurement,' numeric value > 0.265; unit: "millimole per liter."
4. measurements of 'Creatinine measurement,' numeric value > 3; unit: "milligram."

Limit cohort entry events to the earliest event per person.

B.7.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.7.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.7.4 Concept: Creatinine measurement

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
3016723	Creatinine [Mass/volume] in Serum or Plasma	2160-0	LOINC	NO	YES	NO
3022243	Creatinine [Mass/volume] in Serum or Plasma –pre dialysis	11042-9	LOINC	NO	YES	NO
3020564	Creatinine [Moles/volume] in Serum or Plasma	14682-9	LOINC	NO	YES	NO

B.8 Revascularization

B.8.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. procedure occurrences of 'PCI.'

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

2. procedure occurrences of 'CABG.'

B.8.2 Additional Inclusion Criteria

- Hospitalization

Entry events having at least 1 visit occurrence of 'Hospitalization,' starting between 0 days before and 0 days after cohort entry start date.

B.8.3 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.8.4 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.8.5 Concept: PCI

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4006788	Percutaneous transluminal coronary angioplasty	11101003	SNOMED	NO	YES	NO
4264285	Percutaneous transluminal coronary angioplasty by rotoablation	397193006	SNOMED	NO	YES	NO
4265293	Percutaneous transluminal coronary angioplasty with rotoablation, single vessel	397431004	SNOMED	NO	YES	NO
4225903	Percutaneous transluminal coronary angioplasty, multiple vessels	85053006	SNOMED	NO	YES	NO
4283892	Placement of stent in coronary artery	36969009	SNOMED	NO	YES	NO
4337738	Percutaneous endarterectomy of coronary artery	232726007	SNOMED	NO	YES	NO
4139198	Percutaneous transluminal thrombolysis of artery	426485003	SNOMED	NO	YES	NO
44511532	Percutaneous transluminal thrombolysis of artery	L71.6	OPCS4	NO	YES	NO
45770795	Percutaneous transluminal balloon angioplasty and insertion of drug eluting stent into coronary artery	936451000000108	SNOMED	NO	YES	NO
44789455	Insertion of drug-eluting coronary artery stent	203741000000101	SNOMED	NO	NO	NO
44784573	Percutaneous transluminal atherectomy of coronary artery by rotary cutter using fluoroscopic guidance	698740005	SNOMED	NO	YES	NO
44512256	Percutaneous transluminal arterial thrombolysis and reconstruction	L66.1	OPCS4	NO	YES	NO
44511273	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	K75.9	OPCS4	NO	YES	NO
44511272	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	K75.8	OPCS4	NO	NO	NO
44511271	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC	K75.4	OPCS4	NO	YES	NO
44511269	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery	K75.2	OPCS4	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

44511268	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery	K75.1	OPCS4	NO	YES	NO
44511133	Other specified transluminal balloon angioplasty of coronary artery	K49.8	OPCS4	NO	NO	NO
44511131	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	K49.3	OPCS4	NO	YES	NO
44511130	Percutaneous transluminal balloon angioplasty of multiple coronary arteries	K49.2	OPCS4	NO	YES	NO
43533353	Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	C9602	HCPCS	NO	YES	NO
43533352	Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	C9601	HCPCS	NO	NO	NO
43533248	Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	C9603	HCPCS	NO	YES	NO
43533247	Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	C9600	HCPCS	NO	NO	NO
43531440	Percutaneous transluminal insertion of metal stent into coronary artery using fluoroscopic guidance	609154002	SNOMED	NO	YES	NO
43531439	Percutaneous insertion of drug eluting stent into coronary artery using fluoroscopic guidance	609153008	SNOMED	NO	NO	NO
43531438	Percutaneous insertion of stent into aneurysm of coronary artery using fluoroscopic guidance	609152003	SNOMED	NO	NO	NO
4329263	Placement of stent in circumflex branch of left coronary artery	429499003	SNOMED	NO	YES	NO
4328103	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty	75761004	SNOMED	NO	NO	NO
4264286	Percutaneous rotational coronary endarterectomy	397194000	SNOMED	NO	NO	NO
4238755	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty, single vessel	91338001	SNOMED	NO	NO	NO
4216356	Infusion of intra-arterial thrombolytic agent with percutaneous transluminal coronary angioplasty, multiple vessels	80762004	SNOMED	NO	NO	NO
4214516	Insertion of drug coated stent	414509005	SNOMED	NO	NO	NO
4181025	Percutaneous transluminal balloon angioplasty with insertion of stent into coronary artery	429639007	SNOMED	NO	YES	NO
4178148	Placement of stent in anterior descending branch of left coronary artery	428488008	SNOMED	NO	YES	NO
4175997	Percutaneous transluminal thrombolysis and reconstruction of artery	428068004	SNOMED	NO	YES	NO
4171077	Fluoroscopic angiography of coronary artery and insertion of stent	418982001	SNOMED	NO	NO	NO
4020653	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	175066001	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

2001506	Insertion of drug-eluting coronary artery stent(s)	36.07	ICD9Proc	NO	NO	NO
2001505	Insertion of non-drug-eluting coronary artery stent(s)	36.06	ICD9Proc	NO	NO	NO
2000064	Percutaneous transluminal coronary angioplasty [PTCA]	00.66	ICD9Proc	NO	YES	NO
2001500	Single vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy without mention of thrombolytic agent	36.01	ICD9Proc	NO	YES	NO
2001504	Multiple vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy performed during the same operation, with or without mention of thrombolytic agent	36.05	ICD9Proc	NO	NO	NO
2001501	Single vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy with mention of thrombolytic agent	36.02	ICD9Proc	NO	YES	NO

B.8.6 Concept: Hospitalization

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.8.7 Concept: CABG

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
2001516	Abdominal-coronary artery bypass	36.17	ICD9Proc	NO	YES	NO
4284104	Aortocoronary artery bypass graft	67166004	SNOMED	NO	YES	NO
4229433	Aortocoronary artery bypass graft with prosthesis	8876004	SNOMED	NO	YES	NO
4146972	Aortocoronary artery bypass graft with saphenous vein graft	3546002	SNOMED	NO	YES	NO
4228305	Aortocoronary artery bypass graft with three vein grafts	405599002	SNOMED	NO	YES	NO
4228304	Aortocoronary artery bypass graft with two vein grafts	405598005	SNOMED	NO	YES	NO
4063237	Aortocoronary artery bypass graft with vein graft	17073005	SNOMED	NO	YES	NO
4148030	Aortocoronary bypass grafting	309814006	SNOMED	NO	YES	NO
4008625	Aortocoronary bypass of four or more coronary arteries	10190003	SNOMED	NO	YES	NO
4106548	Aortocoronary bypass of one coronary artery	29819009	SNOMED	NO	YES	NO
4031996	Aortocoronary bypass of three coronary arteries	14323007	SNOMED	NO	YES	NO
4234990	Aortocoronary bypass of two coronary arteries	90487008	SNOMED	NO	YES	NO
45889469	Arterial Grafting for Coronary Artery Bypass	1006216	CPT4	NO	YES	NO
4240486	Carotid-subclavian artery bypass graft with vein	59012002	SNOMED	NO	YES	NO
4336464	Coronary artery bypass graft	232717009	SNOMED	NO	YES	NO
4337056	Coronary artery bypass graft x 1	232719007	SNOMED	NO	YES	NO
4000733	Coronary artery bypass graft, anastomosis of artery of thorax to coronary artery	119565001	SNOMED	NO	YES	NO
4336467	Coronary artery bypass grafts greater than 5	232724005	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4336465	Coronary artery bypass grafts x 2	232720001	SNOMED	NO	YES	NO
4339629	Coronary artery bypass grafts x 3	232721002	SNOMED	NO	YES	NO
4337737	Coronary artery bypass grafts x 4	232722009	SNOMED	NO	YES	NO
4336466	Coronary artery bypass grafts x 5	232723004	SNOMED	NO	YES	NO
4233421	Coronary artery bypass with autogenous graft of internal mammary artery, single graft	359601003	SNOMED	NO	YES	NO
4305509	Coronary artery bypass with autogenous graft, five grafts	82247006	SNOMED	NO	YES	NO
4309432	Coronary artery bypass with autogenous graft, four grafts	39202005	SNOMED	NO	YES	NO
4011931	Coronary artery bypass with autogenous graft, three grafts	10326007	SNOMED	NO	YES	NO
4253805	Coronary artery bypass with autogenous graft, two grafts	74371005	SNOMED	NO	YES	NO
45887879	Coronary artery bypass, using arterial graft(s)	1006217	CPT4	NO	YES	NO
2107242	Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	33534	CPT4	NO	YES	NO
2107243	Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	33535	CPT4	NO	YES	NO
2107244	Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	33536	CPT4	NO	YES	NO
2107231	Coronary artery bypass, using arterial graft(s); single arterial graft	33533	CPT4	NO	YES	NO
45889898	Coronary artery bypass, using venous graft(s) and arterial graft(s)	1006208	CPT4	NO	YES	NO
2107223	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (List separately in addition to code for primary procedure)	33518	CPT4	NO	YES	NO
2107224	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (List separately in addition to code for primary procedure)	33519	CPT4	NO	YES	NO
2107226	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (List separately in addition to code for primary procedure)	33521	CPT4	NO	YES	NO
2107227	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (List separately in addition to code for primary procedure)	33522	CPT4	NO	YES	NO
2107228	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (List separately in addition to code for primary procedure)	33523	CPT4	NO	YES	NO
2107222	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (List separately in addition to code for primary procedure)	33517	CPT4	NO	YES	NO
45887862	Coronary artery bypass, vein only	1006200	CPT4	NO	YES	NO
2107217	Coronary artery bypass, vein only; 2 coronary venous grafts	33511	CPT4	NO	YES	NO
2107218	Coronary artery bypass, vein only; 3 coronary venous grafts	33512	CPT4	NO	YES	NO
2107219	Coronary artery bypass, vein only; 4 coronary venous grafts	33513	CPT4	NO	YES	NO
2107220	Coronary artery bypass, vein only; 5 coronary venous grafts	33514	CPT4	NO	YES	NO
2107221	Coronary artery bypass, vein only; 6 or more coronary venous grafts	33516	CPT4	NO	YES	NO
2107216	Coronary artery bypass, vein only; single coronary venous graft	33510	CPT4	NO	YES	NO
2001515	Double internal mammary-coronary artery bypass	36.16	ICD9Proc	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4000732	Internal mammary-coronary artery bypass graft	119564002	SNOMED	NO	YES	NO
2001514	Single internal mammary-coronary artery bypass	36.15	ICD9Proc	NO	YES	NO
4233420	Single internal mammary-coronary artery bypass	359597003	SNOMED	NO	YES	NO
45889467	Venous Grafting Only for Coronary Artery Bypass	1006199	CPT4	NO	YES	NO
4020216	Revision of bypass for coronary artery	175036008	SNOMED	NO	NO	NO
4305852	Off-pump coronary artery bypass	418824004	SNOMED	NO	NO	NO

B.9 Stroke

B.9.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND-T2DM] Stroke (ischemic or hemorrhagic).'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting between all days before and 1 days after cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.9.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.9.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.9.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.9.5 Concept: [LEGEND-T2DM] Stroke (ischemic or hemorrhagic)

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
372924	Cerebral artery occlusion	20059004	SNOMED	NO	NO	NO
375557	Cerebral embolism	75543006	SNOMED	NO	NO	NO
376713	Cerebral hemorrhage	274100004	SNOMED	NO	NO	NO
443454	Cerebral infarction	432504007	SNOMED	NO	YES	NO
441874	Cerebral thrombosis	71444005	SNOMED	NO	NO	NO
439847	Intracranial hemorrhage	1386000	SNOMED	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

432923	Subarachnoid hemorrhage	21454007	SNOMED	NO	NO	NO
43530727	Spontaneous cerebral hemorrhage	291571000119106	SNOMED	NO	NO	NO
4148906	Spontaneous subarachnoid hemorrhage	270907008	SNOMED	NO	NO	NO

B.10 Sudden cardiac death

B.10.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Sudden cardiac death.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.10.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.10.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.10.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.10.5 Concept: [LEGEND HTN] Sudden cardiac death

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4048809	Brainstem death	230802007	SNOMED	NO	YES	NO
321042	Cardiac arrest	410429000	SNOMED	NO	YES	NO
442289	Death in less than 24 hours from onset of symptoms	53559009	SNOMED	NO	YES	NO
4317150	Sudden cardiac death	95281009	SNOMED	NO	YES	NO
4132309	Sudden death	26636000	SNOMED	NO	YES	NO
437894	Ventricular fibrillation	71908006	SNOMED	YES	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.11 Abnormal weight gain

B.11.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. observations of '[LEGEND HTN] Abnormal weight gain.'

B.11.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.11.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.11.4 Concept: [LEGEND HTN] Abnormal weight gain

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
439141	Abnormal weight gain	161833006	SNOMED	NO	YES	NO

B.12 Abnormal weight loss

B.12.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. observations of '[LEGEND HTN] Abnormal weight loss.'

B.12.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.12.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.12.4 Concept: [LEGEND HTN] Abnormal weight loss

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
435928	Abnormal weight loss	267024001	SNOMED	NO	YES	NO
40303297	Weight loss (& abnormal)	139091004	SNOMED	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.13 Acute pancreatitis

B.13.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Acute pancreatitis.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting anytime on or before cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.13.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.13.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.13.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.13.5 Concept: [LEGEND HTN] Acute pancreatitis

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
199074	Acute pancreatitis	197456007	SNOMED	NO	YES	NO
2109394	Placement of drains, peripancreatic, for acute pancreatitis	48000	CPT4	NO	NO	NO
2109400	Resection or debridement of pancreas and peripancreatic tissue for acute necrotizing pancreatitis	48105	CPT4	NO	NO	NO
2109395	Placement of drains, peripancreatic, for acute pancreatitis; with cholecystostomy, gastrostomy, and jejunostomy	48001	CPT4	NO	NO	NO
42737025	Resection or debridement of pancreas and peripancreatic tissue for acute necrotizing pancreatitis (Deprecated)	48005	CPT4	NO	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.14 All-cause mortality

B.14.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. death of any form.

Limit cohort entry events to the earliest event per person.

B.14.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.14.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.15 Bladder cancer

B.15.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of 'Bladder cancer' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

B.15.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.15.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.15.4 Concept: Bladder cancer

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
197508	Malignant tumor of urinary bladder	399326009	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

B.16 Bone fracture

B.16.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Bone fracture.'

B.16.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.16.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.16.4 Concept: Bone fracture

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
75053	Fracture of bone	125605004	SNOMED	NO	YES	NO
4071354	Open reduction of fracture with internal fixation	20701002	SNOMED	NO	YES	NO

B.17 Breast cancer

B.17.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of 'Malignant tumor of breast' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

B.17.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.17.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.17.4 Concept: Malignant tumor of breast

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4112853	Malignant tumor of breast	254837009	SNOMED	NO	YES	NO

B.18 Diabetic ketoacidosis

B.18.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. condition occurrences of 'Diabetic ketoacidosis.'

Restrict entry events to having at least 1 visit occurrence of 'Inpatient or ER visit,' starting between all days before and 1 days after cohort entry start date and ending between 0 days before and all days after cohort entry start date.

B.18.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 7 days.

B.18.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.18.4 Concept: Inpatient or ER visit

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
262	Emergency Room and Inpatient Visit	ERIP	Visit	NO	YES	NO
9203	Emergency Room Visit	ER	Visit	NO	YES	NO
9201	Inpatient Visit	IP	Visit	NO	YES	NO

B.18.5 Concept: Diabetic ketoacidosis

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
443727	Diabetic ketoacidosis	420422005	SNOMED	NO	YES	NO

B.19 Diarrhea

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.19.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN} Diarrhea.'

B.19.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.19.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.19.4 Concept: [LEGEND HTN} Diarrhea

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
196523	Diarrhea	62315008	SNOMED	NO	YES	NO
4134607	Diarrheal disorder	128333008	SNOMED	NO	YES	NO
201773	Enteritis of small intestine	64613007	SNOMED	NO	NO	NO
80141	Functional diarrhea	47812002	SNOMED	NO	YES	NO
4207688	Infectious enteritis	55184003	SNOMED	NO	NO	NO
4324838	Noninfectious enteritis	71207007	SNOMED	NO	NO	NO
197596	Toxic gastroenteritis	71583005	SNOMED	NO	YES	NO
196620	Viral enteritis	78420004	SNOMED	NO	YES	NO

B.20 Genitourinary infection

B.20.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'UTI.'

Limit qualifying entry events to the earliest event per person.

B.20.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.20.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.20.4 Concept: UTI

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
81902	Urinary tract infectious disease	68566005	SNOMED	NO	YES	NO
4167328	Pyuria	4800001	SNOMED	NO	YES	NO
77340	Genitourinary tract infection in pregnancy	267204006	SNOMED	NO	YES	NO
4265485	Bacteriuria	61373006	SNOMED	NO	YES	NO
4126297	Chronic obstructive pyelonephritis	236379002	SNOMED	NO	YES	NO
195588	Cystitis	38822007	SNOMED	NO	YES	NO
198806	Abscess of prostate	8725005	SNOMED	YES	YES	NO
4126267	Chronic radiation cystitis	236629009	SNOMED	YES	YES	NO
194997	Prostatitis	9713002	SNOMED	YES	NO	NO
4077499	Sterile pyuria	275742001	SNOMED	YES	YES	NO
442345	Syphilis of kidney	59530001	SNOMED	YES	YES	NO
4062493	Mumps nephritis	17121006	SNOMED	YES	YES	NO
45757237	Diphtheria tubulointerstitial nephropathy	1086071000119103	SNOMED	YES	YES	NO
36714969	Asymptomatic bacteriuria	720406004	SNOMED	YES	YES	NO
195743	Diphtheritic cystitis	48278001	SNOMED	YES	YES	NO
201353	Irradiation cystitis	11251000	SNOMED	YES	YES	NO
4047937	Neonatal urinary tract infection	12301009	SNOMED	YES	YES	NO
201792	Nongonococcal urethritis	84619001	SNOMED	YES	YES	NO
4128384	Non-infective cystitis	236623005	SNOMED	YES	NO	NO
78357	Reactive arthritis triad	67224007	SNOMED	YES	YES	NO
195313	Urethral abscess	67277002	SNOMED	YES	YES	NO
197919	Urethral stricture due to infection	80375002	SNOMED	YES	YES	NO
439349	Cystitis associated with another disorder	197845000	SNOMED	YES	NO	NO
4227291	Hemorrhagic cystitis	87696004	SNOMED	YES	NO	NO
4060312	Infections of urethra in pregnancy	199206009	SNOMED	YES	NO	NO
4127564	Acute cystitis - culture-negative	236624004	SNOMED	YES	YES	NO
4126141	Chronic cystitis - culture negative	236626002	SNOMED	YES	NO	NO
4127565	Recurrent cystitis - culture-negative	236625003	SNOMED	YES	YES	NO
4207186	Viral infection by site	312130009	SNOMED	YES	YES	NO
4207190	Fungal infection by site	312146001	SNOMED	YES	YES	NO
434557	Tuberculosis	56717001	SNOMED	YES	YES	NO
432251	Disease caused by parasite	17322007	SNOMED	YES	YES	NO
36102152	Protozoal infectious disorders	10037072	MedDRA	YES	YES	NO
433417	Gonorrhea	15628003	SNOMED	YES	YES	NO
36102938	Chlamydial infections	10008561	MedDRA	YES	YES	NO

B.21 Hyperkalemia

B.21.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Hyperkalemia.'
2. measurements of '[LEGEND HTN] Potassium measurement,' numeric value > 5.6; unit: "millimole per liter."

B.21.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.21.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.21.4 Concept: [LEGEND HTN] Hyperkalemia

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
434610	Hyperkalemia	14140009	SNOMED	NO	YES	NO

B.21.5 Concept: [LEGEND HTN] Potassium measurement

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40789890	Potassium	Bld-Ser-Plas	LP42189-8	LOINC	NO	YES
4245152	Potassium measurement	59573005	SNOMED	NO	YES	NO
4276440	Potassium level - finding	365760004	SNOMED	NO	YES	NO

B.22 Hypoglycemia

B.22.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Hypoglycemia.'

B.22.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.22.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.22.4 Concept: Hypoglycemia

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
380688	Hypoglycemic coma	267384006	SNOMED	NO	YES	NO
4048805	Non-diabetic hypoglycemic coma	230796005	SNOMED	YES	YES	NO
4226798	Hypoglycemic coma due to diabetes mellitus	421725003	SNOMED	NO	YES	NO
4228112	Hypoglycemic coma due to type 1 diabetes mellitus	421437000	SNOMED	YES	YES	NO
36714116	Hypoglycemic coma due to type 2 diabetes mellitus	719216001	SNOMED	NO	YES	NO
24609	Hypoglycemia	302866003	SNOMED	NO	YES	NO
23034	Neonatal hypoglycemia	52767006	SNOMED	YES	YES	NO
4029424	Non-diabetic hypoglycemia	237637005	SNOMED	YES	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4029423	Hypoglycemia due to diabetes mellitus	237633009	SNOMED	NO	YES	NO
45769876	Hypoglycemia due to type 1 diabetes mellitus	84371000119108	SNOMED	YES	YES	NO
45757363	Hypoglycemia due to type 2 diabetes mellitus	120731000119103	SNOMED	NO	YES	NO
4096804	Drug-induced hypoglycemia without coma	190448007	SNOMED	NO	YES	NO

B.23 Hypotension

B.23.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Hypotension.'

B.23.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.23.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.23.4 Concept: [LEGEND HTN] Hypotension

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
313232	Hemodialysis-associated hypotension	408667000	SNOMED	YES	YES	NO
317002	Low blood pressure	45007003	SNOMED	NO	YES	NO
314432	Maternal hypotension syndrome	88887003	SNOMED	YES	YES	NO

B.24 Joint pain

B.24.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Joint pain.'

B.24.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.24.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.24.4 Concept: Joint pain

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
77074	Joint pain	57676002	SNOMED	NO	NO	NO

B.25 Lower extremity amputation

B.25.1 Cohort Entry Events

People may enter the cohort when observing any of the following:

1. procedure occurrences of 'below-knee amputations.'

Restrict entry events to having no procedure occurrences of 'below-knee amputations,' starting in the 30 days prior to cohort entry start date.

B.25.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 0 days.

B.25.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.25.4 Concept: below-knee amputations

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4264289	Amputation of ankle	397218006	SNOMED	NO	YES	NO
2006242	Amputation of ankle through malleoli of tibia and fibula	84.14	ICD9Proc	NO	YES	NO
2105446	Amputation, leg, through tibia and fibula	27880	CPT4	NO	YES	NO
2105804	Amputation, foot; midtarsal (eg, Chopart type procedure)	28800	CPT4	NO	YES	NO
2105805	Amputation, foot; transmetatarsal	28805	CPT4	NO	YES	NO
2105806	Amputation, metatarsal, with toe, single	28810	CPT4	NO	YES	NO
2105807	Amputation, toe; metatarsophalangeal joint	28820	CPT4	NO	YES	NO
2105808	Amputation, toe; interphalangeal joint	28825	CPT4	NO	YES	NO
2105451	Amputation, ankle, through malleoli of tibia and fibula (eg, Syme, Pirogoff type procedures), with plastic closure and resection of nerves	27888	CPT4	NO	YES	NO
2105447	Amputation, leg, through tibia and fibula; with immediate fitting technique including application of first cast	27881	CPT4	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

4338257	Amputation of leg through tibia and fibula	88312006	SNOMED	NO	YES	NO
2105448	Amputation, leg, through tibia and fibula; open, circular (guillotine)	27882	CPT4	NO	YES	NO
4108565	Amputation of the foot	180030006	SNOMED	NO	YES	NO
2006229	Amputation of toe	84.11	ICD9Proc	NO	YES	NO
4159766	Amputation of toe	371186005	SNOMED	NO	YES	NO
4054983	Amputation through foot	211570009	SNOMED	NO	YES	NO
2006230	Amputation through foot	84.12	ICD9Proc	NO	YES	NO
4143797	Amputation through metatarsal bones	265739006	SNOMED	NO	YES	NO
2105450	Amputation, leg, through tibia and fibula; re-amputation	27886	CPT4	NO	YES	NO
2006231	Disarticulation of ankle	84.13	ICD9Proc	NO	YES	NO
2006244	Disarticulation of knee	84.16	ICD9Proc	NO	YES	NO
4018719	Midtarsal amputation of foot	209724005	SNOMED	NO	YES	NO
2006243	Other amputation below knee	84.15	ICD9Proc	NO	YES	NO
2105449	Amputation, leg, through tibia and fibula; secondary closure or scar revision	27884	CPT4	YES	YES	NO
4219032	Amputation of lower limb	397117006	SNOMED	NO	YES	NO

B.26 Nausea

B.26.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Nausea.'

B.26.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.26.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

B.26.4 Concept: [LEGEND HTN] Nausea

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
30284	Motion sickness	37031009	SNOMED	YES	YES	NO
31967	Nausea	422587007	SNOMED	NO	YES	NO

B.27 Peripheral edema

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.27.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Edema.'

B.27.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.27.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.27.4 Concept: Edema

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
433595	Edema	267038008	SNOMED	NO	YES	NO
133299	Swelling of limb	80068009	SNOMED	NO	YES	NO

B.28 Photosensitivity

B.28.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of 'Photosensitivity.'

B.28.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.28.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 90 days of each other.

B.28.4 Concept: Photosensitivity

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4300445	Acantholytic actinic keratosis	403199007	SNOMED	YES	NO	NO
4263325	Actinic cheilitis	46795000	SNOMED	YES	NO	NO
4031007	Actinic folliculitis	238529007	SNOMED	YES	NO	NO
442179	Actinic granuloma	79144000	SNOMED	YES	NO	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

For peer review only

37312586	Actinic intraepidermal squamous cell carcinoma	789051005	SNOMED	YES	NO	NO
138825	Actinic keratosis	201101007	SNOMED	YES	NO	NO
4304266	Actinic keratosis of eyelid	418686001	SNOMED	YES	NO	NO
4064057	Actinic lichen planus	200999007	SNOMED	YES	NO	NO
141374	Actinic prurigo	201015007	SNOMED	YES	NO	NO
4031006	Actinic reaction	238528004	SNOMED	YES	NO	NO
439096	Actinic reticuloid	52636001	SNOMED	YES	NO	NO
4070156	Acute actinic otitis externa	21543000	SNOMED	YES	NO	NO
4290728	Acute effect of ultraviolet radiation on normal skin	402165001	SNOMED	YES	NO	NO
4241471	Acute phytophotodermatitis	58306008	SNOMED	YES	NO	NO
36674412	Ataxia, photosensitivity, short stature syndrome	773769008	SNOMED	YES	NO	NO
4293437	Atrophic actinic keratosis	403200005	SNOMED	YES	NO	NO
4066470	Berloque dermatitis	200836002	SNOMED	YES	NO	NO
4119822	Bowenoid actinic keratosis	304524009	SNOMED	YES	NO	NO
4033832	Brachioradial summer pruritus	109252001	SNOMED	YES	NO	NO
37116482	Burn of skin caused by exposure to artificial source of ultraviolet radiation	733209003	SNOMED	YES	NO	NO
37116483	Burn of skin caused by ultraviolet radiation due to ultraviolet light therapy	733210008	SNOMED	YES	NO	NO
4290729	Chronic effect of ultraviolet radiation on normal skin (photo-aging)	402166000	SNOMED	YES	NO	NO
4239682	Chronic phototoxic dermatitis	69231004	SNOMED	YES	NO	NO
4242265	Chronic phytophotodermatitis	58419006	SNOMED	YES	NO	NO
36715275	Cutaneous photosensitivity and lethal colitis syndrome	720820000	SNOMED	YES	NO	NO
4230340	Cutis rhomboidalis nuchae	89019003	SNOMED	YES	NO	NO
4300796	Diffuse actinic hyperkeratosis	403208003	SNOMED	YES	NO	NO
141650	Disseminated superficial actinic porokeratosis	41495000	SNOMED	YES	NO	NO
4301164	Drug-induced pellagra	403626007	SNOMED	YES	NO	NO
4299673	Familial actinic prurigo of lip	403210001	SNOMED	YES	NO	NO
4234867	Food-induced photosensitivity	90386003	SNOMED	YES	NO	NO
36715367	Hair defect with photosensitivity and intellectual disability syndrome	721007005	SNOMED	YES	NO	NO
4308081	Hydroa vacciniforme	200837006	SNOMED	YES	NO	NO
42709861	Hyperkeratotic actinic keratosis	449733007	SNOMED	YES	NO	NO
4112749	Hypertrophic solar keratosis	254667001	SNOMED	YES	NO	NO
4300444	Idiopathic photo-onycholysis	403196000	SNOMED	YES	NO	NO
4031005	Juvenile spring eruption	238526000	SNOMED	YES	NO	NO
4116197	Lentigo maligna	302836005	SNOMED	YES	NO	NO
4299672	Lichenoid actinic keratosis	403198004	SNOMED	YES	NO	NO
4080922	Light - exacerbated acne	238530002	SNOMED	YES	NO	NO
4293560	Multiple actinic keratoses	403202002	SNOMED	YES	NO	NO
4293562	Multiple actinic keratoses involving face	403204001	SNOMED	YES	NO	NO
4300794	Multiple actinic keratoses involving forehead and temples	403205000	SNOMED	YES	NO	NO
4300795	Multiple actinic keratoses involving hands	403206004	SNOMED	YES	NO	NO
4293563	Multiple actinic keratoses involving legs	403207008	SNOMED	YES	NO	NO
4293561	Multiple actinic keratoses involving scalp	403203007	SNOMED	YES	NO	NO
37110331	Neonatal burn due to phototherapy caused by ultraviolet radiation	724551009	SNOMED	YES	NO	NO
4006157	Nodular elastosis with cysts and comedones	111200005	SNOMED	YES	NO	NO
37110590	Occupational phototoxic reaction to skin contact with exogenous photoactive agent	724873006	SNOMED	YES	NO	NO
4292224	Photoaggravated psoriasis	402318000	SNOMED	YES	NO	NO
4293593	Photoaggravated rosacea	403365004	SNOMED	YES	NO	NO
4290732	Photoaggravation of disorder	402179009	SNOMED	YES	NO	NO
42537710	Photodermatitis co-occurrent and due to autoimmune disease	737249005	SNOMED	YES	NO	NO
4318376	Photoonycholysis	95342006	SNOMED	YES	NO	NO
4234104	Photosensitivity	90128006	SNOMED	NO	YES	NO

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

42537712	Phototoxic reaction of skin caused by cosmetic	737251009	SNOMED	YES	NO	NO
42537711	Phototoxic reaction of skin caused by fragrance	737250005	SNOMED	YES	NO	NO
4290730	Phototoxic reaction to dye	402174004	SNOMED	YES	NO	NO
4298594	Phototoxic reaction to tar or derivative	402175003	SNOMED	YES	NO	NO
4298593	Phototoxic reaction to topical chemical	402173005	SNOMED	YES	NO	NO
4270722	Phototoxic reaction to topically applied medicament	402176002	SNOMED	YES	NO	NO
42539382	Pigmentation of skin caused by artificial ultraviolet light	762664003	SNOMED	YES	NO	NO
42709860	Pigmented actinic keratosis	449732002	SNOMED	YES	NO	NO
4080921	Polymorphous light eruption	238525001	SNOMED	YES	NO	NO
4176424	Polymorphous light eruption, diffuse erythematous type	51048002	SNOMED	YES	NO	NO
4223992	Polymorphous light eruption, eczematous type	84036008	SNOMED	YES	NO	NO
4204365	Polymorphous light eruption, papular type	54116000	SNOMED	YES	NO	NO
4195589	Polymorphous light eruption, papulovesicular type	79372000	SNOMED	YES	NO	NO
4278846	Polymorphous light eruption, plaque type	6618004	SNOMED	YES	NO	NO
4297664	Porphyria-induced phototoxic burn	402480004	SNOMED	YES	NO	NO
4296207	Proliferative actinic keratosis	403201009	SNOMED	YES	NO	NO
4066838	Pruritus estivalis	201024003	SNOMED	YES	NO	NO
4031625	Solar comedone	238518008	SNOMED	YES	NO	NO
4185267	Solar degeneration	43982006	SNOMED	YES	NO	NO
4031162	Solar lentiginosis	238712007	SNOMED	YES	NO	NO
4217502	Solar lentigo	72100002	SNOMED	YES	NO	NO
4296189	Solar pruritus	402177006	SNOMED	YES	NO	NO
4033831	Solar pruritus of elbows	109251008	SNOMED	YES	NO	NO
4031004	Strimmer dermatitis	238522003	SNOMED	YES	NO	NO
4296206	Sun-induced wrinkles	403197009	SNOMED	YES	NO	NO

B.29 Renal cancer

B.29.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of 'Primary malignant neoplasm of kidney' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

B.29.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.29.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.29.4 Concept: Primary malignant neoplasm of kidney

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
198985	Primary malignant neoplasm of kidney	93849006	SNOMED	NO	YES	NO
4215373	Renal cell carcinoma	41607009	SNOMED	NO	NO	NO

B.30 Thyroid tumor

B.30.1 Cohort Entry Events

People with continuous observation of 365 days before event enter the cohort when observing any of the following:

1. condition occurrence of 'Neoplasm of thyroid gland' for the first time in the person's history.

Limit cohort entry events to the earliest event per person.

B.30.2 Cohort Exit

The person also exists the cohort at the end of continuous observation.

B.30.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 0 days of each other.

B.30.4 Concept: Neoplasm of thyroid gland

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
4131909	Neoplasm of thyroid gland	127018007	SNOMED	NO	YES	NO

B.31 Venous thromboembolism

B.31.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Venous thromboembolism (pulmonary embolism and deep vein thrombosis).'

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.31.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.31.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 180 days of each other.

B.31.4 Concept: [LEGEND HTN] Venous thromboembolism (pulmonary embolism and deep vein thrombosis)

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
435616	Amniotic fluid embolism	17263003	SNOMED	YES	YES	NO
435887	Antepartum deep vein thrombosis	49956009	SNOMED	YES	YES	NO
196715	Budd-Chiari syndrome	82385007	SNOMED	YES	YES	NO
4062269	Cerebral venous thrombosis in pregnancy	200259003	SNOMED	YES	YES	NO
442055	Obstetric air pulmonary embolism	200286003	SNOMED	YES	YES	NO
433832	Obstetric blood-clot pulmonary embolism	200299000	SNOMED	YES	YES	NO
435026	Obstetric pulmonary embolism	200284000	SNOMED	YES	YES	NO
440477	Obstetric pyemic and septic pulmonary embolism	267284008	SNOMED	YES	YES	NO
318137	Phlebitis and thrombophlebitis of intracranial sinuses	192753009	SNOMED	YES	YES	NO
199837	Portal vein thrombosis	17920008	SNOMED	YES	YES	NO
438820	Postpartum deep phlebothrombosis	56272000	SNOMED	YES	YES	NO
440417	Pulmonary embolism	59282003	SNOMED	NO	YES	NO
254662	Pulmonary infarction	64662007	SNOMED	NO	YES	NO
4235812	Septic thrombophlebitis	439731006	SNOMED	YES	YES	NO
195294	Thrombosed hemorrhoids	75955007	SNOMED	YES	YES	NO
4187790	Thrombosis of retinal vein	46085004	SNOMED	YES	YES	NO
444247	Venous thrombosis	111293003	SNOMED	NO	YES	NO
44834756	Acute venous embolism and thrombosis of other specified veins	453.8	ICD9CM	NO	NO	NO

B.32 Vomiting

B.32.1 Cohort Entry Events

People enter the cohort when observing any of the following:

1. condition occurrences of '[LEGEND HTN] Vomiting.'

B.32.2 Cohort Exit

The cohort end date will be offset from index event's start date plus 1 day.

B.32.3 Cohort Eras

Entry events will be combined into cohort eras if they are within 30 days of each other.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

B.32.4 Concept: [LEGEND HTN] Vomiting

Concept ID	Concept Name	Code	Vocabulary	Excluded	Descendants	Mapped
40480290	Hyperemesis	444673007	SNOMED	YES	YES	NO
4216862	Postoperative vomiting	72245005	SNOMED	YES	YES	NO
441408	Vomiting	422400008	SNOMED	NO	YES	NO
440785	Vomiting of pregnancy	90325002	SNOMED	YES	YES	NO

C Negative Control Concepts

Negative outcome controls specified through condition occurrences that map to (a descendent of) the indicated concept ID

	Concept ID
Abnormal posture	439935
Abnormal pupil	436409
Abrasion and/or friction burn of multiple sites	443585
Abrasion and/or friction burn of trunk without infection	199192
Absence of breast	4088290
Absent kidney	4092879
Acquired hallux valgus	75911
Acquired keratoderma	137951
Anal and rectal polyp	73241
Anomaly of jaw size	45757682
Benign paroxysmal positional vertigo	81878
Bizarre personal appearance	4216219
Burn of forearm	133655
Cachexia	134765
Calcaneal spur	73560
Cannabis abuse	434327
Changes in skin texture	140842
Chondromalacia of patella	81378
Cocaine abuse	432303
Colostomy present	4201390
Complication due to Crohn's disease	46269889
Complication of gastrostomy	434675
Contact dermatitis	134438
Contusion of knee	78619
Crohn's disease	201606
Derangement of knee	76786
Developmental delay	436077
Deviated nasal septum	377910
Difficulty sleeping	4115402
Disproportion of reconstructed breast	45757370
Effects of hunger	433111
Endometriosis	433527
Epidermoid cyst	4170770
Exhaustion due to excessive exertion	437448
Feces contents abnormal	4092896
Feces contents abnormal	4092896
Foreign body in ear	374801
Foreign body in orifice	259995
Foreskin deficient	4096540

(Continued on Next Page...)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Negative outcome controls specified through condition occurrences that map to (a descendent of) the indicated concept ID *(continued)*

	Concept ID
Galactosemia	439788
Ganglion cyst	40481632
Ganglion cyst	40481632
Genetic disorder carrier	4168318
Hammer toe	433577
Hereditary thrombophilia	4231770
High risk sexual behavior	4012570
Homocystinuria	4012934
Impacted cerumen	374375
Impacted cerumen	374375
Impingement syndrome of shoulder region	4344500
Inadequate sleep hygiene	40481897
Ingrowing nail	139099
Injury of knee	444132
Jellyfish poisoning	4265896
Kwashiorkor	432593
Lagophthalmos	381021
Late effect of contusion	434203
Late effect of motor vehicle accident	438329
Lipid storage disease	4027782
Lymphangioma	433997
Macular drusen	4083487
Malingering	4051630
Marfan's syndrome	258540
Mechanical complication of internal orthopedic device, implant AND/OR graft	432798
Melena	4103703
Minimal cognitive impairment	439795
Nicotine dependence	4209423
Nicotine dependence	4209423
Noise effects on inner ear	377572
Non-toxic multinodular goiter	136368
Nonspecific tuberculin test reaction	40480893
Nonspecific tuberculin test reaction	40480893
Opioid abuse	438130
Opioid abuse	438130
Opioid intoxication	4299094
Passing flatus	4091513
Physiological development failure	437092
Poisoning by tranquilizer	433951
Postviral fatigue syndrome	4202045
Presbyopia	373478
Psychalgia	439790
Ptotic breast	81634
Regular astigmatism	380706
Senile hyperkeratosis	141932
Social exclusion	4019836
Somatic dysfunction of lumbar region	36713918
Splinter of face without major open wound	443172
Sprain of ankle	81151
Strain of rotator cuff capsule	72748
Symbolic dysfunction	432436
Tear film insufficiency	378427
Tobacco dependence syndrome	437264
Tooth loss	433244
Toxic effect of lead compound	436876
Toxic effect of tobacco and nicotine	440612
Tracheostomy present	4201387
Unsatisfactory tooth restoration	45757285

(Continued on Next Page...)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

Negative outcome controls specified through condition occurrences that map to (a descendent of) the indicated concept ID *(continued)*

	Concept ID
Verruca vulgaris	140641
Wrist joint pain	4115367
Wristdrop	440193

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-057977 on 9 June 2022. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.