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Risk Factors Associated with Severe Hypoglycemia Among Patients with Type 2 Diabetes Mellitus Treated with Insulin

Protocol Electronically Signed and Approved by Lilly: approval date provided below

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2. List of Abbreviations

Term	Definition
PMTX+	PharMetrics Plus (IQVIA's Real World Adjudicated Claims Database)
ERB	Ethical review board
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AR	Adverse reaction
CCI	Charlson comorbidity index
CRF	Case report form
DRS	Disease risk score
DCSI	Diabetes complications severity index
T2DM	Type 2 diabetes mellitus
SH	Severe hypoglycemia
SAR	Serious adverse reaction

3. Abstract

Title

Risk Factors Associated with Severe Hypoglycemia Among Type 2 Diabetes Mellitus Patients Treated with Insulin

Rationale and background

Diabetes mellitus is one of the most common chronic health conditions in the world, affecting roughly 422 million (8.4%) adults around the world and an estimated 30.2 million (12.2%) adults in the U.S. While T2DM can initially be managed with noninsulin therapies, insulin therapy is typically required to achieve glycemic control after disease progression. However, progression of T2DM and insulin therapy can lead to a higher risk of hypoglycemia. Although hypoglycemia has been accepted by patients and providers as an inevitable consequence of preventing long-term diabetes complications, recent studies have found that hypoglycemia, including the severe form, is a potentially preventable cause of morbidity, mortality, high costs and impaired quality of life. Identification of additional risk factors will help clinicians recognize that there are factors which can lead to severe hypoglycemia and that it is essential that patients be prepared for hypoglycemia and severe hypoglycemia at all times if they are taking insulin.

Research question and objectives

The research questions motivating this study are focused on risk factors for and the economic burden of severe hypoglycemia in patients with type 2 diabetes (T2DM) mellitus treated with insulin.

- Besides well-established risk factors, what other patient clinical characteristics are associated with higher risk of developing severe hypoglycemia in patients with T2DM?

Primary and secondary study objectives are detailed below:

1. To identify risk factors for severe hypoglycemic (SH) events in insulin-treated T2DM patients. Identification of patients at different risk of SH will be based on an evaluation of risk factors of SH using a retrospective nested case-control design.
2. To describe and compare baseline demographic and clinical characteristics in the following patient subgroups:
    - Patients who experience at least a SH event during the index period
    - Patients who have not experienced a SH event
3. To describe and compare healthcare resource utilization (HCRU) and cost in T2DM patients on insulin in the patient subgroups described above.

Study design

For the primary and secondary objectives, a retrospective nested case-control study with incidence density sampling utilizing adjudicated healthcare administrative claims data will be used to identify risk factors of SH based on demographic and clinical characteristics in insulin-treated T2DM patients. For the primary objective, patients with (cases) and at risk for (controls) a SH event while on insulin treatment will be exact matched on well-established risk factors and

will be assessed for presence of potential risk factors during the 12-month pre-index period, with acute exposure to specific risk factors assessed during the 1-month period prior to the index date. Baseline demographic and clinical characteristics will be assessed over a 12-month pre-index period. Economic outcomes will be assessed in the fixed 6-month post-index period in the subgroup of patients with sufficient post-index follow-up.

Population

Patients with evidence of T2DM and insulin treatment in IQVIA's Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) during the index period (1/1/2013 – 12/31/2018) will be identified. Patients will have at least 1 year of continuous enrollment prior to the first insulin claim occurring during the index period. For the primary objective there will be no defined follow-up period. Patients with evidence of cancer, pregnancy, gestational diabetes, type 1 diabetes, bariatric surgery, and data quality issues during the study period will be excluded. Patients with SH occurring while a patient is actively on insulin treatment will be included as cases in the study, with the index date defined as the date of first SH event. Patients on insulin therapy who have not had a SH event at the time of case identification will serve as potential controls. Once a patient has a SH event while on insulin therapy, they will be removed from the pool of potential controls. Cases will be direct matched to potential controls on well-established risk factors, and the index date for controls will be defined as the index date of the matched case. Once a control patient has been matched to a case, they will exit the control pool (i.e., controls can only be matched to one case).

Variables

Well-established risk factors of SH include older age, sulfonylurea use, renal insufficiency, and prior SH. Other potential risk factors for SH include type of insulin used, anti-diabetic use (by drug class), concomitant use of non-diabetes medications (including beta blockers, opioids, psychotropic medications, estrogen, corticosteroids), and cognitive dysfunction. Patient demographics (age, sex, region, payer type, health plan type) and clinical characteristics (Charlson comorbidity index [CCI], comorbid conditions, risk factors above, diabetes complications severity index [DCSI]) will also be described. Economic variables include healthcare resource utilization (inpatient, outpatient, pharmacy) and costs (total and broken out by service type). Finally glucagon use before and after SH will be reported.

Data sources

Data from IQVIA's Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) will be utilized. PMTX+ is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage from 2011 represent approximately 40 million active lives annually. The database has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area of the US are represented, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies.

Study size

A power calculation estimated that the study will need approximately 440 to 2,250 patients with and without SH to have 80% power to detect odds ratios ranging from 1.5 to 1.2, respectively. A preliminary count of patients with T2DM with severe hypoglycemia and insulin use within 6 months prior to the index SH event found 61,200 patients meeting these criteria. We estimate that roughly 70% will be excluded from the study after applying selection criteria and a match rate of 70%, leaving an estimated 12,852 patients with SH to be matched to controls.

Data analysis

Descriptive statistics will be reported using frequency and percentage distributions for categorical variables. Mean, median, and standard deviation will be generated as measures of central tendency and variance for continuous and count variables. Conditional logistic regression will be used to identify potential risk factors for SH after matching. Forward or backward variable selection procedures may be used to determine which variables to include in the final model. All-cause total healthcare costs, Emergency Department costs, and inpatient hospitalization costs may be compared among patients with and without SH using generalized linear models (GLM), with gamma distribution and log link to adjust for potential confounders. Emergency Department utilization and inpatient utilization may be compared among patients with and without SH using GLM with Poisson or negative binomial distribution and log link.

Milestones

Milestone	Planned date
Data extraction	01 November 2019
Cohort build, matching, and descriptive analysis of matched/unmatched populations	08 November 2019
Data analysis and presentation of results tables	06 December 2019
Final report of study results	30 December 2019

4. Amendments and Updates

None

5. Milestones

Milestone	Planned date
Data extraction	01 November 2019
Cohort build, matching, and descriptive analysis of matched/unmatched populations	08 November 2019
Data analysis and presentation of results tables	06 December 2019
Final report of study results	30 December 2019

6. Rationale and Background

Diabetes mellitus is one of the most common chronic health conditions in the world, affecting roughly 422 million (8.4%) adults around the world (Silbert et al., 2018) and an estimated 30.2 million (12.2%) adults in the U.S. Type 2 diabetes mellitus (T2DM) accounts for roughly 95% of diabetes cases. It is one of the leading causes of blindness, heart attacks, kidney failure, stroke, and lower extremity amputation and is the 7th leading cause of death in the U.S (CDC, 2017).

While T2DM can initially be managed with noninsulin therapies, insulin therapy is typically required to achieve glycemic control after disease progression. However, insulin therapy contributes to a higher risk of hypoglycemia when administered incorrectly or in the presence of patient-related risk factors (e.g. inadequate or erratic carbohydrate consumption following administration of insulin). While mild or nocturnal hypoglycemia is usually resolved at home, severe hypoglycemia (SH) requires assistance from others to recover (e.g. family members, caregivers) that may require medical assistance which may result in an emergency room or inpatient visit (ADA 2019, Holstein et al., 2012, Leese et al., 2003). While commonly accepted by patients and their healthcare providers as an inevitable consequence of preventing long-term diabetes complications, hypoglycemia is increasingly recognized an important and potentially preventable cause of morbidity, mortality, high costs, diminished productivity, and impaired quality of life (Silbert et al., 2018). In a recent observational healthcare claims database study of patients with T2DM treated with basal insulin, patients with a SH event in the first year after basal insulin initiation had nearly $10,000 more in healthcare expenditures at baseline compared to patients who did not have a SH event. Total healthcare expenditures during 1-year follow-up increased by over $11,000 in the SH group, while there was no change in the non-SH group (Fonseca et al., 2017).

While the risk of SH is known to be elevated in the T1DM population, the risk has been understudied in the T2DM population, which makes up the majority of all diabetes patients. Among the T2DM population, a strong risk factor for SH is insulin use (Geller et al. 2014, Misra-Hebert et al., 2018, Lee et al., 2017, Karter et al. 2017, Han et al. 2018), however, there is a paucity of knowledge about the range of SH risk factors among the insulin-treated sub-population. Frequently reported risk factors of SH among patients with T2DM are older age (Fonseca et al. 2017, Lee et al., 2017, Karter et al. 2017, Han et al. 2018, Shao et al. 2018),

sulfonylurea use (Misra-Hebert et al. 2018, Karter et al. 2017), previous history of hypoglycemia-related medical visit (severe or non-severe) (Fonseca et al. 2017, Misra-Hebert et al. 2018), duration of diabetes (Han et al. 2018, Shao et al. 2018), and renal disease (Lin et al. 2010, Fonseca et al. 2018, Karter et al. 2017, Han et al. 2018). Other understudied but potential risk factors include concomitant medication use (e.g., beta blockers, psychotropics, opioids, estrogen hormone replacement therapy, corticosteroids) (Kenny et al. 2013, Graveling & Frier 2009, White et al. 2007, Martin-Timon & Ganizo-Gomez, 2015), oral anti-diabetic medications (Misra-Hebert et al. 2018, Han et al. 2018, Lee et al. 2017), and cognitive impairment (Kostev et al. 2014, Lee et al. 2017).

This study aims to identify risk factors other than those that have already been reported (such as non-diabetes medication use, other co-morbidities) among insulin-treated adults withT2DM using an administrative healthcare claims database. Furthermore, the study will describe and compare baseline demographic and clinical characteristics as well as healthcare resource utilization and cost in insulin-treated patients with T2DM who do and do not experience a SH event.

7. Research Question and Objectives

The research questions motivating this study are focused on risk factors for and the economic burden of severe hypoglycemia in patients with T2DM treated with insulin.

- Besides well-established risk factors, what other patient clinical characteristics are associated with higher risk of developing severe hypoglycemia in patients with T2DM?

7.1. Primary Objective

1. To identify risk factors for severe hypoglycemic (SH) events in insulin-treated patients with type 2 diabetes mellitus (T2DM). Risk factors will be evaluated using a retrospective nested case-control study design. Risk factors will be grouped into those that are well-established, as reported in the literature, and other potential risk factors. Conditional logistic regression will be used after direct matching on well-established risk factors to uncover new risk factors for SH in this patient population.

7.2. Secondary Objectives

2. To describe and compare baseline demographic and clinical characteristics in the following patient subgroups:
    - Patients who experience at least one SH event during the index period
    - Patients who have not experienced a SH event
3. To describe and compare healthcare resource utilization (HCRU) and cost in patients with T2DM on insulin in the patient subgroups described above.

8. Research Methods

8.1. Study design

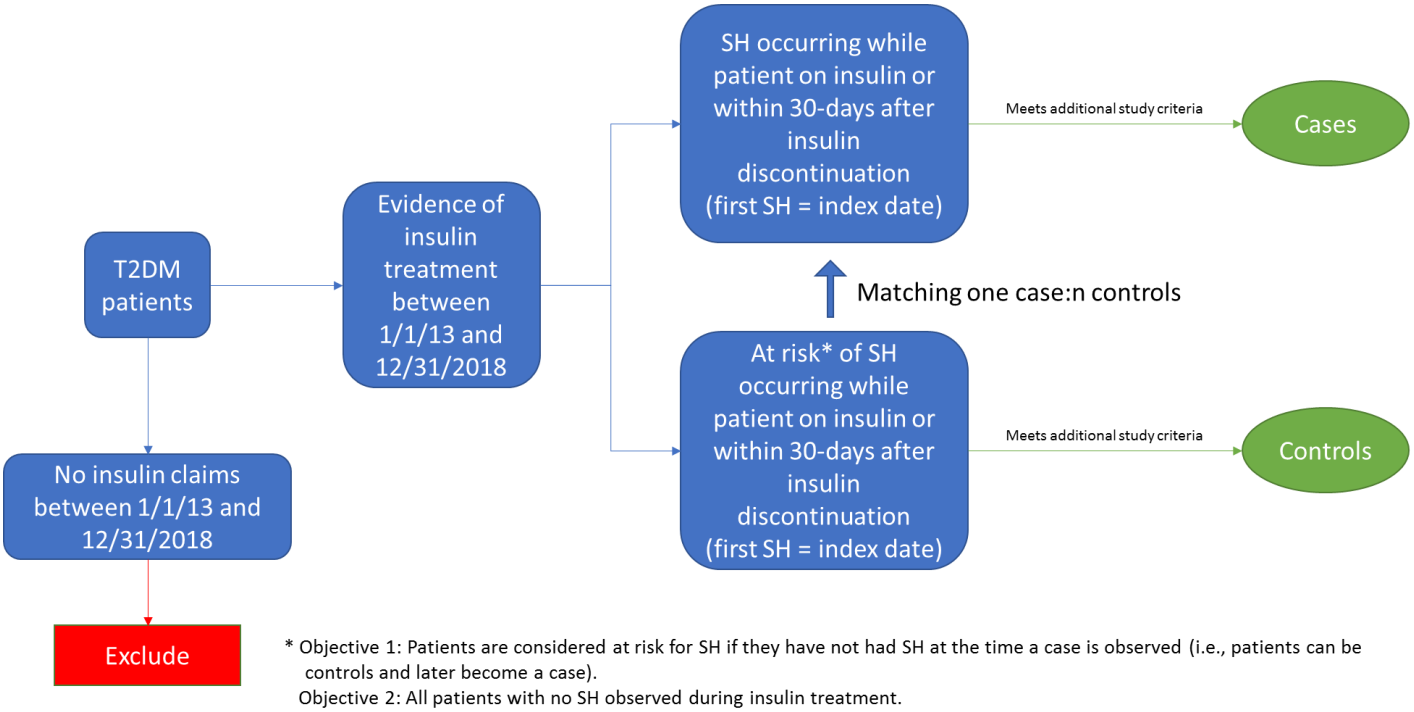
For the primary and secondary objectives, a retrospective nested case-control study with incidence density sampling (Richardson DB. 2004) utilizing adjudicated healthcare administrative claims data (IQVIA's Read World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) will be used to identify risk factors of SH among patients with insulin-treated type 2 diabetes mellitus (T2DM) and to describe the demographic and clinical characteristics in patients with and without SH. The study will be comprised of the following patient cohorts:

- Patients who experience a SH event while on insulin therapy (cases)
- Patients who are at risk of a SH event while on insulin therapy (controls)

Patients with evidence of T2DM during the index period (1/1/2013 - 12/31/2018) will be identified. Patients with insulin use will be identified and followed from the first insulin claim until insulin discontinuation (defined as a gap in treatment of > 90 days [Moura CS, et. al. 2018]) to establish the insulin treatment period. Patients will be evaluated for SH occurring during the insulin treatment period. Cases will be defined as patients with at least 1 SH occurring during the insulin treatment period or within 30-days after insulin discontinuation, indexed on the first SH, and, for the primary objective, exact-matched to control patients on well-established risk factors (i.e., age, use of sulfonylurea, renal insufficiency). Controls will be selected from all patients still at risk for SH at the time a case is found, and will be indexed on the same date as the matched case. Once a control patient is selected as a match, that patient will exit the control pool. Figure 8-1 illustrates the cohort selection process. Figure 8-2 illustrates the overall study design.

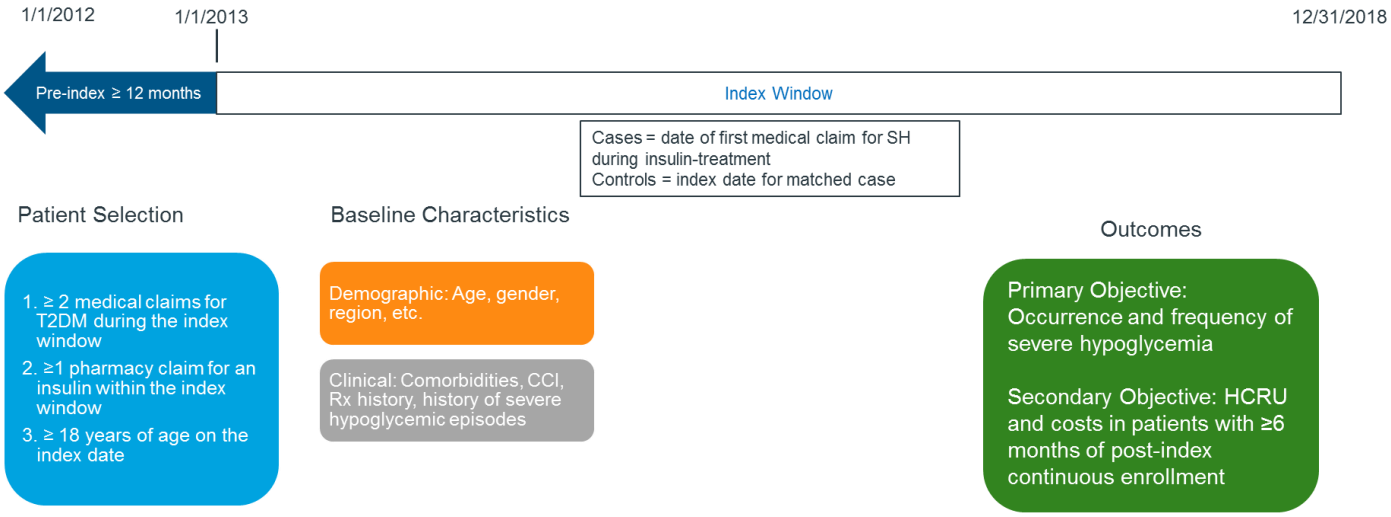
For the primary objective, patients with SH will be matched to patients without SH as described above. For the secondary objective, all control patients with no evidence of SH during the insulin treatment period will be included in the no SH cohort. Baseline demographic and clinical characteristics will be assessed over a 12 month pre-index period, with some variables also reported within 1-month prior to SH to capture acute events. Economic outcomes will be assessed during the fixed 6-month post-index period.

Figure 8-1. Patient Selection Process



* Objective 1: Patients are considered at risk for SH if they have not had SH at the time a case is observed (i.e., patients can be controls and later become a case).
Objective 2: All patients with no SH observed during insulin treatment.

Figure 8-2. Overall Study Design



8.2. Setting

8.2.1. Study Time Periods

- Study period: 1/1/2012 to 12/31/2018
- Index period: 1/1/2013 to 12/31/2018
- Index date:
    - Cases: date of first SH occurring between 1/1/2013 and 12/31/2018, while a patient remains on insulin treatment
    - Controls: index date for matched case
- Pre-index period:
    - 12 months prior to index date
- Post-index period:
    - Primary Objective: no defined post-index period
    - Secondary objective #2: fixed 6 months after index date

8.2.2. Selection Criteria

Patients will be included in the study if they meet the below selection criteria:

8.2.2.1. Inclusion Criteria

1) ≥2 diagnoses for T2DM (ICD-9-CM codes: 250.x0, 250.x2; ICD-10-CM codes: E11.xx) OR 1 diagnosis code for T2DM and 1 claim for antidiabetic medication between 1/1/2013 and 12/31/2018 (Klompas et. al. 2013)
2) ≥ 1 claim for insulin between 1/1/2013 and 12/31/2018
3) ≥ 18 years of age on the date of first insulin claim occurring during the index period
4) ≥ 1 year of continuous health plan enrollment with both medical and pharmacy benefits prior to the index date (Defined as date of first SH in cases. For controls, the index date will be assigned as the date of first SH for the corresponding matched case).

8.2.2.2. Exclusion Criteria

Patients will be excluded if they meet any of the below criteria:

1) Diagnosis of type 1 diabetes (ICD-9-CM: 250.x1, 250.x3; ICD-10-CM: E10.xx), gestational diabetes (ICD-9-CM: 648.8x; ICD-10-CM: O24.4), diabetes mellitus complicating pregnancy, childbirth or the puerperium (ICD-9-CM: 648.0x; ICD-10-CM: O24.4), nonclinical diabetes ((ICD-9-CM: 790.29; ICD-10-CM: R73.09), secondary diabetes (ICD-9-CM: 249.x; ICD-10-CM: E13.x), pregnancy (ICD-9-CM: 630.xx-679.xx, v22.x-v24.x; ICD-10-CM: O00-O9A, Z30-Z39), neonatal diabetes mellitus (ICD-9-CM: 75.1; ICD-10-CM: P70.2) (Klompas e. al. 2013)
2) Evidence of cancer or bariatric surgery during the study period
3) Data quality issues, defined as missing or invalid year of birth, unknown sex, unknown region, aged ≥ 65 years not covered by Medicare Advantage, missing or invalid payer type (i.e., covered by Medicare Supplemental, State Children's Health Insurance Program (SCHIP), or pharmacy only coverage due to incomplete data capture)

8.2.3. Cohort Selection

Once the cohort of insulin-treated T2DM patients is selected, the insulin treatment period will be established for each patient, and calculated as the number of days between the first insulin claim and the earliest of: the end of the index period or the insulin discontinuation date. Insulin discontinuation will be defined as a gap >90 days between the end of supply of an insulin claim and the date of the next insulin claim (Moura et al. 2018) or last day of enrollment.

Cases will be defined as patients with ≥ 1 SH event occurring during the insulin treatment period or within 30-days after insulin discontinuation and will be indexed on the date of the first SH, based on ICD-9-CM and ICD-10-CM diagnosis codes proposed by Karter et al. (Karter et al., 2019), described in Section 8.7.1. Insulin patients still at risk for SH (i.e., still on insulin treatment and with no SH events) will serve as potential controls.

Primary Objective

Potential controls will be direct matched to cases on well-established risk factors (described in Section 8.7.2), with a ratio of up to 4 controls to 1 case, and the index date will be defined as the index date for the matched case. If there is a sufficient sample size of cases, 1:1 matching will be used (Strom, Kimmel and Hennessy 2012).

Secondary Objectives

Demographic and baseline clinical characteristics will be compared among all eligible patients, with no post-index continuous enrollment requirement. For analyses on post-index HRU and costs, only patients with ≥6 months of continuous health plan enrollment with both medical and pharmacy benefits after the index date will be included. Specific subgroups for comparison are outlined in Section 8.2.4.

8.2.4. Subject Groups

For the primary and secondary objectives, patients will be grouped into the following cohorts:

- Cases: Patients with ≥ 1 SH event occurring during the insulin treatment period
- Controls: Patients who are still on insulin therapy and have not had SH prior to or at the time of case identification (i.e., patients still at risk of SH when a case is identified). A control that later became a case within 12 months after the occurrence date of the current case will be excluded from the risk set of controls for each case to avoid potential overlap of 12-month risk factor assessment periods.

Primary Objective

Risk factors for SH will be identified among the matched cases and controls. Controls who are not matched to a case will not be included in the patient cohorts for the primary objective.

Secondary Objectives

Patients will be grouped into the following subgroups:

- Cases (as defined above)
- Controls (as defined above)

Analysis for the secondary objective will compare the following:

- Matched cases vs. controls

8.3. Variables

8.3.1. Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics will be collected during the 12-month pre-index period, including the index date unless otherwise specified. Some variables will also be reported within 1-month prior to the index date, to capture acute exposure. The baseline demographic and clinical characteristics of interest are detailed in Table 1. Other variables of interest may be added after data exploration and will be captured during the 12-month pre-index

period and/or within 1 month prior to the index date. And in the final report and manuscript, we will make sure these additional variables, if any, will be reported appropriately as non pre-specified in the protocol.

Table 8-1. Baseline Variables and Definitions

Variable	Definition
Age, continuous	The age at index date will be defined as the number of years between the year of index and the year of birth
Age, categorical	18–49, 50–64, 65–74, and 75+ years
Sex	Male/Female as reported in the data
Geographic region	5 regions as reported in the data: Northeast, Midwest, South, West, Unknown
Insurance type	Insurance type at index, as reported in the data and grouped into the following categories: Commercial, Medicaid, Medicare Risk, Self-Insured, other/unknown
Health plan type	Health plan type, as reported in the data and grouped into the following categories: HMO, PPO, POS, Consumer-directed, Indemnity, Other
Index year	The year of the index date will be extracted and reported as follows: 2014, 2015, 2016, 2017, 2018
Charlson comorbidity index (CCI), continuous	A CCI score will be assigned by assessing all claims occurring in the 12-month pre-index period (including the index date) for ICD-9-CM and ICD-10-CM codes indicative of comorbid conditions for the Dartmouth-Manitoba modification of the Charlson Comorbidity Index. the distribution of raw CCI scores will be reported
CCI, categorical	CCI score will be grouped into the following categories: 0, 1, 2, 3, 4+
Diabetes Complications Severity Index (DCSI)	A DCSI score will be assigned by assessing all claims occurring in the 12-month pre-index period (including the index date) for ICD-9-CM and ICD-10-CM codes indicative of diabetes complications. A higher DCSI score is indicative of more severe diabetes at baseline. The distribution of raw DCSI will be reported.
DCSI, categorical	DCSI will be grouped into the following categories: 0, 1, 2, 3, 4, 5+.
Alcohol/Drug Abuse	A binary indicator variable will be created for patients with any claims for alcohol/drug abuse occurring during the 12-month pre-index period
Anxiety	A binary indicator variable will be created for patients with any claims for anxiety occurring during the 12-month pre-index period
Asthma	A binary indicator variable will be created for patients with any claims for asthma occurring during the 12-month pre-index period

Variable	Definition
Cardiac Arrhythmia	A binary indicator variable will be created for patients with any claims for cardiac arrhythmia occurring during the 12-month pre-index period
Cardiac Valvular Disease	A binary indicator variable will be created for patients with any claims for cardiac valvular disease occurring during the 12-month pre-index period
Cerebrovascular Disease	A binary indicator variable will be created for patients with any claims for cerebrovascular disease occurring during the 12-month pre-index period
Chronic Kidney Disease (excluding end stage renal disease)	A binary indicator variable will be created for patients with any claims for chronic kidney disease occurring during the 12-month pre-index period
Chronic Pain/Fibromyalgia	A binary indicator variable will be created for patients with any claims for chronic pain or fibromyalgia occurring during the 12-month pre-index period
Congestive Heart Failure	A binary indicator variable will be created for patients with any claims for congestive heart failure occurring during the 12-month pre-index period
COPD	A binary indicator variable will be created for patients with any claims for COPD occurring during the 12-month pre-index period
Dementia	A binary indicator variable will be created for patients with any claims for dementia occurring during the 12-month pre-index period
Depression	A binary indicator variable will be created for patients with any claims for depression occurring during the 12-month pre-index period
Diabetic retinopathy	A binary indicator variable will be created for patients with any claims for diabetic retinopathy occurring during the 12-month pre-index period
Dyslipidemia	A binary indicator variable will be created for patients with any claims for dyslipidemia occurring during the 12-month pre-index period
Epilepsy/Seizure Disorder	A binary indicator variable will be created for patients with any claims for epilepsy/seizure disorders occurring during the 12-month pre-index period
Hepatitis	A binary indicator variable will be created for patients with any claims for hepatitis occurring during the 12-month pre-index period
HIV/AIDS	A binary indicator variable will be created for patients with any claims for HIV/AIDS occurring during the 12-month pre-index period
Hypertension	A binary indicator variable will be created for patients with any claims for hypertension occurring during the 12-month pre-index period
Liver/Gallbladder/Pancreatic Disease	A binary indicator variable will be created for patients with any claims for liver/gallbladder/pancreatic disease occurring during the 12-month pre-index period

Variable	Definition
Myocardial Infarction(MI)/CAD	A binary indicator variable will be created for patients with any claims for MI/CAD occurring during the 12-month pre-index period
Osteoarthritis	A binary indicator variable will be created for patients with any claims for osteoarthritis occurring during the 12-month pre-index period
Paralysis/Hemiplegia/Paraplegia	A binary indicator variable will be created for patients with any claims for paralysis/hemiplegia/paraplegia occurring during the 12-month pre-index period
Peptic Ulcer Disease	A binary indicator variable will be created for patients with any claims for peptic ulcer disease occurring during the 12-month pre-index period
Peripheral Vascular Disease	A binary indicator variable will be created for patients with any claims for peripheral vascular disease occurring during the 12-month pre-index period
Renal Failure/Dialysis	A binary indicator variable will be created for patients with any claims for renal failure/dialysis occurring during the 12-month pre-index period
Rheumatologic Disease (SLE, RA, AS, PsA)	A binary indicator variable will be created for patients with any claims for rheumatologic disease occurring during the 12-month pre-index period
Schizophrenia	A binary indicator variable will be created for patients with any claims for schizophrenia occurring during the 12-month pre-index period
Sleep Disorders	A binary indicator variable will be created for patients with any claims for sleep disorders occurring during the 12-month pre-index period
Smoking or History of Smoking	A binary indicator variable will be created for patients with any claims for smoking or history of smoking occurring during the 12-month pre-index period
Thyroid Disease	A binary indicator variable will be created for patients with any claims for thyroid disease occurring during the 12-month pre-index period
Prior diabetes medication use	A series of binary indicator variables will be created for patients with claims for the following anti-diabetics: basal insulin, rapid-acting insulin, short-acting insulin, NPH, insulin mixes, and oral anti-diabetics by drug class (alpha-glucosidase inhibitors, amylin analogs, antidiabetic combos, biguanides, dipeptidyl peptidase IV inhibitors, GLP-1 agonistsincretin mimetic agents, meglitinides, sodium-glucose cotransporter inhibitor, sulfonylureas, thiazolidinediones) occurring during the 12-month pre-index period
New insulin user	A binary indicator variable will be created for patients considered new to insulin therapy, defined as having duration of insulin therapy < 6 months
Use of beta-blockers	A binary indicator variable will be created for patients with any claims for beta-blockers during the 12-month pre-index period

Variable	Definition
Acute use of beta-blockers	A binary indicator variable will be created for patients with any claims for beta-blockers within 1-month pre-index
Use of opioids	A binary indicator variable will be created for patients with any claims for opioids during the 12-month pre-index period
Acute use of opioids	A binary indicator variable will be created for patients with any claims for opioids within 1-month pre-index
Use of psychotropic medications	A series of binary indicator variables will be created for patients with any claims for psychotropic medications (by drug class) during the 12-month pre-index
Acute use of psychotropic medications	A series of binary indicator variables will be created for patients with any claims for psychotropic medications (by drug class) within 1-month pre-index
Use of estrogen	A binary indicator variable will be created for patients with any claims for estrogen during the 12-month pre-index period
Acute use of estrogen	A binary indicator variable will be created for patients with any claims for estrogen within 1-month pre-index
Use of testosterone	A binary indicator variable will be created for patients with any claims for testosterone during the 12-month pre-index period
Acute use of testosterone	A binary indicator variable will be created for patients with any claims for testosterone within 1-month pre-index
Use of corticosteroids	A binary indicator variable will be created for patients with any claims for corticosteroids during the 12-month pre-index period
Acute use of corticosteroids	A binary indicator variable will be created for patients with any claims for corticosteroids within 1-month pre-index
Use of glucagon	A binary indicator variable will be created for patients with any claims for glucagon during the 12-month pre-index period
History of pre-index SH events	A binary indicator variable will be created for patients with evidence of SH events in the 12-month pre-index period, not including the index date
Number of pre-index SH events, continuous	The total number of pre-index SH events occurring during the 12-month pre-index period (not including the index date) will be calculated
Total all-cause 12-month pre-index healthcare costs, continuous	The allowed amount on all pre-index claims (not including the index date) will be summed.
Pre-index healthcare resource utilization	Variables for pre-index healthcare utilization occurring during the 12-month pre-index period (not including the index date) will be tabulated, as described in Section 8.3.3.

8.3.2. Risk factors for SH (Primary Objective)

Risk factors for SH will be evaluated over the 12-month pre-index period. Acute risk factors will be assessed within 1-month prior to index.

Well-Established Risk Factors Measurable in Claims

- Age

    - Continuous
- Sulfonylurea use
    - During 12-months prior to index
    - During 1-month prior to index
- Prior hypoglycemia-related medical visits
    - Binary indicator flag
    - Number of prior visits
- Renal disease
    - During 12-months prior to index
    - During 1-month prior to index

Other Potential Risk Factors Measurable in Claims

- Concomitant use of medications of interest observed during the 12-months prior to index and during 1-month prior to index
    - Beta-blockers
    - Opioids
    - Psychotropic medications
        - Antidepressants
            - Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, sertraline, paroxetine, escitalopram
            - Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine
            - Bupropion
        - Anti-anxiety medications
            - Benzodiazepines, such as clonazepam, alprazolam, and lorazepam
            - Buspirone
        - Stimulants, such as methylphenidate, amphetamine, dextroamphetamine, and lisdexamfetamine dimesylate
        - Antipsychotics
            - Typical antipsychotics, such as chlorpromazine, haloperidol, perphenazine, and fluphenazine
            - Atypical antipsychotics, such as risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, and lurasidone
    - Estrogen
    - Testosterone
    - Corticosteroids
    - Thyroid medications
    - Thiazides
    - Epinephrine
    - Sympathomimetics
    - Niacin
- Type of insulin used – possibly measured during 12-month prior to index and also insulin used immediately prior to index date

  - basal insulin
  - rapid-acting/ultra-rapid insulin
  - short-acting insulin
  - NPH insulin
  - insulin mixes
- Anti-diabetic use - possibly measured during 12-month prior to index and also insulin used immediately prior to index date
  - Oral
    - Alpha-glucosidase inhibitors
    - Antidiabetic combos
    - Biguanides
    - Dipeptidyl peptidase IV inhibitors
    - Meglitinides
    - Sodium-glucose cotransporter inhibitor
    - Thiazolidinediones
  - Injectable
    - Amylin analogs
    - GLP-1 agonists
- Insulin use alone vs. in combination with oral/injectable anti-diabetic medication use (as broken out above)
- Cognitive dysfunction, defined as evidence of anxiety, dementia, depression, or schizophrenia – possibly measured during 12-months prior to index and also within 1-month prior to index

8.3.3. Post-index Economic Endpoints

HCRU and associated costs will be assessed during the fixed 6-month post-index period, including the index date. HCRU will be reported by service type. The following service types will be reported:

- Inpatient:
  - Length of stay (LOS)
  - Total hospital days
- Outpatient, further broken down into:
  - Patient observation (defined as outpatient claims with CPT codes: 99218-99220, 99224-99226)
  - Physician office visits, possibly calling out specific physician specialties such as endocrinologist
  - Surgical services
  - Laboratory services
  - Radiological services
  - Emergency Department visits
  - Ancillary/supportive care services
- Pharmacy, further broken out into:

- Diabetes-related medications
- All other medications

The number and proportion of patients with each service type, as well as the total number of visits/services received will be reported.

Healthcare costs will be reported overall and by service type. Allowed cost on the claims will be used (total reimbursable amount allowed by the health plan plus patient out-of-pocket expenses) to determine the economic burden of SH in T2DM patients using insulin. Costs will be inflation-adjusted to 2018 US dollars based on the healthcare component of the Consumer Price Index (CPI).

8.4. Data Sources

The aggregated IQVIA Real World Data Adjudicated Claims Database (PharMetrics Plus [PMTX+]) is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage from 2011 represent approximately 40 million active lives annually. Data are available from 2006 onwards; with a typical 3-4-month lag due to claims adjudication.

The PMTX + database has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area of the US are represented, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies.

In addition to standard fields such as inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, PMTX + has detailed information on the pharmacy and medical benefit (co-payment, deductible), the inpatient stay (admission type and source, discharge status) and provider details (specialty, provider ID). All 3-digit zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography.

Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, sex, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), and start and stop dates of health-plan enrolment. Due to the

broad reach of the data, records in the PMTX + database are representative of the national, commercially insured population in terms of age and sex for individuals aged 65 and under. The data are also longitudinal, with more than 30 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. All data are HIPAA compliant to protect patient privacy.

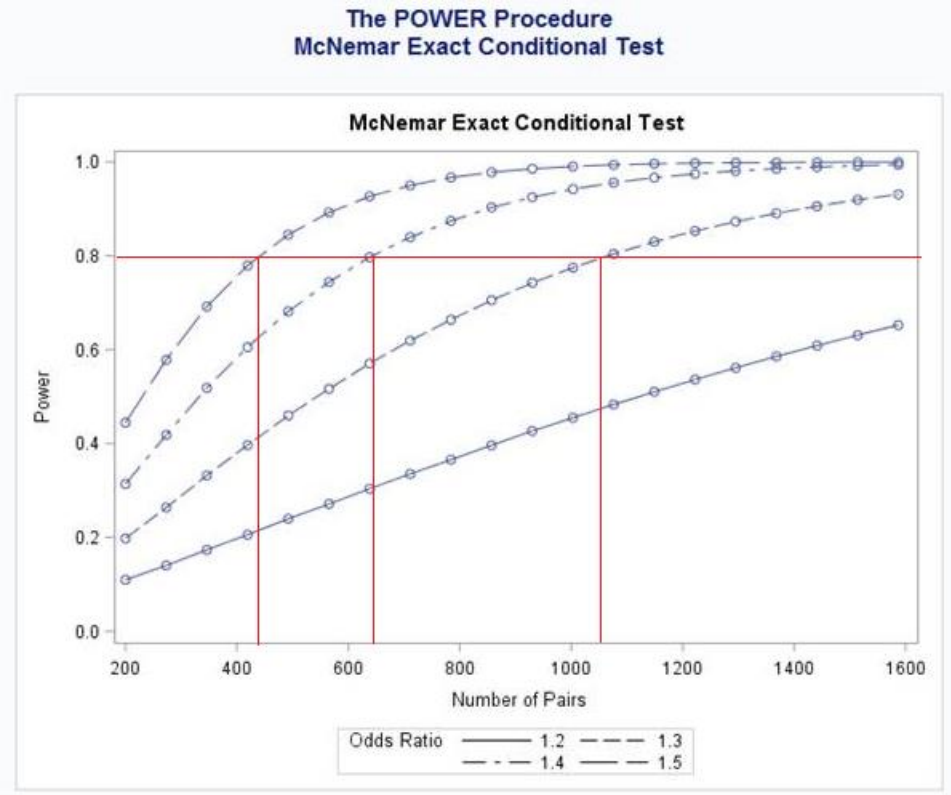
The PMTX+ database includes the following patient level information:

- Year of birth, sex
- Geography
- Diagnoses codes
- Procedure codes (CPT4, ICD, HCPCS, Revenue Center)
- Date of service
- Location of care
- Amounts allowed and paid by payer
- Patient liability amount (copay, coinsurance, deductible)
- Payer types
- Enrollment status

8.5. Study Size

A power calculation using the McNemar Exact Conditional test with alpha = 0.05 and assuming a 21% prevalence of the risk factor for SH in the population of T2DM patients on insulin (Edridge CL et al., 2015) with estimated correlation between SH and non-SH patients (R^2) of 0.2 was conducted. Roughly 440 to 2,250 cases would be needed to detect odds ratios ranging from 1.5 to 1.2, respectively (Figure 8-3).

Figure 8-3. Power analysis



A preliminary count of T2DM with severe hypoglycemia and insulin use within 6 months prior to the index SH event found 61,200 patients meeting these criteria. It is expected that the Klompas algorithm (Klompas et al. 2013) will identify slightly more T2DM patients and the diagnosis codes proposed by Karter et al (Karter et al. 2019) will identify more SH patients than what is reported in Table 8-2 below. We estimate that roughly 70% of patients will be excluded from the study after applying the remaining criteria, leaving an estimated 18,360 SH patients. Assuming a match rate of 70%, we estimate that 12,852 SH patients will match to non-SH patients

Table 8-2. Preliminary Patient Counts

Inclusion Criteria	**N patients**
PMTX+ base population	142,672,596
≥ 2 claims on different dates with a diagnosis of T2DM between 1/1/14 and 6/30/2017	3,699,991

≥ 1 claim of SH between 1/1/14 and 6/30/17 and ≥ 18 years of age. First claim for SH is the index date	120,176
≥ 2 claims for insulin within 6 months prior to the index date	57,879

8.6. Data Management

Datasets and analytic programs will be kept on a secure server and archived per Lilly record retention procedures. If the study is being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's (IQVIA) procedures.

8.7. Data Analysis

8.7.1. Identification of SH Events

Identification of SH events

SH events will be identified using ICD-9/10-CM codes below recently validated (Figure 8-4; Karter et al., 2019; Ginde et al., 2008). All ICD-9/10-CM codes listed in Figure 8-4 will be used to define a SH event depending on whether the event occurred before or after October 1, 2015. Events occurring within 24 hours of each other will count as one episode. To ensure that rule-out diagnoses are not captured, only non-ancillary claims will be used to identify SH events. We note that these events are those severe enough to require health care encounters – as such any healthcare visit with these codes will be considered as a SH event. The study investigates risk factors for the events as defined, which do not necessarily capture all hypoglycemia events.

Figure 8-4. ICD-9/10-CM Diagnosis Codes for Identification of Hypoglycemic Events

ICD-9 Code	**Description**
251.0	Hypoglycemic coma
251.1	Other specified hypoglycemia
251.2	Hypoglycemia, unspecified
962.3	Poisoning by insulins and antidiabetic agents
250.8	Diabetes with other specified manifestations (without the following co-diagnoses codes on the same claim: 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.1-707.9, 709.3, 730.0-730.2, 731.8)
ICD-10 Code	**Description**
E08.641	Diabetes mellitus due to underlying condition with hypoglycemia with coma
E08.649	Diabetes mellitus due to underlying condition with hypoglycemia without coma

E09.641	Drug or chemical induced diabetes mellitus with hypoglycemia with coma
E09.649	Drug or chemical induced diabetes mellitus with hypoglycemia without coma
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E13.641	Other specified diabetes mellitus with hypoglycemia with coma
E13.649	Other specified diabetes mellitus with hypoglycemia without coma
E15	Nondiabetic hypoglycemic coma
E16.0	Drug-induced hypoglycemia without coma
E16.1	Other hypoglycemia
E16.2	Hypoglycemia, unspecified
T38.3X1A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), initial encounter
T38.3X1D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), subsequent encounter
T38.3X1S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, accidental (unintentional), sequela
T38.3X2A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, initial encounter
T38.3X2D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, subsequent encounter
T38.3X2S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, intentional self-harm, sequela
T38.3X3A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, initial encounter
T38.3X3D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, subsequent encounter
T38.3X3S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, assault, sequela
T38.3X4A	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, initial encounter
T38.3X4D	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, subsequent encounter
T38.3X4S	Poisoning by insulin and oral hypoglycemic [antidiabetic] drugs, undetermined, sequela
T38.3X5A	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, initial encounter
T38.3X5D	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, subsequent encounter
T38.3X5S	Adverse effect of insulin and oral hypoglycemic [antidiabetic] drugs, sequela

8.7.2. Matching

Before matching, the patient pool will be reduced to qualified cases and potential controls by verifying the inclusion and exclusion criteria. For the cases, all the inclusion and exclusion criteria will be checked, since the index date is simply the date of the first SH, as shown in Figure 8-1. For the controls, all but one inclusion and exclusion criteria will be checked, the exception being the continuous enrollment requirements. This criterium will be checked dynamically at the time of matching.

Cases and controls will be exact matched on well-established risk factors as detailed in Section 8.3.2.

- Age: Age will be calculated on the date of first insulin use, and grouped into 5-year increments
- Prior sulfonylurea use: Binary indicator variables will be created for the 12-month and 1-month pre-index period
- Renal disease: Binary indicator variables will be created for the 12-month and 1-month pre-index period
- Prior SH: Binary indicator variables will be created for the 12-month pre-index period

Final decisions regarding which well-established risk factor measures (e.g., measured during 12-month vs. 1 month prior to index date) to include will be made after exploration of the data. For each case, a risk set composed of all potential controls that fall within the same 5-year age category will be created. The remaining matching variables will be calculated for patients in the risk set and patients within each risk set will be exact matched on the remaining variables, beginning with the hardest to match cases (those with the least potential controls). A random sample of up to 4 controls who match on all variables will be selected. This will be repeated until all cases have been matched, or no further matches can be made. Unmatched controls will be removed from the sample for subgroup analyses comparing SH to non-SH patients. If the sample size for cases is sufficient, patients will be matched with a ratio of 1:1 (Strom, Kimmel and Hennessy 2012).

If exact matching fails to attain an acceptable level of matching, disease risk score (DRS) matching may be used. A multivariable logistic regression model will be used to assign a disease risk score (Wyss et. al., 2016) to each patient, based on the presence of well-established risk factors. The dependent variable for the disease risk score model will be SH. All well-established risk factors will be included as independent variables in the model. The disease risk score is the predicted probability of having SH, conditioned on presence of well-established risk factors. Greedy nearest neighbor DRS matching without replacement with a caliper width of 0.2 of the SD of the logit of the propensity score will be used to create a cohort of final matched SH and non-SH patients at a ratio of 1:4 in order to identify new risk factors for SH.

8.7.3. Missing Data

Patients with missing data on demographics (age, sex, and geographic region) will be excluded from all analyses. Data cleaning measures may be applied to days' supply of insulin claims

pending data exploration, and may include setting missing or extreme values to the median by NDC/HCPCS code. Since the study is utilizing adjudicated claims with available healthplan enrolment information, the absence of diagnoses/procedures/medications are not assumed to be missing data.

8.7.4. Significance Levels

All tests will be 2-sided with a 0.05 alpha level of significance. All analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

8.7.5. Outcomes Analyses

8.7.5.1. Univariate Analyses (Secondary and Exploratory Objectives)

Descriptive statistics will be reported using frequency and percentage distributions for categorical variables. Mean, median, and standard deviation will be generated as measures of central tendency and variance for continuous and count variables. Comparison of baseline demographics, clinical characteristics, pre-index HRU/cost, and pre-/post-index glucagon use between different cohorts of interest will be made using McNemar's/Stuart-Maxwell (Sun X, Yang Z, 2008; matched samples) and Chi-Square (unmatched samples) tests for binary/categorical variables and paired t-test (matched samples) and t-tests (unmatched samples) for continuous variables. Standardized differences will be used to assess differences between matched cohorts, as these are not influenced by sample size.

8.7.5.2. Multivariate Analyses

Evaluation of risk factors for severe hypoglycaemia (Primary Objective)

A conditional logistic regression model will be used to evaluate the relative contribution of independent variables as risk factors according to the intensity of their influence on the development of SH events. The dependent variable will be the occurrence of a SH event during the insulin treatment period. Independent variables for the model will include demographic and clinical characteristics described in Section 8.3.1 and Section 8.3.2 that were not used as matching variables. For variables defined both during the 12 months and 1 month prior to index date, only the 1-month version will be input to the model as a covariate. Some interactions, especially for significant covariates or those defined by the study team a priori may be considered for inclusion in the model. Correlation matrices and Spearman's rank correlation will

be used to determine correlation between variables, with a value of >0.5 indicating high correlation. For correlated variables, those of most importance to Lilly will be included in the model.

Results for the model will be presented in terms of odds ratios (OR) along with corresponding 95% confidence intervals (CI). A forward (or backward) elimination procedure will be applied to keep only significant covariates (at level 0.05) in the model. Dropped covariates will be identified with their last in-model OR p-value. Variables with OR > 1.0 having a 95% CI that does not include 1.0 will be identified as risk factors for SH. Some variables may also be found to be protective (OR < 1.0 and 95% CI excludes 1.0).

Healthcare resource utilization and cost (Secondary Objectives)

All-cause total healthcare costs from the measures in Section 8.3.3 will be compared among matched sets of cases and controls that have at least 6 months of enrollment post index date. A Generalized Linear Model (GLM) will be fit, with gamma distribution and log link to control for demographic and baseline clinical characteristics that were not included as matching variables. The outcome will be total all-cause costs accumulated during the the 6-months post-index. The 6-month pre-index cost will be added to the model as a covariate. The final model will include demographic and baseline clinical characteristics which have p-values <0.05. The impact of outliers may be assessed using sensitivity analysis excluding patients in the top and bottom 1% of total cost.

All-cause hospitalization costs accrued during the 6-month post-index period will be compared among matched sets of cases and controls that have at least 6 months of continuous enrolment post-index using a GLM with gamma distribution and log link. The outcome will be total all-cause hospitalization costs accumulated during the 6-month post-index period. Hospitalization costs incurred during the 6-months prior to the index date will be included as a covariate, along with baseline demographic and clinical characteristics that were not used in matching.

All-cause emergency department costs accrued during the 6-month post-index period will be compared among matched sets of cases and controls that have at least 6 months of continuous enrolment post-index using a GLM with gamma distribution and log link. The outcome will be total all-cause emergency department costs accumulated during the 6-month post-index period.

Emergency department costs incurred during the 6-months prior to the index date will be included as a covariate, along with baseline demographic and clinical characteristics that were not used in matching.

Two Poisson regression or negative binomial GLMs will be fit to HRU count data during the 6 months post index, using the Poisson/negative binomial distribution and log link. For these models, the outcomes will be: (1) number of emergency department visits occurring during the 6-month post-index period, and (2) number of inpatient visits occurring during the 6-month post-index period. The count of events during the 6 months prior to the index date (baseline) will be included as covariates in the models. Additional covariates will include baseline and clinical characteristics that were not used for matching which have p-values <0.05. Zero-inflated Poisson regression or zero-inflated negative binomial regression may be used if the distribution of the outcomes is skewed toward 0 (i.e., a high proportion of patients have no emergency department visits/hospitalizations).

A nested case-control study with no matching will be employed as a sensitivity analysis for the primary objective to determine which covariates emerge as risk factors, including those known risk factors in the study sample. All patients with a SH occurring during the insulin treatment period will be designated as cases and patients with no SH occurring during the insulin treatment period will be designated as controls. To define the index date for controls, the distribution of time from the first insulin claim during the index period until the index date in cases will be grouped into deciles. Patients in the control group will be randomly assigned to one of ten subgroups and index dates will be generated by adding to the first insulin claim a random number of days that falls within the assigned decile among the cases. For example, if a patient in the control pool is randomly assigned to the 4^{th} decile, the index date for this patient would be generated by adding a random number of days between 122 and 210 to the date of first insulin claim observed during the index period (Table 8-3). This method will ensure that the distribution of time between insulin and the index date will have similar distributions in the case and control samples. After the index dates are generated for the controls, a logistic regression model will be used to evaluate the relative contribution of independent variables as risk factors according to the intensity of their influence upon the development of SH events. The dependent variable will be the occurrence of a SH event during the index period. Independent variables for the model will include demographic and clinical characteristics described in Section 8.3.1 and Section 8.3.2,

including the well-established risk factors. The correlation matrix produced by the model will be used to determine correlations between parameter estimates, with a value of >0.5 indicating high correlation.

Table 8-3. Example of time between insulin and SH per decile in cases.

Decile	Range of number of days between insulin date and index date
1	0-20
2	21-75
3	76-121
4	122-210
5	211-268
6	269-300
7	301-330
8	331-353
9	354-380
10	381-405

8.8. Quality Control

Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing steps, the validation analyst will review the programme along with input and output datasets. For the analysis steps of the project, double-programming techniques to reduce the potential for programming errors may be employed.

Dual programming will be limited to the conditional logistic regression model for the primary objective, and to the logistic regression model in the sensitivity analysis.

8.9. Limitations of the Research Methods

Studies conducted using administrative claims databases have inherent limitations. Data were collected for billing rather than research purposes so some variables that may be of interest are not available. Specifically, the absence of claims with diagnosis codes for hypoglycaemia does not imply that patients do not experience any hypoglycaemic events. It is possible that patients in the non-SH group experience hypoglycemic events, however, these events are not considered severe since they did not trigger a billable visit to healthcare provider. Similarly, behavioural and social-economic factors which may be associated with severe hypoglycaemia are not available for study. The PMTX+ database is nationally representative of commercially/self-insured patients. Patients aged ≥ 65 years are underrepresented as Medicare fee-for-service claims are not included in the data, and the Medicaid population is not well represented.

9. Protection of Human Subjects

This study will use only de-identified patient records and will not involve the collection of any prospective data from patients, nor will it involve any transmission of individually identifiable data, therefore it is expected that no IRB review or approval is required. An IRB waiver will be obtained prior to analysis.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

10. Management and Reporting of Adverse Events/Adverse Reactions

10.1. Secondary Data Collection Study

This is a non-interventional study based on secondary data use, and therefore no individual case safety report (ICSR) reporting is required. The study protocol-defined AEs include: severe hypoglycemia. All protocol-defined adverse events collected will be summarized in the final study report. No other AEs will be collected.

10.2. Product Complaints

Not applicable, as the study does not involve identifiable patient data associated with an Eli Lilly and Company product.

11. Plans for Disseminating and Communicating Study Results

A final report in Microsoft Word will be developed at the conclusion of the study, with result tables included in a Microsoft Excel workbook in the Appendix. The study findings may be submitted to a scientific congress and/or to a peer reviewed journal.

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Annex 1. List of Standalone Documents

Not applicable.