Observational Study Protocol MB102-103 ST

COMPARISON OF THE RISK OF SEVERE COMPLICATIONS OF URINARY TRACT INFECTIONS BETWEEN PATIENTS WITH TYPE 2 DIABETES EXPOSED TO DAPAGLIFLOZIN AND THOSE EXPOSED TO OTHER ANTIDIABETIC TREATMENTS

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SYNOPSIS

Observational Study Protocol MB102-103 ST

Protocol Title: Comparison of the Risk of Severe Complications of Urinary Tract Infections (UTI) Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments

Department: AstraZeneca Epidemiology

Objectives

Primary Objective: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or emergency department (ED) visit for severe complications of urinary tract infections (UTI), defined as pyelonephritis and urosepsis, among patients with type 2 diabetes mellitus (T2DM) who are new users of dapagliflozin with those who are new users of antidiabetic drugs (ADs) in classes other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

Secondary Objective #1: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or ED visit for pyelonephritis or outpatient diagnosis of pyelonephritis among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

Secondary Objective #2: To compare, by insulin use at the index date, baseline patient characteristics between patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy and to identify important prognostic variables that should be balanced between the study groups.

Secondary Objective #3: To examine potential risk factors for severe complications of UTI if new users of dapagliflozin are found to be at greater risk than new users of other ADs.

Study Design: This will be a cohort study that will be conducted with data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK) and the HealthCore Integrated Research Database (HIRD^{SM}) and Medicare databases in the United States of America (US). The study will compare the incidence of severe complications of UTI among new users of dapagliflozin with the incidence of severe complications of UTI among those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. Patients will be identified at selected intervals during the course of the study. Study duration is planned to be 5 years but will depend on the market uptake of dapagliflozin.

Study Population: Patients will be eligible for inclusion in this study if they meet *all* of the following criteria: (1) receive newly prescribed dapagliflozin (with or without other ADs) or a newly prescribed AD (with or without other ADs) in a class other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy; (2) do not have evidence of type 1 diabetes; (3) are aged 18 years or older at the index date for CPRD patients, 18-64 years for HIRD^{SM} patients, or 65 years or older for Medicare patients; and (4) have been enrolled in the data source for at least 180 days before the first prescription or dispensing dapagliflozin or eligible index comparator AD. Patients with a previous diagnosis of chronic pyelonephritis will be excluded. Patients with a history of diabetic nephropathy will be included, and this history will be accounted for in the analysis. In the HIRD^{SM}, all available eligible comparator patients will be used in the analysis. In the CPRD and Medicare, it may be necessary to select a subsample of AD users before propensity score estimation if all available data cannot be used. If used, the subsample will be identified by frequency matching eligible comparator patients to dapagliflozin patients by 5-year age groups, sex, geographic region, and calendar year of the index date in at least a 6:1 ratio in the CPRD and a 15:1 ratio in Medicare.

Data Collection Methods

Data Sources: The CPRD contains electronic medical records including outpatient diagnoses and prescriptions from general practitioner (GP) practices in the UK and mentions of diagnoses associated with hospitalizations. The HIRD^{SM} contains health insurance claims from the largest commercially insured population in the US. Medicare data include health insurance claims from the federally sponsored health

insurance program for individuals in the US aged 65 years or older and individuals with permanent disabilities.

Exposures: New use of dapagliflozin will be defined to begin on the date of first dapagliflozin prescription or dispensing recorded in the data source. New use of an AD in a class eligible for inclusion will be defined to begin on the date of first prescription or dispensing for these medications in the data source.

Outcomes: The primary outcome in this study will be hospitalization or ED visit for severe complications of UTI, defined as pyelonephritis and urosepsis. The secondary outcome in this study will be hospitalization or ED visit for pyelonephritis or outpatient diagnosis of pyelonephritis. To validate the identified cases or a sample of electronically identified cases, in the CPRD, additional clinical details will be obtained via a questionnaire sent to the GP. In the HIRD^{SM} and Medicare cohorts, individuals with health insurance claims for hospitalization with UTI will be identified as potential cases, and, for a subset of potential cases, the medical records for that hospitalization will be abstracted or photocopied and redacted to confirm the diagnosis of a severe complication of UTI and diagnosis date. If the electronic algorithm for identifying potential cases is associated with a lower 95% confidence interval for the positive predictive value less than 0.80, then the case ascertainment algorithm will be modified.

Follow-up: Follow-up will begin on the day after the index date, which is the day a patient is first prescribed or dispensed dapagliflozin or a comparator AD. Follow-up time for a given exposure will continue until the study outcome event (severe complications of UTI); death; the end of study data or study period; initiation of an SGLT2 inhibitor other than dapagliflozin; or the end of the risk window for the index AD, defined as 30 days after the estimated discontinuation of dapagliflozin or the comparator AD. Sensitivity analyses will involve each of the following variations, one at a time: (1) the risk window will be extended to 90 days after the estimated discontinuation of the index AD, (2) follow-up will end if new use of any study AD is added, and (3) comparator cohorts will be limited to new users of study drug classes.

Data Analyses: Descriptive statistics will be generated to compare baseline characteristics (e.g., demographic information, comorbidities, and medication use at the index date) between dapagliflozin initiators versus comparator AD initiators, by insulin use at the index date. Propensity scores will be estimated by logistic regression analyses, incorporating measured potential predictors of therapy and calendar year of the index date as independent variables in the regression model and exposure (dapagliflozin group vs. comparator group) as the outcome. Duration of lookback time and timing of information on key covariates will be included in the model. Incidence rates of severe complications of UTI will be determined in each cohort. Propensity score–stratified analysis will be used to estimate unadjusted and adjusted incidence rate ratios (IRR) (with 95% confidence intervals) of the outcome of interest in dapagliflozin initiators versus other AD initiators. If necessary, further adjustment for therapies added during follow-up will be performed via time-dependent Cox proportional hazards regression. Analyses will be conducted in each data source, and a pooled estimate will be calculated if deemed appropriate.

Sample Size/Power: A weighted average of the rates of pyelonephritis in the population with diabetes was estimated to be 10.3 per 1,000 person-years in women and greater than 3.0 per 1,000 person-years in men. It is currently projected that at the end of 5 years, there will be a total of 91,927 person-years of exposure to dapagliflozin across the three data sources (CPRD: 3,600 person-years; HIRD^{SM}: 42,473 person-years; and Medicare: 45,854 person-years). This includes approximately 73,542 person-years among those not on insulin at the index date and 18,385 person-years among those on insulin at the index date. Using these estimates and assuming that the true dapagliflozin: comparator IRR is 1.0 and 73,000 person-years of dapagliflozin follow-up among new users of dapagliflozin not on insulin at the index date, there will be an 89% probability that the upper 95% confidence limit of the IRR will be less than 1.2 among females or less than 1.4 among males, if the 73,000 person-years are split evenly between the males and females.

Limitations/Strengths: The UK is an ideal setting for population-based studies of diabetes because diabetes care is largely coordinated by the GP, and information about metabolic parameters, cardiovascular risk factors, diabetes comorbidities, and disease outcomes are collected electronically. Furthermore, clinical guidelines in the UK facilitate consistency in patterns of care. However, there are still limitations. In the CPRD, there may be inaccuracies in the recorded dates of hospitalization and information about care provided by specialists may be missing. Patient-specific variability in the availability of laboratory data and medical records, misclassification of exposures and outcome, and limitations in the numbers of available study patients are the major potential limitations of this study**.**

In the HIRD[SM] and Medicare cohorts, the health insurance claims database includes claims for all medical services for cohort members during the study period. The Medicare data cover a very large proportion of US residents aged 65 years or older, and the HIRD[SM] covers a large proportion of the US population younger than 65 years of age. Information on potentially important confounders such as high body mass index and smoking is virtually nonexistent unless treatment for either is detectable through claims. Therefore, an evaluation of the impact of missing confounders is planned.

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1 INTRODUCTION

Dapagliflozin (BMS-512148) is a highly potent, selective, and reversible inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin, the first approved drug in an emerging therapeutic class in the treatment of type 2 diabetes mellitus (T2DM), lowers plasma glucose by inhibiting the renal reabsorption of glucose, thereby promoting urinary excretion of glucose (Bristol-Myers Squibb [BMS] and AstraZeneca [AZ], 2011).

Epidemiology of Severe Complications of Urinary Tract Infections

Untreated urinary tract infections (UTI) can lead to acute or chronic kidney infections (pyelonephritis), which could permanently damage the kidneys, and to urosepsis (Foxman, 2002; Wagenlehner et al., 2008). People with T2DM have a higher risk for infections, including UTI, than people without diabetes (Muller et al., 2005). Most of the information about UTI in T2DM is in women, and very little information is available about men. Based on case-control studies, women with T2DM are approximately 2 times more likely to have culture-confirmed UTI than women without diabetes (Boyko et al., 2002; Boyko et al., 2005; Brown et al., 2005). Based on adverse event (AE) reporting from clinical trials, 2.4% of patients with T2DM had UTI, with a cumulative incidence of 2% during the first 6 months. Compared with men, women had a relative risk of developing UTI of 3.4 (95% confidence interval [CI] 2.3–5.1) (Hammar et al., 2010).

A study in the United States (US) of hospital discharges for acute pyelonephritis suggests a rate of 11.7 per 10,000 persons-years in females and 2.4 per 10,000 persons-years in males (Foxman et al., 2003). Among the female population, annual rates of pyelonephritis were 12–13 outpatient cases per 10,000 population and 3–4 inpatient cases per 10,000 population; among the male population, the rates were 2–3 outpatient cases per 10,000 population and 1–2 inpatient cases per 10,000 population (Czaja et al., 2007).

In a population-based study of hospitalization rates for pyelonephritis in Manitoba, women with diabetes were more likely than women without diabetes to be hospitalized for pyelonephritis, and the same was true for men (Nicolle et al., 1996). The difference was most pronounced at younger ages (see Table 1). Among women aged 25 to 44 years, those with diabetes were 15 times more likely to be hospitalized for pyelonephritis than those without diabetes. Among middle-aged women (aged 45 to 64 years) those with diabetes were 24 times more likely to be hospitalized for pyelonephritis than those without diabetes. The difference was not as large for women aged 65 years or older, but still appreciable. A similar pattern was observed for men, but the magnitude of the difference in rates between men with diabetes and those without diabetes was less than that for women.

Table 1: Rate of Hospitalization for Pyelonephritis, by Age, Sex, and Diabetes Status

Age Group (Years)	Women		Men	
	With Diabetes	Without Diabetes	With Diabetes	Without Diabetes
25 to 44	128.8	8.6	28.5	1.7
45 to 64	144.4	6.0	24.6	4.0
≥ 65	66.2	11.2	34.3	10.0

Note: Hospitalization rates are per 10,000 population.
Source: Adapted from Nicolle et al. (1996).

The observation of substantially higher rates of hospitalization for pyelonephritis in patients with diabetes most likely reflects actual differences in disease occurrence, but may also be influenced by factors related to the probability of diagnosis and hospitalization.

Sepsis is a severe and frequently fatal condition. The incidence of sepsis in the United States has been reported to be 3 cases per 1,000 population, and the site of the infection was determined to be genitourinary in 9.1 % of the cases (Angus et al., 2001).

Challenges in the Identification of Severe Complications of UTI in Health Databases

Medical administrative and claims databases afford investigators the opportunity to study severe complications of UTI in vast numbers of patients admitted over multiple years to a wide spectrum of hospitals, including those not ordinarily represented in prospective cohort studies. A major limitation of claims-based administrative databases is the lack of detailed clinical and laboratory information.

In the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), emergency department (ED) visits are not part of the linkable information and are recorded only if the general practitioner (GP) or hospital doctor wants to specifically include them. Information that GPs consider important for clinical care (e.g., results from complementary exams, procedures, hospitalizations, and reports from specialists—which generally require validation) is included. In addition, a subset of CPRD data (approximately 50%) can be linked to census data and hospital data (Hospital Episode Statistics [HES]). Information on outpatient diagnosis is universal in the CPRD.

In US claims data sources, such as the HealthCore Integrated Research Database (HIRD^{SM}) and Medicare databases, claims for emergency department visits and inpatient stays are routinely available, as are claims for outpatient visits with diagnoses. Billings for procedures are also likely to be available in the data.

1.1 Study Rationale

This post-authorization safety study is being conducted as part of the BMS/AZ Dapagliflozin Risk Management Plan to monitor the safety of dapagliflozin in real-world use. Because of the increased frequency of UTI reported among clinical trials comparing dapagliflozin use with other antidiabetic therapies, there is interest in evaluating whether there is an increased risk of severe

complications of UTI among individuals using dapagliflozin. This protocol describes a cohort study to be conducted in the CPRD (UK) and two US data sources: the HIRD^{SM} and Centers for Medicare and Medicaid Services (CMS) Medicare databases. The study will compare the incidence of severe complications of UTI among new users of dapagliflozin with the incidence of severe complications of UTI among those who are new users of antidiabetic drugs (ADs) in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

1.2 Research Questions

- What is the risk of hospitalization or ED visit for severe complications of UTI, defined as having a diagnosis of pyelonephritis and urosepsis, for patients with T2DM who are new users of dapagliflozin compared with those who are new users of other AD treatments?
- What is the risk of hospitalization or ED visit for pyelonephritis or outpatient diagnosis of pyelonephritis for patients with T2DM who are new users of dapagliflozin compared with those who are new users of other AD treatments?

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or ED visit for severe complications of UTI, defined as pyelonephritis and urosepsis, among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

2.2 Secondary Objectives

Secondary Objective #1: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or ED visit for pyelonephritis or outpatient diagnosis of pyelonephritis among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

Secondary Objective #2: To compare, by insulin use at the index date, baseline patient characteristics between patients with T2DM who are new users of dapagliflozin and those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy and to identify important prognostic variables that should be balanced between the study groups.

Secondary Objective #3: To examine potential risk factors for severe complications of UTI if patients taking dapagliflozin are found to be at greater risk for this outcome than patients newly starting other ADs.

2.3 Exploratory Objectives

Not applicable.

3 STUDY DESIGN

3.1 Overview of Study Design

This cohort study will compare the incidence of hospitalization or ED visit for severe complications of UTI and outpatient visits for pyelonephritis among new users of dapagliflozin and among those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The source study populations are the UK and the US. A cohort design will allow direct estimation of the incidence and risk of the outcome of interest associated with dapagliflozin. Further, the cohort design permits assessment of the outcome at multiple time points. The planned study duration is 5 years; however, actual duration will depend on the market uptake of dapagliflozin.

The index date for each patient will be defined as the date the patient is newly prescribed or dispensed either dapagliflozin (single-entity dapagliflozin or the fixed-dose combination of dapagliflozin and metformin) or an eligible comparator AD after the beginning of the study observation period, according to the time of approval of dapagliflozin in each country. The lookback time, all available data before the index date, will be used to evaluate patient characteristics among the exposure groups and the potential for confounding. The follow-up time, which begins the day after the index date, will be used to evaluate the incidence of severe complications of UTI and will be used to identify other confounders, effect modifiers, and exposures not controlled at baseline or that change during follow-up. Propensity scores will be estimated at each planned data cut and will be adjusted by calendar year. Multiple logistic regression models will be used to compute propensity scores, and adjusted incidence rate ratios (IRRs) will be derived by propensity score stratification. Other analytic methods that do not control for intermediate variables to evaluate and adjust for added concomitant AD during follow-up will be considered.

3.2 Study Population

During the conduct of the study, patients will be identified at selected intervals. Study populations of patients with T2DM will be identified using data on GP diagnoses and prescriptions in the CPRD in the UK and health insurance claims for outpatient medication dispensings in the HIRD^{SM} and CMS Medicare databases of the US. These patients will be new users of dapagliflozin or other selected ADs, as detailed in Section 3.2.1, Inclusion Criteria.

3.2.1 Inclusion Criteria

Patients are eligible for the study if they meet *all* of the following criteria:

- Were newly prescribed or dispensed dapagliflozin (with or without other ADs) or are newly prescribed or dispensed an AD (with or without other ADs) in a class other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy (see Appendix 4)
- Were enrolled in the data source for at least 180 days before the first prescription or dispensing of dapagliflozin or other AD qualifying for the comparator group

- Were aged (at the index date)
  - 18 years or older in the CPRD
  - 18-64 years in the HIRD^{SM} or
  - 65 years or older in Medicare and were participants only in the fee-for-service program (i.e., were not in a managed care program); were enrolled in Parts A, B, and D of the Medicare program for at least 180 days before entering the study (follow-up will be censored if Part D coverage was discontinued); had a residence in a US state or district of Columbia; and Medicare eligibility was not due to end-stage renal disease.

Our rationale for comparing new users of dapagliflozin with new users of ADs *in a class other than SGLT2 inhibitors* is to ensure that we do not miss potentially important associations that are due to the SGLT2 class after more such compounds become available. Analysis results in each cohort will be evaluated by insulin use at the index date because insulin use is clinically considered to be associated with a longer history of diabetes.

Our rationale for not including new users of metformin monotherapy or sulfonylurea monotherapy is that patients diagnosed with T2DM are likely to be prescribed these medications early in the course of the disease—e.g., following guidelines of the UK National Institute for Health and Clinical Excellence (2015) and the American Diabetes Association, (2014)—whereas dapagliflozin is expected to be used after initial treatment with these therapies. In addition, the long history of availability of sulfonylureas and metformin could result in misclassification of new use when these medications are started again after an interruption of treatment.

Further, in clinical practice, patients may be newly prescribed dapagliflozin or another AD with or without other ADs already prescribed as part of their regimen (i.e., patients may have new AD medications "added on" or they may "switch" agents). Therefore, we plan to include patients regardless of whether or not they are taking other ADs at the time they are newly prescribed either dapagliflozin or an eligible comparator AD. In addition, we will collect information on whether patients received prior AD therapy and/or if they were "added on" or "switched to" dapagliflozin or other ADs at the time of inclusion in the study.

3.2.2 Exclusion Criteria

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

- The patient experienced chronic pyelonephritis at any time before the index date (i.e., during the available lookback time). Read and *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes for chronic pyelonephritis are in Appendix 1.
- The patient was prescribed an SGLT2 inhibitor other than dapagliflozin on or before the index date.
- The patient initiated metformin or sulfonylurea as AD monotherapy at the index date.
- The patient initiated insulin monotherapy at the index date.
- The patient had evidence of type 1 diabetes before cohort entry or first recorded AD is insulin monotherapy.

3.2.3 Selection of Patients

Eligible study patients will be selected from the study data sources separately. All eligible patients in each data source who meet inclusion and exclusion criteria and are new users of dapagliflozin will be selected for inclusion. In the HIRD^{SM}, all available eligible comparator patients will be used in the analysis. In the CPRD and Medicare, it may be necessary to select a subsample of AD users before propensity score estimation if it is not feasible to use all available data. If used, the subsample will be identified by frequency matching eligible comparator patients with eligible comparator episodes to dapagliflozin new users by 5-year age groups, sex, geographic region, and calendar year of the index date in at least a 6:1 ratio in the CPRD and at least a 15:1 ratio in Medicare. The rationale for selecting at least 6 comparator AD new users for each dapagliflozin new user in CPRD and at least 15 comparator AD new users in Medicare is to ensure that we have sufficient numbers of patients to develop the propensity score and to conduct secondary analyses, as needed.

Patients will enter the study cohort based on the first new use of a qualifying study medication after all inclusion criteria are met. However, inclusion in the study cohort as a new user of dapagliflozin or one of the comparator AD medications does not preclude the patient from being included as a new user of another study medication if the criteria for inclusion in the study cohort are met.

3.2.4 Follow-up of Patients

Follow-up will begin on the day after, but not including, the index date, which is the day after a patient is newly prescribed or dispensed dapagliflozin or a comparator AD. Since severe complications of UTI could occur soon after exposure to a medication, we assume that patients prescribed dapagliflozin or comparator AD could be at risk for the study outcome the day after the index date.

Follow-up time in a given exposure category will continue until the occurrence of severe complications of UTI, death, the end of study data or study period, or until the end of the risk window for the index AD, whichever occurs first. Discontinuation will be defined as no further prescription 30 or more days after the end of the days' supply of the last consecutive prescription in the index exposure episode (assigned to be 30 days if days' supply is missing). Follow-up will be censored at the addition of a non-dapagliflozin SGLT2 inhibitor in either group. Follow-up will *not* be censored if other ADs are prescribed in addition to dapagliflozin or the comparator AD after the index date. If a patient develops type 1 diabetes during follow-up (physician diagnosis in the CPRD or fulfillment of a claims definition in the HIRD^{SM} or Medicare), follow-up time will be censored at the date of diagnosis.

3.2.5 Exposure and Time at Risk

We assume that the potential risk of severe complications of UTI related to drug use could occur at the beginning of therapy, be maintained at an increased level during the duration of treatment, and decrease gradually to the background risk after stopping treatment. Therefore, the time window of risk relating to use of the index drug will start the day after the index date and will

end 30 days after the last day of the last prescription's days' supply (assigned to be 30 days if missing) for the index drug.

For most patients, the risk window will end 60 days after start of the last prescription date (assuming the last prescription was a 30-day supply) for the index AD. Adding 30 days to the days' supply after the estimated end of supply will capture a potential effect after stopping therapy and any delay in the detection of and hospitalization for severe complications of UTI. For sensitivity analyses, the risk window for the index drug will extend to 90 days after the end of the last prescription's days' supply for the index AD. This sensitivity assessment will allow exploration of any further potential delay in effect. We selected 90 days because this period is long enough to account for noncompliant and extended use of the discontinued index exposure and a delay in effect.

See Appendix 2 for descriptions of how switching study exposure groups and the assignment of person-time will be handled under various AD initiation scenarios. If a comparator initiator starts on dapagliflozin, that patient will switch to the dapagliflozin group. If any patient discontinues the index AD and starts on another AD that qualifies as a study exposure, some person-time at risk will pertain both to the tailing off of the first AD and to the startup of the second AD. Person-time during follow-up with combined exposure to dapagliflozin and a comparator AD will be grouped into a combined exposure category and analyzed separately from the dapagliflozin-only exposed person-time.

3.3 Data Source/Data Collection Process

This study requires data sources that longitudinally capture inpatient, ED, and outpatient diagnoses and procedures; capture prescription information; and allow validation of data source listings of severe complications of UTI. This study will be conducted using three sources of longitudinal data: the CPRD in the UK, and the HIRD^{SM} and Medicare databases in the US. A detailed summary of the available data fields and other characteristics of the data in each data source is provided in Appendix 3.

3.3.1 Clinical Practice Research Datalink (CPRD) – UK

In the UK, GPs are the gatekeepers for the health care of the patients registered with them. In practices that contribute information to the CPRD, common software is used to create the electronic medical record that GPs keep for the clinical follow-up of their patients (http://www.cprd.com/intro.asp). The CPRD includes information on patient demographics, lifestyle factors (admittedly not complete for all patients), outpatient diagnoses (documented to be complete), additional clinical information (completeness dependent upon the type of information), referrals, prescriptions issued by GPs (complete), and other information that GPs consider important for clinical care (e.g., results from complementary exams, procedures, hospitalizations, and reports from specialists—these generally require validation). In addition, validation of outcomes can be implemented by surveying the GPs. Approximately 65% of the English practices contributing to the CPRD have consented to have their patient information linked, via a trusted third party, to other health care data sets, including HES, via the patient's National Health Service number, sex, date of birth, and postal code. English practices represent

approximately 75% of all practices contributing to the CPRD; therefore, approximately half of the total CPRD practices can be linked to HES data if needed. Previous experience with linkage of CPRD and HES data suggests that the hospitalization dates listed in the CPRD may be up to 120 days later than the actual hospital admission date. The CPRD has information on 5.1 million individuals (active contributors), which represents approximately 8% of the UK population.

The CPRD contains information on lifestyle factors with a variable proportion of missing values. Although information on race is not available, other user characteristics of interest are likely to be captured. In particular, the diagnosis of T2DM, after excluding individuals with type 1 diabetes diagnoses, has been validated in the CPRD and found to have a high positive predictive value (PPV): 98.6% (95% CI, 92.2%-99.7%, calculated using Episheet, [Rothman, 2012]) (Van Staa and Abenhaim, 1994).

The validity of the diagnosis codes for severe complications of UTI or pyelonephritis has not yet been determined and does not appear in a recent systematic review of the validated outcomes in the CPRD (Khan et al., 2010). The combined infectious and parasitic endpoints studied in the CPRD have a median proportion of cases confirmed of 93%; for the combined genitourinary system endpoints, the median proportion of cases confirmed is 91% (Herrett et al., 2010).

The UK is an ideal setting for population-based studies of diabetes because diabetes care is largely coordinated by the GP, and metabolic parameters, cardiovascular risk factors, diabetes comorbidities, and disease outcomes are collected electronically. Furthermore, clinical guidelines in the UK facilitate consistency in patterns of care (Rubino et al., 2007). The prevalence of diabetes has increased in the UK from 2.8% in 1996 to 4.3% in 2005. The incidence of diabetes has increased from 2.7 per 1,000 person-years in 1996 to 4.4 per 1,000 person-years in 2005. During the period 1996-2005, a change in first-line AD use has occurred, predominantly from sulfonylureas to metformin (González et al., 2009).

3.3.2 HealthCore Integrated Research Database – US

HealthCore, Inc., (hereafter, HealthCore) is a wholly owned subsidiary of Anthem, Inc., which is the largest health benefits company in the US in terms of medical membership. Anthem is an independent licensee of the Blue Cross and Blue Shield Association and serves its members as the Blue Cross licensee in 14 states and through UniCare. Anthem is also the parent of Health Management Corporation, a preventive health and disease management company.

The HIRD^{SM} contains fully adjudicated paid claims from the largest commercially insured population in the US, with dates of service for all noncapitated ambulatory, emergency department, inpatient, and outpatient encounters (including administrative claims for laboratory tests) for members with eligibility at the time of service. It also includes claims for outpatient dispensings of prescription pharmaceuticals from pharmacies. The full HIRD^{SM} dates back to 01 January 2006. The majority of data can be accessed from that time period through the most recent update. Data are updated monthly, with an approximate 3-month time lag for up to 95% full capture of paid medical claims. The lag for pharmacy data is shorter, with approximately 99% paid within 30 days. As of January 2014, the HIRD^{SM} contained claims information for approximately 35.8 million lives available for research. In addition, HealthCore has the ability to

redact or abstract inpatient and outpatient medical records for the health plan members represented in the HIRD^{SM}, identify and contact providers and members for survey research through vendor relationships, and link data to national vital records. The HIRD^{SM} enables rapid access to US population-based health care data resources representing all major geographic regions and health care settings and varied clinical indications that permit long-term longitudinal patient follow-up. The specific geographic regions represented in the HIRD^{SM} are the Northeast, Mid-Atlantic, Southeast, Midwest, Central, and West regions of the US. The HIRD^{SM} has been used as a data source in multiple studies related to safety outcomes and validation.

Health plans contributing data to the HIRD^{SM} include several different lines of business such as health maintenance organizations, point-of-service plans, preferred provider organizations, and indemnity plans.

Data on patient enrollment, medical care (professional and facility claims), outpatient prescription drug use, laboratory test results, and health care utilization may be tracked for patients in the database. Diagnoses and procedures are identified by ICD-9-CM or ICD-10-CM,[1] Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes for both outpatient visits and inpatient stays. Drug claims are captured by National Drug Codes (NDCs), which can be translated to broader, more meaningful classification systems such as Generic Product Identifier codes. Standard Logical Observation Identifiers Names and Codes are used to define specific laboratory test result data. Physician, specialist, and emergency department visits, as well as hospital stays, are captured through CPT codes, uniform billing (UB-92) revenue codes (e.g., room and board), and place-of-service codes. Information on physician specialty is also retained in the database.

Patients aged 65 years or older will be excluded from this data source to avoid any duplication with Medicare data. In addition, patients in the HIRD^{SM} will be censored during follow-up the day before their 65th birthday.

3.3.3 Medicare – US

Medicare is a federally sponsored health insurance program in the US that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with a permanent disability (Cubanski et al., 2010). Most adults become eligible for Medicare when they reach 65 years of age, although younger adults can qualify if they are permanently disabled. Medicare beneficiaries make up approximately 15% of the total US population and include more than 98% of the US population aged 65 years or older (Research Data Assistance Center, 2013). In 2012, over 11.2 million people aged 65 years or older had been diagnosed with diabetes (Centers for Disease Control and Prevention, 2014), and most would have Medicare coverage. Therefore, Medicare data are particularly useful for the current study.

Medicare consists of Part A, which is hospitalization insurance; Part B, which covers physician services and outpatient care; and Part D, which is outpatient prescription drug coverage. Parts B

[1] ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification;*
ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification.*

and D are optional, and enrollees must pay a monthly premium for this coverage. Part D coverage has been available since 2006 and is purchased by beneficiaries through private insurance companies approved by Medicare. As of 2010, about 60% of Medicare beneficiaries were enrolled in Part D.

Analytic files on claims contain information collected by Medicare to pay for health care services provided to Medicare beneficiaries. Data are available for each claim type: institutional (inpatient, outpatient, skilled nursing facility, hospice, or home health agency) and noninstitutional (physician and durable medical equipment providers). Similar to the HIRD^{SM}, diagnoses and procedures are identified by ICD-9-CM or ICD-10-CM, CPT, and HCPCS codes for both outpatient visits and inpatient stays. Additionally, the Part D data claims file contains information on prescription drug fills, including product codes (NDCs), quantity dispensed, and days' supply.

There is currently a 2-year lag in accessing Medicare Part D data. Generally, Medicare releases Part D data each January. Therefore, if the first interim analysis occurs in January 2018, Medicare data would be available through the end of 2015.

3.4 Definitions of Study Variables

3.4.1 Outcomes/Endpoint Variables

In each data source, electronically available diagnosis data will be utilized to screen for potential cases of UTI. After all potential cases are identified, a validation effort will be implemented to obtain more detail to classify potential cases. Depending upon the total number of potential cases in each data source, the validation process may be initiated for all potential cases. If the number of potential cases is relatively large, e.g., more than 125 potential cases in any single data source, validation of a potential algorithm would be implemented for a sample of potential cases. Resampling and validation may be required if the algorithm requires modification (for criteria, see Section 3.4.1.2 on case validation via medical review).

3.4.1.1 Electronic Case Identification

Potential cases of severe complications of UTI will be identified from available electronic data as follows:

- Hospitalization, ED visit, or outpatient visit for pyelonephritis (see Read and ICD-9-CM codes in Appendix 1; ICD-10[1] codes will be included in the statistical analysis plan)

OR

- Hospitalization or ED visit for urosepsis. This entails a combination within 1 week of a hospitalization or ED diagnosis for sepsis and any outpatient, inpatient, or ED diagnosis of UTI (see Read and ICD-9-CM codes in Appendix 1).

Potential cases of severe complications of UTI will be identified as follows:

- In the CPRD: via GP mentions of hospitalizations, ED visits, or outpatient visits associated with the required diagnoses. Due to limitations of the CPRD, we will also link

[1] ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision.*

to the HES data to identify relevant hospitalizations with relevant diagnoses not listed in the CPRD (see Appendix 1 for Read codes) and to confirm or ascertain the correct hospitalization date for any relevant hospitalization listed in the CPRD. Therefore, potential cases will be those with hospitalizations for the included diagnoses dated in the CPRD during follow-up and up to 120 days after the end of follow-up. Linkage to the HES is currently limited to approximately 55% of study patients (Gallagher et al., 2011).

- In HIRD^{SM} and Medicare data: via claims for inpatient admissions, ED visits, and outpatient visits associated with the required diagnoses (see Appendix 1 for ICD-9-CM codes).

3.4.1.2 Validation via Medical Record Review

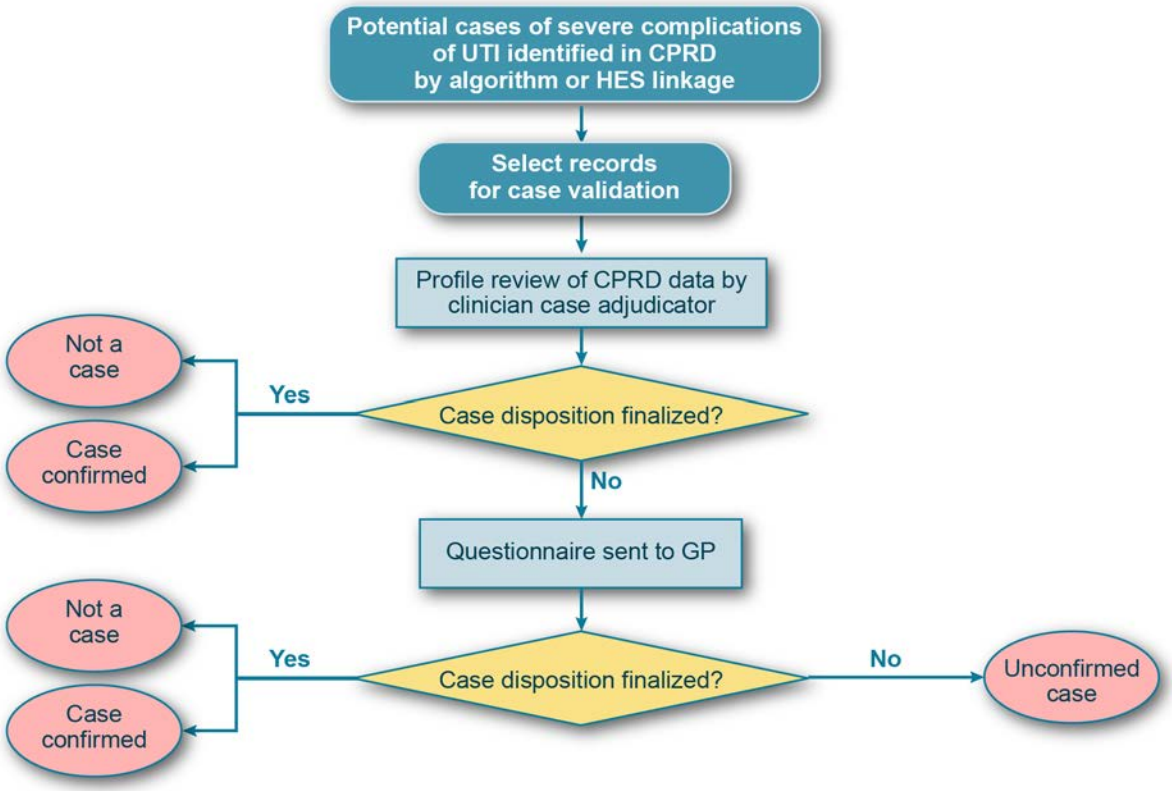
For each data source, the validation process will be detailed in the validation plan, to be developed in the future. In summary, the medical records for up to 125 potential cases will be requested and abstracted to assess whether algorithms based on codes accurately identify the events of interest. The resulting medical record data will be reviewed by endpoint adjudicators with relevant clinical expertise. We aim to identify an electronic algorithm of codes that results in a positive predictive value greater than 80% for medical record–confirmed outcomes (see Section 3.4.1.3 for specific case definition for confirmed case).

If the lower bound of the 95% CI for the positive predictive value of the coding algorithm for UTI is found to be below 80% in one or more of the data sources, we will update the coding algorithm for that outcome to achieve a higher positive predictive value; if necessary, we will draw another sample of medical records to validate the revised algorithm. The algorithm development process will be described in the validation plan.

CPRD

The presence of the clinical criteria (see Section 3.4.1.3, Case Validation: Case Definition) in each potential case of severe complications of UTI will be evaluated through review of the patient profiles of recorded information in the CPRD. For patients for whom available clinical data in the CPRD cannot rule out severe complications of UTI, including those for whom no HES linkage is available, we will further attempt to validate the severe UTI diagnosis by collecting the relevant clinical information through a questionnaire to the GP. The process for case validation in the CPRD is shown in Figure 1.

Figure 1: Case Validation in the CPRD

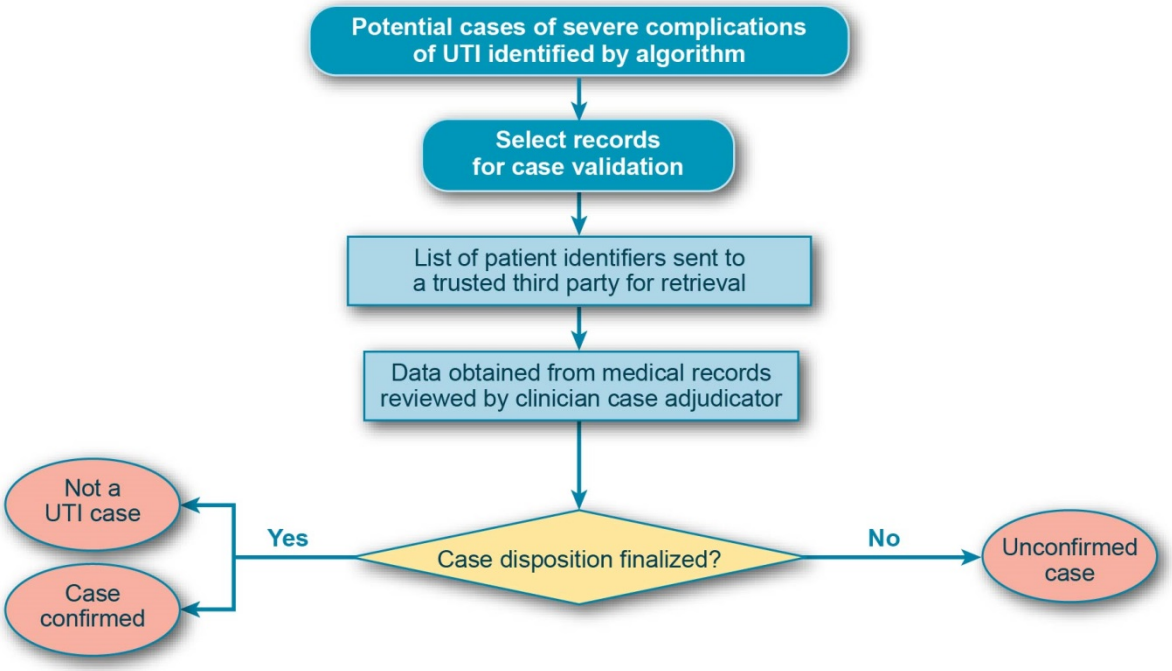


CPRD = Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics; UTI = urinary tract infection.

Medicare/ HIRD^{SM}

The process for case validation in Medicare data and the HIRD^{SM} is shown in Figure 2. Patient identifiers (name, date of birth, and social security number) are included in the Medicare files and can be used for further data abstraction. Additionally, individual and institutional providers have a unique identification number that is used to identify specific providers. Patients meeting the outcome definition of UTI based on diagnosis codes associated with hospital or ED claims will be identified, and information about the individual provider for these patients will be collected. Relevant potential cases will be identified from each cohort, and a list will be sent to separate individual trusted third parties for Medicare and for HIRD^{SM}. Each third party will contact the individual provider to obtain to obtain the required information from relevant medical records. For patients in the Medicare data, details from the medical record will be obtained by record abstraction. For patients in the HIRD^{SM}, redacted copies of the medical record for the hospitalization of interest will be obtained. Structured forms for abstraction in Medicare and for guiding the copying of relevant records for HIRD^{SM} patients will be used to collect the relevant information to confirm the outcome (forms will be provided as part of the study report). Final confirmation of cases will be conducted independently by endpoint adjudicators who will be blinded to exposure to medications and will be identified by RTI Health Solutions (RTI-HS) and HealthCore.

Figure 2: Case Validation in Medicare and HIRD^{SM} Data



HIRD^{SM} = HealthCore Integrated Research Database; UTI = urinary tract infection.

3.4.1.3 Case Definition via Medical Record Review

For this study, confirmed cases of UTI are those that meet the definition of having either pyelonephritis or urosepsis.

The following infection criteria for pyelonephritis will be used (Patkar et al., 2009):

- At least two of the following:
  - History of fever or documented fever > 38.0°C/100.4°F
  - Dysuric complaints
  - Flank pain/costovertebral angle tenderness
  - Leukocytosis/white blood cell count > 12,000/cubic mm
  - Abnormal urine (cloudy, frank pus or blood in urine, foul smell)

AND

- Any one of the following:
  - Computed tomography, magnetic resonance imaging, or ultrasonography findings consistent with renal inflammation
  - Computed tomography, magnetic resonance imaging, or ultrasonography findings consistent with renal abscess
  - Computed tomography, magnetic resonance imaging, or ultrasonography findings consistent with hydronephrosis

OR

- Any one of the following:
  - Blood cultures and urine cultures positive for the same organism
  - Blood cultures positive for gram-negative organisms, *Enterococcus* species, or *Staphylococcus saprophyticus*
  - Urine culture positive for > 10^5 gram-negative organisms, *Enterococcus* species, or *S. saprophyticus*
  - Urine culture positive for < 10^5 any organism AND patient treated for ≥ 7 days with antibiotics

Urosepsis is defined as sepsis caused by infection of the urinary tract and/or male genital organs (e.g., prostate). The patients are affected by microorganisms capable of inducing inflammation within the urinary and male genital tract. For the diagnosis of urosepsis, the following three conditions need to be present (Wagenlehner et al., 2008):

- Diagnosis of infection of urinary tract and/or male genital organs

AND

- One of criteria I:
  - Proof of bacteriemia or
  - Clinical suspicion of sepsis

AND

- Two or more of criteria II: systemic inflammatory response syndrome (SIRS)
  - Body temperature ≥ 38°C/100.4°F or ≤ 36°C/96.8°F
  - Tachycardia ≥ 90 beats per minute
  - Tachypnea ≥ 20 breaths per minute
  - Respiratory alkalosis, $PaCO_2$ (partial pressure of arterial carbon dioxide) ≤ 32 mm Hg
  - Leucocytes ≥ 12,000 per μL or ≤ 4,000 per μL or band forms > 10%

3.4.2 Exposure/Independent Variables of Interest

For this study, we plan to identify the study medications of interest among eligible patients from GP prescriptions in the CPRD and from outpatient pharmacy claims in the HIRD^{SM} and Medicare data. New use of dapagliflozin will be defined as the date of first dapagliflozin prescription (CPRD) or dispensing (HIRD^{SM} and Medicare) in the data source. New use of an AD in a class other than a SGLT2 inhibitor, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy will be defined as the date of first prescription or dispensing of these medications in the data source. As illustrated in Appendix 2, more than one treatment episode within the person-time of a patient can be selected as comparator exposures if a qualifying drug is initiated at a point in time after the first eligible treatment episode ends and is a different drug than the first. Potential comparators are eligible to enter the pool of patients from which comparators can be selected multiple times (i.e., if they qualify with drug A and then later switch to drug B, which also qualifies as a new comparator drug, they can enter both times). Follow-up

will not be censored with addition of any other antidiabetic drug (other than a non-dapagliflozin SGLT2 inhibitor) during the index risk window.

The index medication is the dapagliflozin or comparator AD exposure that qualifies the patient to enter the study. When the episodes (time windows at risk) of study medications overlap, only one of medications will be used as the index medication. If the overlapping episodes include dapagliflozin, then dapagliflozin will be used as the index medication. If the overlapping episodes do not include dapagliflozin, then the first episode will be used as the index medication. If the episodes of two or more comparator AD episodes start at the same date, we will randomly choose one as the index medication, and the exposure will be classified as index combined therapy.

New users of the antidiabetic medications listed in Appendix 4 will be included in the comparison group.

3.4.3 Other Covariates/Control Variables

Information to characterize the cohorts at the time of study drug initiation will be collected from the period ending on the index date, using all available information in the data source. Because all patients in the study are required to have at least 180 days of data before the index date, there will be a minimum of 180 days of data from which to evaluate covariate values. For some patients, more information will be available, and all information will be considered to reduce misclassification of covariate information. During development of propensity scores, use of indicator variables for the duration of lookback time and timing of information on key covariates will address possible differential availability of information on covariates by exposure group, as well as control for associations that vary by time of recorded information. Exclusion diagnoses will be identified based on recorded GP diagnoses (CPRD) or claims diagnoses (HIRD^{SM} and Medicare) during the lookback period. Data on likely predictors of severe complications of UTI (Table 2) will be identified for all patients prior to and including the index date. Although severity of T2DM may be a predictor for UTI, indicators for severity, e.g., glycated hemoglobin (HbA1c) values, will be available in the CPRD and approximately 30% of patients in HIRD^{SM}. All of these variables and additional variables that could potentially differ by exposure (e.g., history of UTI diagnoses, age > 75 years, see Appendix 5) will be included in a logistic regression model that will be used to generate propensity scores, which will be used for the final analysis. The propensity scores will quantify the probability of receiving dapagliflozin at the time of the index date (see Section 4.1.1).

Table 2: Variables of Interest to be Collected for Propensity Score Development

Demographic or Lifestyle	Medications
Age Sex Calendar year of index date Duration of lookback time Body mass index > 30 (CPRD only) or obesity surgery Smoking history (CPRD only) History of alcohol abuse (CPRD only) Socioeconomic status: Index of multiple socioeconomic deprivation, quintiles—first least deprived to fifth most deprived (CPRD only) Geographic region of residence	Antihypertensives/diuretics including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, calcium-channel blockers, other antihypertensives, antiarrhythmics, digoxin, nitrates NSAIDs (nonsteroidal anti-inflammatory drugs) Opioids Statins, fibrates Oral steroids Zoledronic acid Lipid-modifying agents Other: acetaminophen, antibiotics (penicillins, sulfa),, anticonvulsants, antifungals, antituberculars, chemotherapeutic agents, methotrexate, aspirin and other antiplatelets (e.g., clopidogrel, ticlopidine, prasugrel), anticoagulants, systemic antivirals Concomitant antidiabetics (including specification of add-on or switch)
Medical Comorbidities[a]	**Indicators of Diabetes Severity**
Hospitalization for a serious condition that requires intensive care in the 180 days before the index date Length of hospitalization Kidney diseases Kidney and genitourinary stones and disease Pregnancy in the 180 days before and including the index date	Renal insufficiency or diabetic nephropathy Retinopathy Peripheral neuropathy Peripheral vascular disease Coronary heart disease Cerebrovascular disease Amputations Time since first diagnosis of type 2 diabetes mellitus, (CPRD only)

CPRD = Clinical Practice Research Datalink.

[a] Additional medical comorbidities that may be considered for inclusion can be found in Appendix 5.

Other variables to include in the propensity score models will be indicators of health care utilization in the 180 days before but not including the index date. These variables are number of outpatient visits, number of hospitalizations, number of emergency department visits, and number of specialty care visits.

Another variable to be examined will be whether patients, at the time of the index date, “added on” dapagliflozin or new use of another AD, that is, whether prescriptions or dispensings for any AD that the patient was receiving in the 90 days before the prescription or dispensing for dapagliflozin or the newly initiated AD are continued in the 90 days after the index date (i.e., at least one more prescription is recorded after the index date). Patients will be classified as having “switched to” dapagliflozin or new use of another AD if there is a prescription or dispensing for the medication recorded in the 90 days before the index date and no prescriptions or dispensings for that medication are recorded from the index date to 90 days after the index date. Days’ supply

will be used to determine the calculated end of previous AD therapy or will be assumed to be 30 days if missing.

To explore the impact of addition of ADs other than the index exposure, we will determine the rates of new AD use during the person-time of the index exposure episode among dapagliflozin initiators and comparator AD initiators (see Section 4.1.3). The additional drug could be any AD that was not a part of the initial treatment episode, including insulin. To be considered exposed to an added AD during follow-up (i.e., added after the index date), one prescription or dispensing for the medication must be added to the regimen during follow-up (recorded as yes/no for whether an AD was prescribed).

Variables other than the addition of other ADs, both fixed and time-dependent, that could represent possible confounders and effect modifiers will be identified, if deemed necessary and feasible, and classified during follow-up time. The degree to which we can pursue analyses of these variables is contingent on the number of events within each outcome.

The approaches to handling concomitant ADs in the analyses are summarized in Table 3.

Table 3: Approaches to Handling Concomitant Antidiabetic Drugs

Timing and Type of Antidiabetic Drug Dispensing or Prescription	Analysis Approach
At index date, any AD taken during baseline that is not the new prescription and is not eligible to be a study exposure	Include in propensity score
At index date, any AD taken during baseline that is not the new prescription and is eligible to be a study exposure	Include in propensity score
Designation whether the AD initiated at the index date is an add-on to current medication or a switch to a different medication	Include in propensity score
Insulin at the index date	Conduct descriptive and comparative analyses separately by insulin use at index date (Yes or No)
ADs that have been used in the past added during follow-up	Consider use of time-varying covariate methods
Potential bias from new use, by exposure status, of a drug class	Sensitivity analysis excluding all individuals not new to the index drug class—e.g., a new user of saxagliptin (comparator group) will be included in the sensitivity analysis only if he/she was not treated with any DPP-4 inhibitor during the baseline time period
SGLT2 inhibitor other than dapagliflozin added during follow-up	End follow-up and censor

AD = antidiabetic drug; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-glucose cotransporter 2.

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

In the following analyses descriptive analyses (i.e., secondary objective #2) will be done before other analyses. The specific variable definitions will be described in the statistical analysis plan, to be developed after finalization of the protocol.

All conversion of the original data to analysis variables will be performed using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Data management for CPRD and Medicare data will be carried out in accordance with RTI-HS standard operating procedures. Routine procedures include checking electronic files, maintaining security and data confidentiality, following the statistical analysis plan, and performing quality-control checks of all programs. Data extraction programming for creating the study population from the HIRD^{SM} and creating the analytic file will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction and data development methods that are referenced in HealthCore standard operating procedures.

4.1.1 Propensity Score Approach

Demographic, medical, and clinical factors that may be associated with the decision to begin therapy with any particular AD may also be associated with the outcome. However, the number of outcomes will likely be small, limiting the number of variables that could be included in a regression model that predicts these outcomes (Cepeda et al., 2003). To address this difficulty, we will summarize the set of confounding variables into a single propensity score, based on the literature on potential confounding variables associated with the outcome. The propensity score is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates (Braitman and Rosenbaum, 2002; D'Agostino, 1998; Perkins et al., 2000).

Within each data source, propensity scores will be estimated by conducting logistic regression modeling and incorporating measured potential predictors of therapy as independent variables and exposure group status (dapagliflozin group vs. comparator group) as the outcome. The variables listed in Table 2 and Appendix 5, if available in the data source, will be assessed on the index date or, for chronic conditions, before the exposure index date, and will be considered for inclusion in the propensity score model.

If matching is performed, the propensity score models will be fitted after matching. The propensity score models will be developed for patients within each data source and will adjust for calendar year of the index date as a continuous variable to allow for changing prescription patterns for dapagliflozin from the time it is first available through the date of receipt of the data. As prescription patterns change over time, the confounding influence of the determinants of the prescription may also change. During development of propensity scores, indicator variables for the duration of lookback time and timing of information on key covariates will be included. Descriptive analyses will be stratified by data source and propensity score deciles and will be conducted at each scheduled data cut.

For data sources for which it is not feasible to obtain data on all eligible comparator cohort members in the data source, propensity scores will be obtained after selection of the comparator cohort through matching. For all analyses, we will exclude patients who have estimated propensity scores outside the range that is common to both exposed and comparator cohorts. This process is known as "trimming." Trimming occurs at both ends of the propensity score scale. At the bottom end, we will exclude all patients, exposed or unexposed, who have a propensity score below the 2.5 percentile value of the distribution of scores among the exposed group. At the upper end, we will exclude all patients, exposed and unexposed, with scores greater than the 97.5 percentile of scores among the comparator patients. This trimming will be performed separately for each index year–specific set of propensity scores.

Within each propensity score analysis, after trimming, the data will be stratified into deciles of propensity scores based on the distribution among dapagliflozin initiators. Within each of these 10 propensity score–based strata, we will investigate the extent to which covariates are balanced between the two treatment groups by use of the absolute standardized difference to assess the balance of measured baseline covariates between the dapagliflozin group and the comparator AD group before and after propensity stratification (Austin, 2009). Any imbalance will be addressed by either revising the propensity score model or by making adjustments in the final outcome model (Braitman and Rosenbaum, 2002; Perkins et al., 2000). We will report the number of patients trimmed from the analysis because of nonoverlap of propensity scores. If using deciles to create stratified results in strata that are too small, it may be necessary to combine adjacent deciles.

4.1.2 Primary Objective—Compare Incidence Rate of Severe Complications of Urinary Tract Infections

The sex-specific incidence rate of hospitalization or ED visits for severe complications of UTI among dapagliflozin initiators and among the comparator group will be estimated. The number of new hospitalized cases of severe complications of UTI during follow-up will be determined using the validated algorithm. Person-time for each patient will be determined as the time between the date of first prescription or dispensing for either dapagliflozin or comparator AD and end of time at risk. The total person-time of observation among individuals at risk will then be calculated. The incidence rate of severe complications of UTI will be estimated by insulin use at the index date in each cohort. Within each data source, incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% CIs. The following incidences and comparisons will be generated:

- Crude incidence, estimated by categories of insulin use at the index date, among dapagliflozin initiators versus among the entire comparator group
- Summary IRRs after adjusting for propensity score decile, calendar year, and data source by categories of insulin use at the index date, among dapagliflozin initiators versus the entire comparator group
- Summary IRRs after adjusting for propensity score decile, calendar year, and data source by categories of insulin use at the index date, among dapagliflozin initiators versus initiators of the most commonly used classes of ADs

The adjusted IRRs will be the primary endpoint. In CPRD and Medicare data, crude IRRs will facilitate comparison with the adjusted IRRs to provide an indication of the degree of confounding. Follow-up time that includes exposure to more than one index AD, e.g., first 30 days after patients switch from dapagliflozin exposure group and selection into the comparator group, will be assigned to a separate category of multiple exposure.

Adjusted incidence rates and IRRs will be calculated by standardizing to the dapagliflozin person-time distribution, that is, weighting the incidence or IRR of each stratum (defined by propensity score decile, calendar year, and data source) by the amount of dapagliflozin person-time within the stratum. More details on the analysis methods will be included in the statistical analysis plan.

4.1.3 Secondary Objectives

4.1.3.1 Secondary Objective #1—Compare Incidence Rate of Pyelonephritis

The sex-specific incidence of hospitalization or ED visit for pyelonephritis or outpatient diagnosis of pyelonephritis among dapagliflozin initiators and among the comparator group will be estimated for each data source. In stratified analyses, follow-up time that includes exposure to more than one index AD, e.g., at time of switch from dapagliflozin exposure group to the comparator group, will be excluded or assigned to a separate category of multiple exposure. The following incidences and comparisons will be generated:

- Crude incidence, estimated by categories of insulin use at the index date, among dapagliflozin initiators versus among the entire comparator group
- Summary IRRs after adjusting for propensity score and data source, by categories of insulin use at the index date, among dapagliflozin initiators versus among the entire comparator group
- Summary IRRs after adjusting for propensity score, calendar year, and data source by categories of insulin use at index date, among dapagliflozin initiators versus initiators of the most commonly used classes of ADs

Adjusted IRRs will be adjusted by propensity score, calendar time, and data source.

4.1.3.2 Secondary Objective #2—Compare Baseline Patient Characteristics

For each data source, descriptive statistics will be generated to compare baseline characteristics between dapagliflozin initiators and comparator AD initiators, by insulin use at the index date. Categorical variables will be summarized by frequencies and proportions, and continuous variables will be summarized by means and standard deviations or medians and interquartile ranges.

The following variables will be characterized:

- Age stratified by sex
- Body mass index (CPRD only)
- Duration of lookback time prior to index date
- Prescription or dispensing of each, specific non-dapagliflozin AD at index date

- Switch versus add-on initiation of study exposure (dapagliflozin or other AD) at index date
- History of diabetic nephropathy diagnosis
- History of UTI diagnosis
- History of severe complications of UTI diagnosis
- History of coronary heart disease diagnosis
- History of cerebrovascular disease diagnosis
- History of hypertension diagnosis
- HbA1c level at the index date (most recent measurement on or before the index date) (CPRD only)
- History of alcoholism or liver disease diagnosis
- History of hyperlipidemia diagnosis or treatment
- History of chronic obstructive pulmonary disease or asthma diagnosis
- History of malignancy diagnosis
- History of peripheral vascular disease diagnosis
- History of vasculitis, scleroderma, or systemic lupus erythematosus diagnosis
- History of trauma diagnosis in the last 6 months

Results of the descriptive analyses will be used to inform subsequent analyses.

4.1.3.3 Secondary Objective #3—Identify Confounders and Effect Modifiers

Other variables (both fixed and time dependent) will be classified during follow-up time, and analyses stratifying exposure time by level of these variables will be performed to explore potential effect modification and confounding by these variables on the relative incidence rates and rate ratios for severe complications of UTI. Some of the stratification variables will include index year, HbA1c levels (when available in the CPRD), whether patients were “added on” or “switched to” dapagliflozin or other ADs, each specific concomitant AD medication class added during follow-up, and prescription for a medication associated with severe complications of UTI during follow-up. Also, variables for which a close balance was not achieved within propensity score strata will be further examined. We will calculate the following statistics:

- Incidence rates by exposure category stratified by potential effect modifiers or confounders and data source
- IRRs stratified by potential effect modifiers or confounders

To explore the impact of differential addition of ADs or factors associated with the need for an additional AD by exposure, we will compare rates of new AD use among dapagliflozin initiators and comparator AD initiators. If necessary, further adjustment for therapies added during follow-up will be performed via time-dependent Cox proportional hazards regression. Techniques to pool the data will be applied to combine IRR estimates across data sources if appropriate (see Section 4.1.7).

4.1.4 Imputation of Missing Values

We expect that relatively few key variables will have notable missing values. Variables such as smoking and alcohol consumption levels, body mass index, and HbA1c will be unavailable or have high levels of missing values. The pharmaceutical exposures and comorbidities are expected to be based on outpatient prescriptions or dispensings and to be complete. If there are considerable missing data for lifestyle covariates, multiple imputation will be used to fill in missing values for the propensity score creation and multivariable analyses. The decision to use multiple imputation will depend on the strength of the association between the variable and treatment and the extent of missing data. Based on information from the observations with nonmissing values, we will impute five simulated versions of the data set. The imputed data sets will be used for creation of propensity scores and in the multivariable analyses, with the results being combined appropriately to generate final point estimates and CIs. In theory, this should give point estimates with equal or less bias than those that would be obtained if we had limited the sample to those with complete data, and it should give greater precision because of the larger number of patients that will be included using this method as opposed to restricting the analysis to observations with complete data. The specific approach will be detailed in the statistical analysis plan.

We have selected the multiple imputation approach because existing methods for imputation penalize the standard errors when imputing data and multiple imputation allows for better bias correction than most alternatives, including the complete-case approach, for many, although not all, applications. The complete-case approach can be very costly of information in a body of high-dimensional data, since the proportion of complete cases will decline with the increase in the number of variables.

4.1.5 Exploratory Objectives

Not applicable.

4.1.6 Sensitivity Analyses

The following sensitivity analyses will be conducted:

- Estimation of IRRs for the dapagliflozin group compared with the comparator group, by applying the extended risk window from 30 days to 90 days in the exposed follow-up time for dapagliflozin initiators and for comparator initiators.
- Assessment of the effect of unmeasured confounders on the association between dapagliflozin use and severe complications of UTI by assuming a plausible range of values for those confounders (Lash et al., 2009).
- Estimate the crude incidence rate without stratification by insulin categories at the index date, among dapagliflozin initiators versus among the entire comparator group.
- Estimate summary IRRs after adjusting for propensity score decile, calendar year, and data source without stratification by insulin categories at the index date, among dapagliflozin initiators versus the entire comparator group.
- Estimate summary IRRs after adjusting for propensity score decile, calendar year, and data source without stratification by insulin categories at the index date, among

dapagliflozin initiators versus initiators of the most commonly used classes of ADs (each class separately).

- Estimate summary IRRs after adjusting for propensity score, calendar year, and data source after excluding individuals not new to the index AD drug class.

4.1.7 Pooled Analysis

The results of two or more data sources with similar results for the primary outcome (i.e., plausibly differing only from sampling variability) will be pooled. The pooled analysis will be designed to estimate the effect of the exposure while controlling for confounding using the data stratified on propensity scores. The data source will be retained as a stratification variable, so the effect within each data source can be estimated. Mantel-Haenszel techniques will be used to pool the data from each data source and calculate overall adjusted incidence rate ratios. This analysis is designed to estimate the effect of the exposure while controlling for confounding by using the data source–specific propensity score stratification.

If residual confounding is suspected in any of the data sources (for example, due to lack of information on one or more confounding variables), external adjustment can be used to assess the impact of unidentified confounders and to reduce the amount of such confounding (see Section 4.1.6) (Lash et al., 2009).

4.2 Power/Sample Size

The observed study size will depend upon the market uptake of dapagliflozin in the US and UK. We estimate a total of 91,927 person-years of follow-up among new users of dapagliflozin across all three data sources. The derivation of this total follows.

It is currently projected that at the end of 5 years, the CPRD will have 3,600 person-years of exposure to dapagliflozin, including approximately 2,900 among those not on insulin at the index date and 700 among those on insulin at the index date. These estimates are based on the following assumptions: number of patients aged 18 years and older with a newly prescribed AD in the CPRD per year is 23,970 (CPRD data as of 31 December 2011); the proportion of new users starting dapagliflozin among patients who meet inclusion criteria will be 1% during year 1, 2% during year 2, 3% during year 3, 4% during year 4, and 5% during year 5 of the study; on average, each new user will contribute 12 months of person-time; and approximately 20% of new dapagliflozin users will be on insulin at the index date (derived from Hall et al., 2012).

In the US data sources, we estimate that there will be approximately 88,327 person-years of follow-up available among all new users of dapagliflozin (HIRD^{SM}: 42,473 person-years; Medicare: 45,854 person-years). This exposure would include approximately 70,662 person-years among those not on insulin at the index date and 17,665 person-years among those on insulin at the index date. These estimates are based on the following assumptions: (1) the age distribution among oral AD users is 61.9% aged 18-64 years and 37.7% aged 65 years or older (Boccuzzi et al., 2001), (2) 34.15% coverage rate for Medicare Part D among Medicare beneficiaries, (3) the HIRD^{SM} covers 6% of the US population aged 64 years or younger, (4) each new dapagliflozin user will contribute 12 months of exposed person-time, and

(5) approximately 20% of new dapagliflozin users will be on insulin at the index date (Hall et al., 2012).

To provide precision estimates in relation to the total projected study size, we first estimated the background incidence rates based on the literature. In a study conducted with Canadian data, the incidence of pyelonephritis in women with diabetes was estimated to be 140 per 10,000 person-years for patients aged less than 65 years and 66 per 10,000 person-years in patients aged 65 years or older. In men with diabetes, the rates per 10,000 person-years were 26.5 for men aged less than 65 years and 34.3 for those aged 65 or more years (Nicolle et al., 1996). If we apply the rates for people aged 65 years or older to the new users of dapagliflozin not on insulin at the index date in Medicare, and the rates for people aged less than 65 years to HIRD^{SM} and CPRD data, we would expect to observe approximately 1,895 events in females and 559 events in males if the 73,542 person-years we anticipate are accrued among this group and are distributed evenly between the sexes. Table 4 shows the expected number of UTI events among all cohort members by study data source.

Table 4: Estimated Number of Urinary Tract Infection Events Among All Cohort Members

	HIRD^{SM}	Medicare	CPRD	Total
Total sample cohort[a]	212,366	229,270	18,000	459,636
Average length of follow-up	1 year	1 year	1 year	1 year
Exposed person-years	42,473	45,854	3,600	91,927
Rate of severe UTI (per 10,000 person-years)				
Females	140	66	140	
Males	26.5	34.3	26.5	
Estimated number of events: Females	1,487	757	126	2,369
Estimated number of events: Males	281	393	24	698
Estimated number of events: Total	1,768	1,150	150	3,068

CPRD = Clinical Practice Research Datalink; HIRD^{SM} = HealthCore Integrated Research Database; UTI = urinary tract infection.

[a] Assumes 34.15% coverage rate for Medicare enrollment study criteria, and 6% population coverage of HIRD^{SM}.

To estimate the anticipated magnitude of the upper 95% confidence limit, we calculated a weighted average of the four expected background incidence rates (women: 140 and 66 per 10,000 person-years; men: 26.5 and 34.3 per 10,000 person-years), based on the age distributions in each data source, the distribution of person-years in each data source, and an equal distribution of person-time between the sexes. We estimated the precision of the study under various scenarios using this weighted incidence rate. Table 5 shows the probability that the upper 95% confidence limit around the observed IRR will be less than specified IRRs for dapagliflozin users not on insulin, assuming that the true IRR is 1.0 and a 1:4 dapagliflozin:comparator person-year ratio. For example, a study size of 73,000 person-years of dapagliflozin follow-up among new users of dapagliflozin not on insulin at the index date will provide a 89% probability that the

upper 95% confidence limit of the IRR will be less than 1.2 among females and an 89% probability that the upper 95% confidence limit of the IRR will less than 1.4 among males, assuming the 73,000 person-years are split evenly between the males and females.

Table 5: Probability That the Upper 95% Confidence Limit of the IRR is Below the Specified Value, Assuming IRR in Population = 1.0

Rate (per 1,000 Person-years) in Comparator	Dapagliflozin Exposed Person-years	Upper 95% Confidence Limit of IRR for Dapagliflozin Versus Comparator				
		1.1	1.2	1.3	1.4	1.5
Males	Males only					
Rate = 3.04	15,000	0.08	0.20	0.36	0.53	0.69
	25,000	0.11	0.30	0.54	0.75	0.89
	36,500	0.14	0.41	0.70	0.89	0.97
	45,000	0.17	0.48	0.79	0.94	0.99
	50,000	0.18	0.52	0.83	0.96	0.99
Females	Females only					
Rate = 10.3	15,000	0.18	0.53	0.83	0.96	0.99
	25,000	0.28	0.75	0.97	1.00	1.00
	36,500	0.38	0.89	1.00	1.00	1.00
	45,000	0.45	0.94	1.00	1.00	1.00
	50,000	0.49	0.96	1.00	1.00	1.00

IRR = incidence rate ratio.

Note: Assuming 3.04 per 1,000 person-years is the rate of severe complications of UTI associated with hospitalization among male patients not exposed to dapagliflozin, 10.3 per 1,000 is the rate for females, a 1:4 dapagliflozin:comparator person-year ratio, and population IRR = 1.0 This table was calculated using Episheet (Rothman, 2012).

4.3 Milestones

For the purpose of periodic regulatory reporting, one descriptive analysis, one interim comparative analysis, and one final comparative analysis are planned. The descriptive analysis, which includes comparison of baseline characteristics for each cohort and total case counts, will be performed after dapagliflozin has been on the market in the US for approximately 30 months. The interim comparative analysis will be performed after dapagliflozin has been available in the US for approximately 48 months, and the final analysis will be conducted after dapagliflozin has been available for 60 months. The interim comparative analysis will be performed if at least two outcome events are observed in the entire study cohort (dapagliflozin and comparator AD cohorts combined). The proposed timeline for analyses is shown in Table 6.

Table 6: Milestones

Report	Data Cut (Time After Dapagliflozin is Available to Patients in the US) Anticipated Month/Year[a]
Interim descriptive analysis	24 months January 2016 (includes only CPRD and HIRD^{SM})
Interim comparative analysis	48 months January 2018 (includes all data sources)
Final analysis	60 months January 2019 (includes all data sources)

CPRD = Clinical Practice Research Datalink; HIRD^{SM} = HealthCore Integrated Research Database; US = United States of America.

[a] Due to database lags, which are typically 4-6 months in HIRD^{SM} and CPRD, the 24-month report will likely include data from the first 18 months of dapagliflozin use in the HIRD^{SM} and CPRD, the 48-month report will include data through the first 42 months of dapagliflozin use in the HIRD^{SM} and CPRD and 18 months of dapagliflozin use in Medicare, and the 60-month report will include data through the first 54 months of dapagliflozin use in the CPRD and HIRD^{SM} and 30 months of dapagliflozin use in Medicare.

5 STUDY LIMITATIONS/STRENGTHS

5.1 Confounding

All potential confounding variables for which there are data will be controlled to the extent possible, primarily through the use of propensity scores. Potential unidentified confounding conditions are those that cannot be identified in this manner and that are differentially distributed between the exposure groups, related to the outcome, and largely uncorrelated with the measurable characteristics.

In the CPRD, the lack of specialist prescriptions may result in lack of information on the early prescriptions for some medications, before prescribing is transferred to the GP. Some variables, such as use of over-the-counter medication, will remain unmeasured in all data sources.

Confounding by indication (or channeling bias) is a common bias in observational pharmacoepidemiology studies whereby the indication for therapy may be associated with both treatment and outcome. Since patients who receive a particular drug therapy typically have more severe disease or a perceived higher risk (due to self-selection or physician preference) than patients not on the medication, selection of treatment can be confounded with clinical and nonclinical patient factors that may be related to outcomes of interest. For example, new medications may be prescribed differentially to healthier patients who physicians believe could tolerate a product with a lesser-known safety profile, or to patients who have more severe disease, for whom previous treatment regimens have failed, or who have contraindications to other drugs (e.g., thiazolidinediones are not recommended for use in patients with heart failure). New medications may also be prescribed differentially by physicians who are “early adopters” of new technologies. As much as possible, such considerations are taken into account by the propensity score, but some aspects may remain unmeasured and could result in residual confounding. Specifically, dapagliflozin could be preferentially prescribed to patients with more severe diabetes or who have failed other therapies. In the CPRD, HbA1c levels are likely to be

available for most patients with T2DM, so such bias may be assessed and adjusted for in analysis. However, this variable is available for only approximately 30% of individuals in the HIRD^{SM} and is not available in Medicare data. Comparisons of adjusted IRRs from the CPRD with those assessed in HIRD^{SM} and Medicare data can facilitate assessment of such uncontrolled confounding in the claims-based data sources. Dapagliflozin could also be preferentially prescribed to patients with fewer risk factors for severe complications of UTI. These channeling patterns could bias the hazard ratio toward or away from the null.

To assess the effect of unmeasured confounders on the association between dapagliflozin use and severe complications of UTI, we will conduct sensitivity analyses to estimate the degree of possible bias that might be present by assuming a plausible range of values for those confounders.

5.2 Other Biases

Misclassification bias can result if study patients are not categorized correctly with regard to exposure or outcome. We expect minimal misclassification with respect to exposure, since this will be determined from prescribing records. However, actual adherence to instructions for taking dapagliflozin or other ADs cannot be confirmed. Further, misclassification as to whether the patient is a new user could exist if providers supplied samples of dapagliflozin or comparator ADs to patients for varying duration at no cost and with no record in the respective data source. Because of the newness of dapagliflozin, we expect little misclassification of dapagliflozin initiators. However, initiators of older antidiabetics will be more likely to be misclassified as new users if they used the medication of interest before the patients' data were included in the data sources.

Classification of type 2 versus type 1 diabetes mellitus may also be a source if misclassification. Potential patients with evidence of type 1 diabetes mellitus (T1DM) are to be excluded. However, with the repeated health care that individuals with T1DM or T2DM require, we anticipate that accuracy of classification of diabetes type will be improved from the relative frequency of the use of these 2 diagnoses for individual patients.

Misclassification of the outcome will be reduced by evaluating severe complications of UTI using medical records and laboratory data, if available, to confirm clinical diagnoses of the outcome. Medical chart review for potential cases ascertained in the HIRD^{SM} and Medicare data will also be used to validate the outcome.

5.3 Study Size

The ability to meet the sample size projections depends upon the uptake of dapagliflozin. It is currently projected that at the end of 5 years, the study will yield 91,927 person-years of exposure to dapagliflozin; approximately 73,542 among those not on insulin at the index date and 18,385 among those on insulin at the index date. With 73,000 person-years among those taking dapagliflozin and not on insulin and if approximately 50% are males, there is an 89% probability that the upper 95% confidence limit of the IRR will be less than 1.4 (assuming that the true IRR is 1.0 and a 1:4 dapagliflozin:comparator person-year ratio). If the uptake of dapagliflozin is one-third of that expected, then the final study size in males would be

approximately 12,000 person-years, with a 72% probability that the upper 95% confidence limit will be less than 1.6 under the null hypothesis of no association.

5.4 Generalizability

Use of the CPRD and US claims data sources provides data entered or submitted by pharmacies, general medical practices, and US clinics and hospitals without any awareness of the hypothesis of studies that may use these data. Study results from the CPRD will be generalizable to UK patients with T2DM meeting the inclusion and exclusion criteria. Results from the Medicare data will be generalizable to US patients with T2DM aged 65 years or older and not in a residential care facility. Results from HIRD^{SM} data will be generalizable to the patients with claims-identified T2DM among the employable US population.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2015) and applicable regulatory requirements. As with all research at RTI International that involves human patients or data on human patients, RTI-HS will request review of the protocol by the RTI International[1] institutional review board (IRB), and we anticipate that the IRB will agree to exemption because the data being analyzed will not have any patient identifiers.

6.1 Ethics Committee Review and Informed Consent

This study does not require review and approval by ethics committees or informed consent.

6.1.1 Ethics Committee Review

6.1.1.1 CPRD

RTI-HS will prepare the request for data and submit the study protocols to the CPRD's Independent Scientific Advisory Committee (ISAC) (http://www.CPRD.com/isac) for approval. The CPRD has obtained ethical approval from a Multicenter Research Ethics Committee (MREC) for all observational research using CPRD data without patient involvement; however, ISAC may recommend that the MREC review the study documentation if any ethical issues arise.

6.1.1.2 HIRD^{SM}

This component of the overall study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. There is no active enrollment or active follow-up of study patients, and no data will be collected directly from individuals.

HealthCore maintains Data Sharing Agreements and Business Associate Agreements with all covered entities who provide data to the HIRD^{SM}. HealthCore's access, use, and disclosure of protected health information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164). HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of

[1] RTI Health Solutions is a business unit of RTI International, a not-for-profit research organization..

authorization (e.g., a HIPAA Waiver of Authorization from an IRB). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

As PHI must be accessed in order to conduct the medical record acquisition, a HIPAA Waiver of Authorization will be applied for from an IRB. HealthCore will submit the protocol to a central IRB for review and approval. Approval is typically provided within 2 to 3 weeks of submission. Once IRB approval is obtained, HealthCore's vendor will proceed with the conduct of medical record acquisition. If changes to the protocol are required, HealthCore will submit an amendment to the IRB. As the IRB is independent, HealthCore cannot control the approval or whether there are conditions for the approval.

Notwithstanding receipt of approval from a central IRB, in some instances, individual institutions may require approval from their local IRB, which would require a separate protocol submission and, in some cases, additional fees. In these cases, HealthCore, RTI-HS, BMS, and AZ will need to agree whether or not to proceed with chart acquisition from these institutions.

HealthCore will provide the vendor only the minimum amount of patient information that is necessary to execute the medical record acquisition. HealthCore uses only vendors that follow federal and state laws and regulations, including but not limited to privacy and security rules such as HIPAA.

At no time during the conduct of this study will HealthCore provide patient- or provider-identifying information to RTI-HS, BMS, or AZ. Only aggregated data will be reported to RTI-HS, BMS, and AZ.

6.1.1.3 Medicare

For use of Medicare data, the CMS requires that IRB review and approval be obtained before use of Medicare data for research can be approved. This protocol will be reviewed by the RTI International IRB before applying to use Medicare data and will undergo a continuing IRB review at least once per year.

Under the Privacy Rule (under 45 CFR 164.512), CMS may disclose protected health information for research without documentation of individual authorization only if an IRB or a CMS Privacy Board has approved a waiver of research. Such a waiver must be provided to CMS.

Data requests for research identifiable data must be reviewed by the CMS Privacy Board to ensure that any study patient's privacy is protected and the need for identifiable data is justified.

6.2 Responsibilities Within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by AZ.

6.2.1 Sponsor Roles and Responsibilities

The sponsor, AZ, is responsible for providing reasonable resources for study implementation and to assure study progress. They are also responsible for communicating with regulatory agencies about the study protocol, the progress of the study, and study findings.

6.2.2 Investigator Roles and Responsibilities

The study investigators at RTI-HS and HealthCore share responsibility with AZ for the design of the study. The investigators at RTI-HS are responsible for conducting the CPRD and Medicare components in a manner that meets regulatory standards, conducting analyses, and preparing scientific reports. The investigators at HealthCore are responsible for conducting the HIRD^{SM} component in a manner that meets regulatory standards, conducting analyses, and preparing scientific reports.

The study shall be conducted as described in the approved protocol. The authors will not develop or implement any deviation or change to the protocol without prior review by AZ.

6.3 Confidentiality of Study Data

The confidentiality of records that could identify patients within the individual data sources must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Data that could directly identify the patient will not be collected in the "study database."

6.4 Quality Control

Experienced RTI-HS programmers in the United States will perform all analyses for the CPRD and Medicare data. To ensure the integrity and quality of the study results, RTI-HS will follow the programming validation life cycle process for all analyses. This includes quality-control checks of programs, logs, and output for accuracy according to relevant standard operating procedures. All programs will be independently reviewed by a second programmer/analyst.

This project will be guided by a written plan to ensure that all collaborators conduct quality-control checks of all aspects of data manipulation and analysis and preparation of study deliverables. The plan will specify that all collaborators will establish and maintain adequate documentation of performance of major tasks. The RTI-HS Office of Quality Assurance will conduct periodic audits during the study period to ensure that such documentation meets the necessary standards, especially the completion of these quality-control checks, according to the plan.

HealthCore's quality system is organized around the Quality Manual, the quality checks with the project life cycle, and the standard operating procedures. HealthCore will perform internal audits to endure adherence to the quality system according to a formal procedure and has procedures for retention of PHI and project data. The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established multiple layers of quality assurance throughout the project life cycle:

- Role-Based Control Checks: Each member of the team is responsible for performing thorough quality assurance checks on his or her work. In addition, the Project Director in collaboration with the Lead Epidemiologist is also accountable for quality of all deliverables.

- Quality Check Points: Centralized “check points” have been implemented during the data management cycle to help ensure accurate translation of programming requests.
- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project life cycle.
- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

HealthCore’s research team documents the progress and scientific and quality review of all study activities and deliverables (e.g., protocol, reports, and manuscripts) in a project log. The project log provides documentation of the major study tasks related to a specific study activity performed by the research team, to develop and execute the requirements of the protocol or other guiding document for a HealthCore research project. In addition, the project log documents the quality assurance measures performed for each study activity during the conduct of the research project. Also, any research team and/or sponsor interaction resulting in a change to study specifications (e.g., protocol, study database, variables in the analytic files) is described in the project log. This is necessary to ensure that such communications are appropriately documented, that the most up-to-date versions of relevant documents are readily identifiable, and that affected documents are clearly tracked in the project log.

6.5 Database Retention and Archiving of Study Documents

Each investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. Investigators must contact the study sponsor prior to destroying any records associated with the study. The location of the study databases and supporting documentation will be outlined in the final observational study report.

6.6 Registration of Study on Public Website

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS Register (ENCePP, 2016) and ClinTrials.gov before the first data cut. The research team and study sponsor adhere to the general principles of transparency and independence in the ENCePP Code of Conduct (ENCePP, 2014).

6.7 Plans for Disseminating and Communicating Study Results

In accordance with the *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2015), there is an ethical obligation to disseminate findings of potential scientific or public health importance, e.g., results pertaining to the safety of a marketed medication. The Consolidated Standards of Reporting Trials (CONSORT) statement refers to randomized studies, but also provides useful guidance applicable to reporting results of nonrandomized studies (Moher et al., 2001). A well-developed publication strategy is encouraged in the Guideline on Good Pharmacovigilance Practices, module VIII, Section B.7 (European Medicines Agency, 2016).

Reports will be provided after each of the analyses, i.e., the descriptive analysis and the comparative analyses. RTI-HS personnel will work with HealthCore to submit the results from

any of these analyses for publication and commit that they will, at least, publish the final results. The authorship of publications shall be in accordance with standards as described in the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* by the International Committee of Medical Journal Editors (2016).

7 ADVERSE EVENT REPORTING

7.1 Adverse Event Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A nonserious AE is any AE that is not classified as serious.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see Note below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the AZ product under study is an SAE.

An ***overdose*** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events are handled as SAEs.

Note: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery, planned prior to signing consent.

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).

7.2 Adverse Event Collection and Reporting

All AEs collected will be reported in aggregate in the final study report.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Not applicable.

8.2 List of Abbreviations

Term	Definition
AD	antidiabetic drug
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca Pharmaceuticals LP
BMS	Bristol-Myers Squibb
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
CONSORT	Consolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
CPT	Current Procedural Terminology
DPP-4	dipeptidyl peptidase-4
ED	emergency department
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	general practitioner
HbA1c	hemoglobin A1c (glycated hemoglobin)
HCPCS	Healthcare Common Procedure Coding System
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability and Accountability Act
HIRD^{SM}	HealthCore Integrated Research Database
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IRB	institutional review board
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
MREC	Multicenter Research Ethics Committee
NDC	National Drug Code
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
PaCO2	partial pressure of arterial carbon dioxide
PHI	protected health information

Term	Definition
PPV	positive predictive value
RTI-HS	RTI Health Solutions
SAE	serious adverse event
SGLT2	sodium-glucose cotransporter 2
SIRS	systemic inflammatory response syndrome
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UK	United Kingdom
US	United States of America
UTI	urinary tract infection

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APPENDIX 1. DIAGNOSIS CODES

Table 1-1: Electronic Algorithm ICD-9-CM Codes for Severe Complications of Urinary Tract Infections and Urinary Tract Infections in the US Data Sources

Code	Type	Description
590.1x	ICD-9-CM	Acute pyelonephritis
590.8x	ICD-9-CM	Pyelonephritis, unspecified
599.0x	ICD-9-CM	Urinary tract infection, site not specified
V13.02	ICD-9-CM	Urinary tract infection
997.5x	ICD-9-CM	Urinary complications
634.7x	ICD-9-CM	Pregnancy w/ spontaneous abortion, urinary tract infection
635.7x	ICD-9-CM	Pregnancy w/ legally induced abortion, urinary tract infection
636.7x	ICD-9-CM	Pregnancy w/ illegally induced abortion, urinary tract infection
637.7x	ICD-9-CM	Pregnancy w/ unspecified abortion, urinary tract infection
638.7x	ICD-9-CM	Pregnancy w/ failed attempt abortive outcome, urinary tract infection
639.8x	ICD-9-CM	Complications following abortion and ectopic and molar pregnancies, urinary tract infection
646.6x	ICD-9-CM	Urinary tract infection following delivery
595.0x	ICD-9-CM	Acute cystitis
597.xx	ICD-9-CM	Urethritis, not sexually transmitted, and urethral syndrome
099.4x	ICD-9-CM	Nonspecific urethritis
601.0x	ICD-9-CM	Acute prostatitis
601.1x	ICD-9-CM	Chronic prostatitis
601.9x	ICD-9-CM	Prostatitis, unspecified

ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; US = United States of America.

ICD-9-CM codes will be mapped to ICD-10 codes.

Table 1-2: Electronic Algorithm Read Codes for Severe Complications of Urinary Tract Infections in the CPRD

Code	Type	Description
K101.00	Read	Acute pyelonephritis
K10y000	Read	Pyelonephritis unspecified
K101z00	Read	Acute pyelonephritis NOS
K100600	Read	Calculous pyelonephritis
K10yz00	Read	Unspecified pyelonephritis NOS
K10y.00	Read	Pyelonephritis and pyonephrosis unspecified
K101000	Read	Acute pyelonephritis without medullary necrosis
K10y300	Read	Pyelonephritis in diseases elsewhere classified

CPRD = Clinical Practice Research Datalink.

NOS = not otherwise specified.

Source: Medical and product dictionary browsers, version 3.0. London: General Practice Research Database (now the CPRD); September 2015.

Table 1-3: Electronic Algorithm Read Codes For Urinary Tract Infections in the CPRD to be Combined With Sepsis

Code	Type	Description
Urinary tract infection		
K190z00	Read	Urinary tract infection, site not specified nos
K15..00	Read	Cystitis
K190.00	Read	Urinary tract infection, site not specified
1AG..00	Read	Recurrent urinary tract infections
K150.00	Read	Acute cystitis
K190.11	Read	Recurrent urinary tract infection
K17y000	Read	Urethritis unspecified
A994.00	Read	Nonspecific urethritis
K190300	Read	Recurrent urinary tract infection
K190500	Read	Urinary tract infection
K15z.00	Read	Cystitis NOS
L166800	Read	Urinary tract infection complicating pregnancy
K190200	Read	Postoperative urinary tract infection
L166.00	Read	Genitourinary tract infections in pregnancy
K17..00	Read	Urethritis due to nonvenereal causes
K171.00	Read	Postmenopausal atrophic urethritis
L166z11	Read	UTI - urinary tract infection in pregnancy

Code	Type	Description
K190400	Read	Chronic urinary tract infection
L166600	Read	Urinary tract infection following delivery
L166300	Read	Genitourinary tract infection in pregnancy - not delivered
L166.11	Read	Cystitis of pregnancy
L166z00	Read	Genitourinary tract infection in pregnancy NOS
K17z.00	Read	Urethritis due to nonvenereal cause NOS
K17y.00	Read	Other urethritis
L166000	Read	Genitourinary tract infection in pregnancy unspecified
K17yz00	Read	Other urethritis NOS
Kyu5500	Read	[X]Other urethritis
L166100	Read	Genitourinary tract infection in pregnancy - delivered
Kyu5100	Read	[X]Other cystitis
K21..11	Read	Prostatitis and other inflammatory diseases of prostate
K211.00	Read	Chronic prostatitis
K210.00	Read	Acute prostatitis
K21z.00	Read	Prostatitis NOS
Sepsis		
A38y.00	Read	Other specified septicaemias
Ayu3E00	Read	[X]Other streptococcal septicaemia
A98yz12	Read	Gonococcal septicaemia
A380400	Read	Septicaemia due to enterococcus
A384211	Read	E.coli septicaemia
A380500	Read	Vancomycin resistant enterococcal septicaemia
A271100	Read	Erysipelothrix septicaemia
A383.00	Read	Septicaemia due to anaerobes
A384400	Read	Serratia septicaemia
A381.00	Read	Staphylococcal septicaemia
R055511	Read	[D]Septicaemic shock
A380.00	Read	Streptococcal septicaemia
A545.00	Read	Herpes simplex septicaemia
A384200	Read	Escherichia coli septicaemia
A380100	Read	Septicaemia due to streptococcus, group B
A384.00	Read	Septicaemia due to other gram negative organisms
A381100	Read	Septicaemia due to coagulase-negative staphylococcus
A380000	Read	Septicaemia due to streptococcus, group A

Code	Type	Description
Ayu3J00	Read	[X]Septicaemia, unspecified
A384300	Read	Pseudomonas septicaemia
A384z00	Read	Other gram negative septicaemia NOS
A021.00	Read	Salmonella septicaemia
Ayu3G00	Read	[X]Septicaemia due to other gram-negative organisms
AB2y300	Read	Candidal septicaemia
A381000	Read	Septicaemia due to Staphylococcus aureus
Ayu3H00	Read	[X]Other specified septicaemia
Ayu3F00	Read	[X]Streptococcal septicaemia, unspecified
A384000	Read	Gram negative septicaemia NOS
A38..00	Read	Septicaemia
A38z.00	Read	Septicaemia NOS
C19..00	Read	Multiple organ failure
R055500	Read	[D]Septic shock
R00B.00	Read	[D]Systemic inflammatory response syndrome [SIRS]
A396.00	Read	Sepsis due to Actinomyces
A3C1z00	Read	Sepsis due to staphylococcus NOS
A3C1000	Read	Sepsis due to Staphylococcus aureus
A3Cz.00	Read	Sepsis NOS
A3C3.11	Read	Sepsis due to Gram negative organisms
A3C0.00	Read	Sepsis due to Streptococcus
A3C0z00	Read	Streptococcal sepsis, unspecified
A3C1y00	Read	Sepsis due to other specified staphylococcus
A3C2.11	Read	Sepsis due to anaerobes
A3C3.00	Read	Sepsis due to Gram negative bacteria
A3C1.00	Read	Sepsis due to Staphylococcus
A3C0y00	Read	Other streptococcal sepsis
A3C0100	Read	Sepsis due to Streptococcus group B
A3C2.00	Read	Sepsis due to anaerobic bacteria
AB2y500	Read	Candidal sepsis
A3C..00	Read	Sepsis
AB2y511	Read	Sepsis due to Candida
A3Cy.00	Read	Other specified sepsis
A3C3y00	Read	Sepsis due to other Gram negative organisms

Code	Type	Description
A38z.11	Read	Sepsis
A3C0000	Read	Sepsis due to Streptococcus group A
Urosepsis		
K190600	Read	Urosepsis

CPRD = Clinical Practice Research Datalink; UTI = urinary tract infection.

NOS = not otherwise specified.

Source: Medical and product dictionary browsers, version 3.0. London: General Practice Research Database (now the CPRD); September 2015.

Table 1-4: Read and ICD-9-CM Codes to Use in Screening for the Chronic Pyelonephritis Exclusion Criteria in the CPRD and US Data Sources

Code	Type	Description
K100.00	Read	Chronic pyelonephritis
K100z00	Read	Chronic pyelonephritis NOS
K104.00	Read	Xanthogranulomatous pyelonephritis
K100400	Read	Nonobstructive reflux-associated chronic pyelonephritis
A160200	Read	Tuberculous pyelonephritis
K100500	Read	Chronic obstructive pyelonephritis
K100100	Read	Chronic pyelonephritis with medullary necrosis
K100000	Read	Chronic pyelonephritis without medullary necrosis
590.0x	ICD-9-CM	Chronic pyelonephritis

CPRD = Clinical Practice Research Datalink; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; NOS = not otherwise specified; US = United States of America.

Note: ICD-9-CM codes will be mapped to ICD-10 codes.

Source: Medical and product dictionary browsers, version 3.0. London: General Practice Research Database (now the CPRD); September 2015.

APPENDIX 2. ASSESSMENT OF INCIDENCE DURING CURRENT USE AND SWITCHING USE AND ESTIMATION OF PERSON-TIME

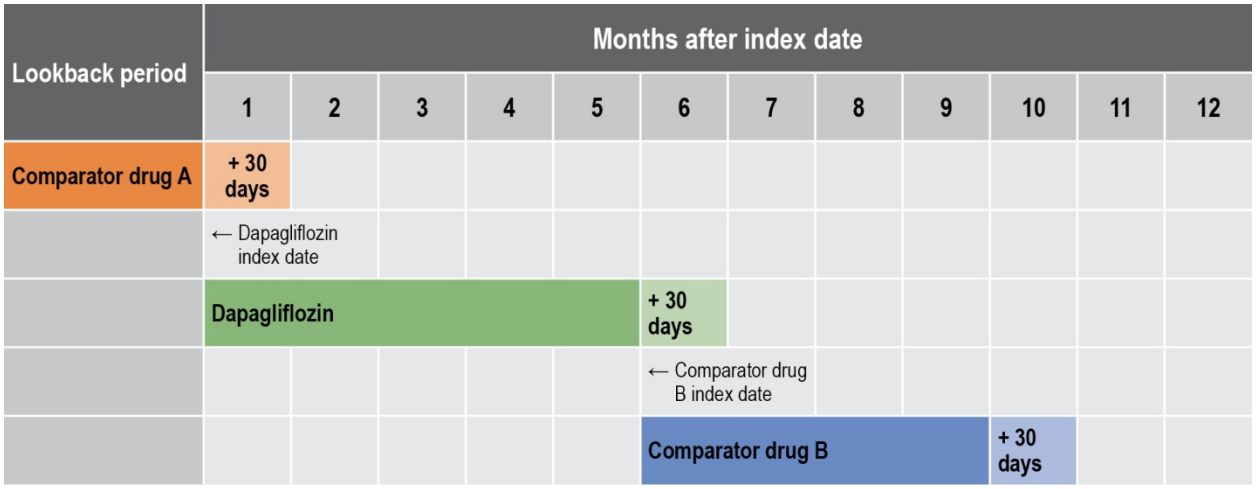
Example 1 through Example 6 on the following pages focus on assessment of incidence during dapagliflozin use compared with (1) use of other comparator ADs as a group and (2) use of specific ADs.

- For calculation of crude incidence and IRRs, the following comparisons can be made:
  - Incidence of UTI during any dapagliflozin-only exposed person-time can be compared with incidence during any comparator-exposed person-time.
  - Incidence of UTI during combined dapagliflozin-plus-comparator–exposed person-time can be compared with comparator-exposed person-time (see Example 1).
- For specific medication comparisons, e.g., comparing dapagliflozin to pioglitazone, the person-time and events during dapagliflozin person-time excluding any time overlapping with pioglitazone person-time can be compared with any non-dapagliflozin person-time in the pioglitazone group.
- For adjusted incidence, (1) propensity score will be used to adjust for concomitant medications at the index date, but only if not newly initiated at the time they were started, and (2) stratification or a multivariable model will be used to adjust for concomitant medications added during follow-up or switched at end of follow-up.

Example 1. Drug A was a medication newly initiated before the study period and is not an excluded AD. Drug A is not eligible to be a comparator drug as it was not newly initiated in the observation period; therefore, the risk window for drug A is not evaluated, but use of drug A is controlled for in development of the propensity score.

The switch is from drug A, a comparator drug that was newly initiated but not during the observation period, to dapagliflozin and then from dapagliflozin to drug B, a newly initiated drug from the comparator group. At the initiation of drug B, the patient is eligible to be sampled for the comparator group.

Figure 2-1: Switch From a Potential Comparator Drug not in Exclusion Criteria to Dapagliflozin and then to a Different, New Comparator Drug



Risk window related to dapagliflozin = months 1-6; dapagliflozin categorized as “add-on” to drug A at the index date.

Risk window is further categorized into the following mutually exclusive categories:

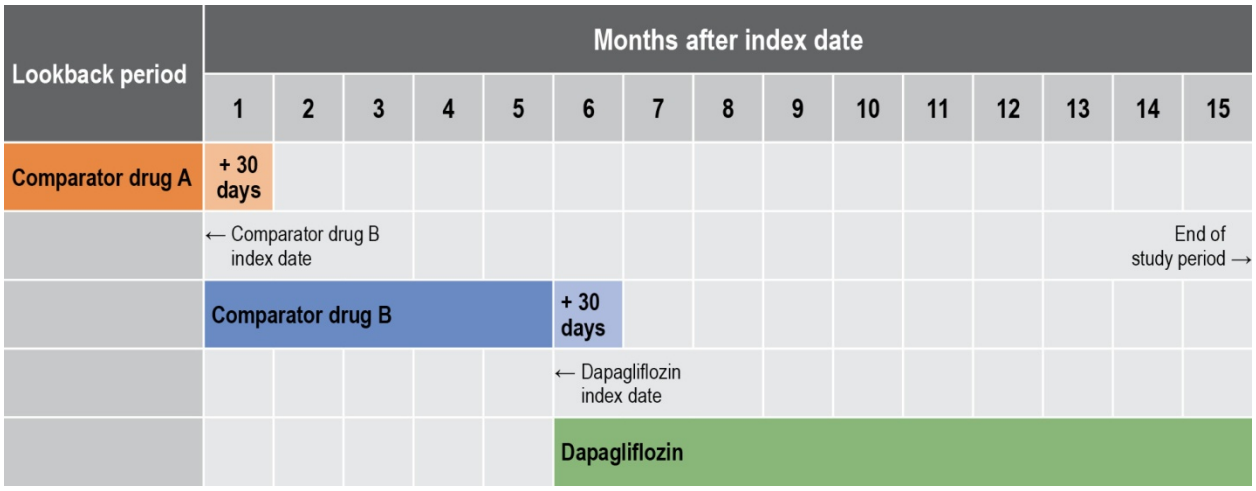
- Single exposure during follow-up: drug A: 0 months; dapagliflozin: months 2-5; drug B: months 7-10
- Multiple exposure during follow-up: months 1 and 6. Person-time in these months will be grouped into a “combined” exposure category and analyzed separately from the dapagliflozin-only exposure time and the comparator drug B–only exposure time.

Example 2. Drug A is not eligible to be a comparator drug; therefore, the risk window for drug A is not evaluated, but use of drug A is controlled for in development of the propensity score.

Drug B is newly initiated and is eligible to be selected for the comparator cohort. If selected, follow-up starts at the beginning of month 1. Drug B risk window = months 1-6. Drug B is categorized as "add-on" to drug A at the index date. Month 1 is counted as "combined" exposure with drug A. Months 2-5 are considered drug B–only exposure.

When patient switches to dapagliflozin, person-time will be counted as "combined" exposure in month 6 and dapagliflozin-only exposed time in months 7-15. Person-time in months 1 and 6 will be grouped into a "combined" exposure category and analyzed separately from the dapagliflozin-only exposure time and the comparator drug B–only exposure time.

Figure 2-2: Switch From Comparator to Dapagliflozin



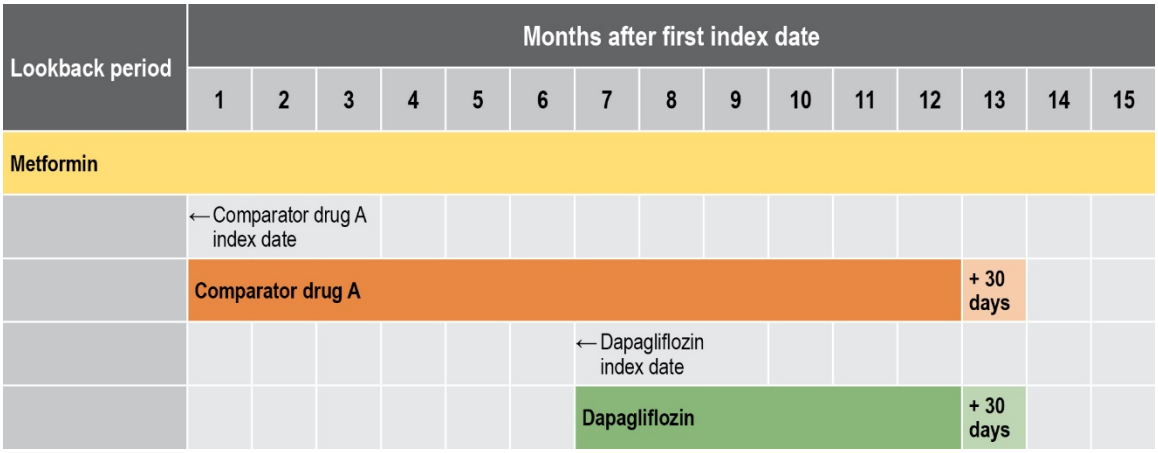
Example 3. Comparator drug A is initiated as an add-on to metformin, then dapagliflozin is added on in month 7 of follow-up. If dapagliflozin is added to a comparator drug treatment episode during follow-up, the person-time with combined exposure to dapagliflozin and comparator drug A (months 7-12) will be analyzed in a separate category of "combined exposure."

At the time of the addition of dapagliflozin (start of month 7), the patient is exposed to comparator drug A and dapagliflozin.

Risk window for drug A only = months 1-6.

Combined (dapagliflozin and comparator) exposure risk window = months 7-13.

Figure 2-3: Addition of Dapagliflozin to Comparator During Follow-up



Example 4. Comparator drug A is initiated as an add-on to metformin, then drug A is switched to comparator drug B, another newly initiated AD.

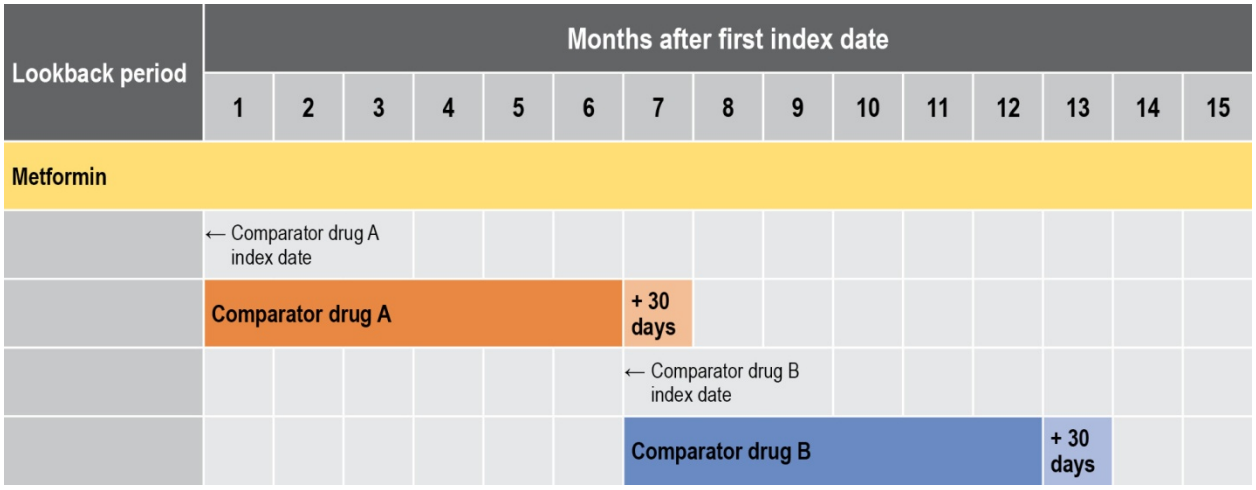
At the time of the switch (start of month 7), the patient is eligible to be selected into the comparator group (again).

Risk window for drug A only = months 1-6.

Risk window for drug A plus drug B (combined exposure) = month 7

Risk window for drug B, if selected into comparator group = months 8-13.

Figure 2-4: Add on Drug A to Metformin, Then Switch to Drug B



Example 5. Sensitivity analysis with 60-day extended risk window

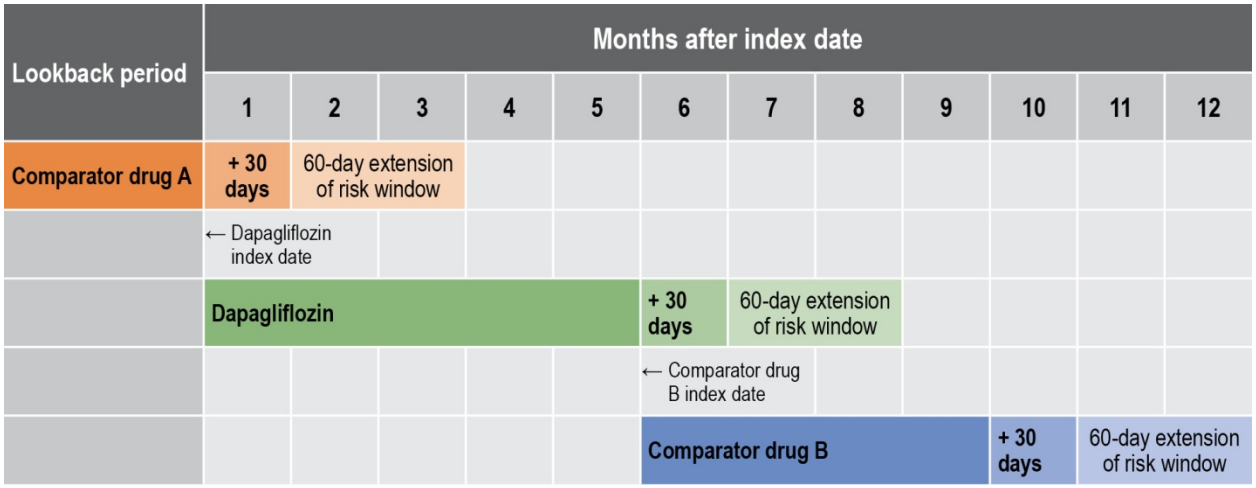
Drug A is not eligible to be a comparator drug; therefore the risk window for drug A is not evaluated, but use of drug A is controlled for in development of propensity score.

Risk window for dapagliflozin only = months 1-5.

Drug B is newly initiated by the patient, so patient is eligible to be selected for the comparator cohort; however, patient is not selected, so months 9-12 do not contribute to person-time exposure to drug B.

Risk window for dapagliflozin plus drug B (combined exposure) = months 6-8.

Figure 2-5: Sensitivity Analysis With Extended Risk Window



Example 6. Sensitivity analysis with exposure limited to only the index exposure episode

A sensitivity analysis will be performed that includes only the index exposure episodes. In Figure 2-6 and Figure 2-7 the follow-up time for the sensitivity analysis will be censored at the end of month 6 for each type of index exposure.

Risk window for dapagliflozin plus drug B (combined exposure) = month 6.

Figure 2-6: Sensitivity Analysis Including Only the Index Exposure Episode, Dapagliflozin

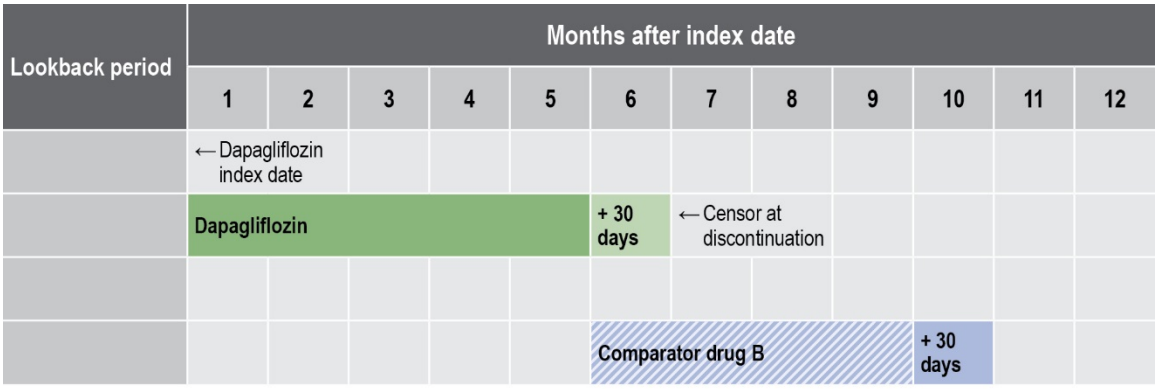
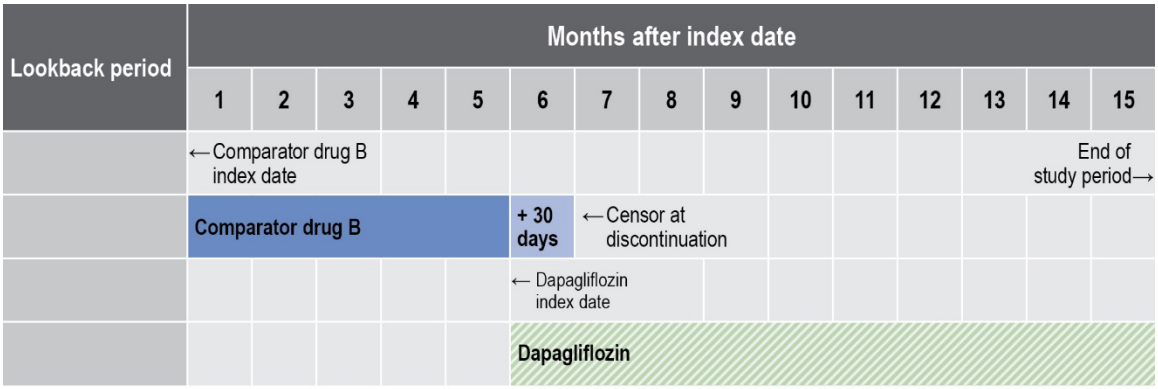


Figure 2-7: Sensitivity Analysis Including Only the Index Exposure Episode, Comparator



APPENDIX 3. OVERVIEW OF DATA SOURCE CHARACTERISTICS

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD[SM], Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Database type	Primary-care electronic medical records of patients enrolled in practices contributing to the CPRD. Linkage to hospital data (Hospital Episode Statistics [HES]), mother-child data, practice-level socioeconomic data, death certificates (Office for National Statistics), cancer and cardiovascular disease registries, and others is possible. Linkage is available for a proportion of the practices.	Health insurance claims of patients enrolled in Anthem-affiliated health plans	Health insurance claims of patients enrolled in Medicare health insurance program; health insurance claims include pharmacy dispensings for those with Part D, hospital and outpatient claims, and procedure claims; medical record review is an option through a trusted third party
Database population (n)	5.1 million	35.8 million lives since 2006[a]	47 million
Population covered, description	Most UK residents are registered with a GP. Patients registered with practices that contribute to the CPRD are included. Prisoners and members of the armed forces are not included. The homeless are underrepresented.	United States residents who are enrolled in a covered employer-sponsored health plan	Federally sponsored health insurance program that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with a permanent disability
Proportion of the country's population covered	8%	8%	60% of individuals aged 65 years or older and with Part D coverage
Representativeness of patients and practices	Age and sex of patients are representative of the UK population	Representative of all major geographic regions and health care settings for commercially insured US population aged less than 65 years	Considered to be representative of US population aged 65 years or older

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD[SM], Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Demographics			
Lifestyle risk factors	Yes, but missing data. Marital status is updated, but there is no information on marital status at the time of a past event	None	None
Geographic location	First digits of physician's practice postal code	US	US
Medication information			
Source	All prescriptions issued by GPs. Repeat prescriptions may be implemented. There is a sequence number to know whether the prescription is new. The presence of a repeat prescription does not ensure that the prescription was picked up (of filled).	All claims submitted to Anthem, Inc.	All pharmacy claims submitted to Medicare
Drug dictionary codes/ therapeutic classification	Multilex/British National Formulary	National Drug Codes for outpatient prescriptions	National Drug Codes for outpatient prescriptions
Unique product code	Yes	Yes	Yes
Prescribed/dispensed drugs	GP prescriptions issued	Dispensed drugs at outpatient pharmacies	Dispensed drugs at outpatient pharmacies
Date drug prescribed/ dispensed	Yes, date the drug was prescribed	Yes, date dispensed	Yes, date dispensed
Dose	Yes, but it is not a mandatory field. The dose is a text code and requires some handling to be transformed into a number. This transformation may be performed by the researcher or by the CPRD.	Yes	Yes

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD[SM], Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Duration	There is a field to record duration, but it is highly incomplete. Duration can be derived from the number of prescriptions.	Days' supply	Days' supply is provided
Clinical indication	There is no field for indication. The user needs to assess diagnoses on the prescription date. Prior diagnosis can be used as a proxy.	There is no field for indication. The user needs to assess diagnoses on the dispensing date. Prior diagnosis can be used as a proxy.	There is no field for indication. The user needs to assess diagnoses on the dispensing date. Prior diagnosis can be used as a proxy.
Inpatient medications	No	No	No
Specialist-prescribed medications	Only if the GP decided to include these in the medical record. GPs typically issue repeat prescriptions; there is a higher risk for not capturing the first specialist-initiated prescriptions than subsequent ones.	Available for many but not all outpatient pharmacy claims	Yes, if dispensed in outpatient setting
Diagnoses and procedures			
Coding system	Read	ICD-9-CM, ICD-10-CM, CPT, HCPCS	ICD-9-CM, ICD-10-CM, CPT, HCPCS
Outpatient visits	Yes, as entered by the GP	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Hospitalization data	Partial linkage to HES; as recorded by GPs	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Specialist visits	Information from referral letters	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Emergency room visits	As entered by the GP	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Time period covered	Since 1987	Since 2006	Medicare Part D available since 2006
Updates	Quarterly	Monthly	Yearly
Approximate time lag	6-12 weeks	3-4 months	Up to 24 months

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD[SM], Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Access to medical records	GPs can be sent questionnaires via the CPRD for validation; also partial linkage to HES	Only through trusted third party	Only through trusted third party
Data transfer	Yes, third-party approval for standard data and linked databases. Data set will be delivered for analysis	No, data remain with at HIRD[SM]	Yes, after CMS protocol review
Approval process	ISAC approval of short protocol	Central institutional review board, possibly local institutional review board(s)	Local institutional review board, CMS Privacy Board

CMS = Centers for Medicare and Medicaid Services; CPRD = Clinical Practice Research Datalink; CPT = Current Procedural Terminology; GP = general practitioner; HCPCS = Healthcare Common Procedure Coding System; HES = Hospital Episode Statistics; HIRD[SM] = HealthCore Integrated Research Database; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ISAC = Independent Scientific Advisory Committee; UK = United Kingdom; US = United States of America.

[a] HIRD[SM] patients of any age enrolled in a qualifying health plan at any time between January 2006 and January 2014.

APPENDIX 4. ANTIDIABETIC DRUGS ELIGIBLE FOR INCLUSION IN THE COMPARATOR GROUP

Blood Glucose–Lowering Drugs (Excluding Insulin) by ATC Subgroup	Active Substance
A10BA, Biguanides	Metformin
A10BB, Sulfonamides, urea	Glibenclamide/glyburide
	Tolbutamide
	Gliclazide
	Glimepiride
	Carbutamide
	Chlorpropamide
	Tolazamide
	Glipizide
	Gliquidone
	Glyclopyramide
	Acetohexamide
A10BD, Combinations	Metformin/glibenclamide
	Metformin/rosiglitazone
	Rosiglitazone/glimepiride
	Pioglitazone/metformin hydrochloride
	Pioglitazone/glimepiride
	Sitagliptin/metformin hydrochloride
	Vildagliptin/metformin hydrochloride
	Pioglitazone/alogliptin
A10BF, Alpha glucosidase inhibitors	Acarbose
	Voglibose
	Miglitol
A10BG, Thiazolidinediones	Pioglitazone
A10BH, DPP-4 (dipeptidyl peptidase-4) inhibitors	Sitagliptin
	Vildagliptin
	Saxagliptin
	Linagliptin
	Alogliptin

Blood Glucose–Lowering Drugs (Excluding Insulin) by ATC Subgroup	Active Substance
A10BH, DPP-4 Combinations	Alogliptin/metformin
	Linagliptin/metformin
	Saxagliptin/metformin
A10BX, Other	Repaglinide
	Nateglinide
	Mitiglinide
	Exenatide
	Liraglutide
	Albiglutide
	Dulaglutide
	Lixisenatide

ATC = Anatomical Therapeutic Chemical (classification system).

Source: World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2015. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 30 October 2015.

APPENDIX 5. ADDITIONAL COVARIATES THAT MAY BE CONSIDERED FOR INCLUSION IN THE PROPENSITY SCORE MODEL

Additional variables that are risk factors specific to the outcome of interest in each protocol are specified in the body of the respective protocol.

Medical Comorbidities	
High blood pressure	Polymyalgia rheumatica
Heart failure	Urinary infections (chronic or recurring)
Liver disease	Colon polyps
Other cardiovascular disease	Crohn's disease
Autoimmune disease	Ulcerative colitis
Chronic obstructive pulmonary disease, emphysema, respiratory insufficiency	Pancreatitis
	Immunosuppressive diseases such as HIV/AIDS
Diffuse diseases of connective tissue	Peptic ulcer disease
Rheumatoid arthritis	Dementia
Osteoarthrosis	Asthma

HIV = human immunodeficiency virus.