Post-Authorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Prepared for:

Astellas Pharma Global Development, Inc.

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CPRD Protocol

Protocol #178-CL-116:

A long-term observational study in the CPRD
to prospectively evaluate the incidence and the validity of new cardiovascular and malignant events (excluding non-melanoma skin cancer) in patients using pharmacological treatments for overactive bladder

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ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitors
AMI	acute myocardial infarction
ARB	angiotensin receptor blockers
BIPS	Institute for Epidemiology and Prevention Research (Germany)
BRCA	breast cancer gene
BRCA1	breast cancer 1, early onset gene
BRCA2	breast cancer 2, early onset gene
CONF-1	type 1 confirmed cases in the neoplasm case validation process (Section 6.6.3.2)
CONF-2	type 2 confirmed cases in the neoplasm case validation process (Section 6.6.3.2)
CONF-3	type 3 confirmed cases in the neoplasm case validation process (Section 6.6.3.2)
CONF-4	type 4 confirmed cases in the neoplasm case validation process (Section 6.6.3.2)
CPRD	Clinical Practice Research Datalink, formerly the General Practice Research Database (UK)
CV	cardiovascular
DL	data linkage—designation for general practices in the CPRD for which data can be linked to hospital episode statistics and vita statistics data
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration (US)
GePaRD	German Pharmacoepidemiological Research Database
GP	general practitioner
GPP	Guidelines for Good Pharmacoepidemiology Practices
GPRD	General Practice Research Database; now the CPRD (UK)
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics (UK)
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IRB	institutional review board
ISAC	Independent Scientific Advisory Committee (CPRD)
ISPE	International Society for Pharmacoepidemiology
MACE	major adverse cardiac events
MHRA	Medicines and Health Care Products Regulatory Agency
NCDR	National Cancer Data Repository, United Kingdom

NDL	no data linkage—designation for general practices in the CPRD for which data cannot be linked to hospital episode statistics and vita statistics data
NHS	National Health Service (UK)
NO PROV	not provisional cases in the neoplasm case validation process (Section 6.6.3.2)
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
OAB	overactive bladder
ONS	Office for National Statistics, United Kingdom
OQA	Office of Quality Assurance (RTI-HS)
OXMIS	Oxford Medical Information Systems (coding system)
PASS	post-authorization safety study
PPV	positive predictive value
PROV-1	type 1 provisional cases in the neoplasm case validation process (Section 6.6.3.2)
RR	relative risk
RTI-HS	RTI Health Solutions, a business unit of RTI International
SAB	scientific advisory board
SCR-1	screening method 1 in the neoplasm case validation process (Section 6.6.3.2)
SCR-2	screening method 2 in the neoplasm case validation process (Section 6.6.3.2)
SCR-3	screening method 3 in the neoplasm case validation process (Section 6.6.3.2)
SEER	Surveillance, Epidemiology and End Results Program (US)
SHI	statutory health insurance (agency), Germany
SOP	standard operating procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
THIN	The Health Improvement Network
TIA	transient ischemic attack
UK	United Kingdom
US	United States
VAL-1	validation method 1 in the neoplasm case validation process (Section 6.6.3.2)

APPROVAL PAGE

Project Title: Post-Authorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

The following people have reviewed the protocol and given their approval:

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The following people have reviewed the protocol and given their approval:

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28 Mar 2013
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1 ABSTRACT

Title

Post-Authorization Safety Program—Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder

Version / Date

Version 3.0 / March 25, 2013

Rationale and Background

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Astellas obtained marketing authorizations for mirabegron on June 28, 2012, in the United States (US) [1] and on December 20, 2012, in the European Union (EU). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) included a post-approval requirement to evaluate cardiovascular safety.[2] The FDA also required a post-approval commitment to evaluate cancer risks.[3] To prepare for a post-approval safety assessment of cardiovascular (CV) and cancer risk, a validation study has been designed to describe drug-use patterns among users of antimuscarinic drugs, to calculate background rates of CV and cancer outcomes among antimuscarinic drug users and to validate outcome-specific case-identification algorithms based on electronic diagnosis codes in the Clinical Practice Research Datalink (CPRD). Upon validation, these algorithms can be implemented within future cohorts that include mirabegron users to evaluate cardiovascular and cancer risk associated with mirabegron as part of the required post-approval safety program to be implemented in the US and the EU.

Research Question and Objectives

The objectives of this study are as follows:

- To characterize users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy.
- To assess and confirm the processes and algorithms used for the diagnosis of the CV and neoplasm endpoints of interest.
- To describe the availability of potential confounders in the CPRD.

- To estimate the incidence rates of CV events in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the incidence rate ratio of CV outcomes in users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.
- To estimate the incidence of two sex-specific, multiple-cancer, composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.
- To refine the study size and statistical power assessment for the post-marketing safety studies of mirabegron.

Program Design

This will be a retrospective cohort study in the CPRD in the United Kingdom (UK). The study period is January 2004 through December 2012.

Population

The cohort will consist of new users of individual OAB medications: oxybutynin, tolterodine, darifenacin, solifenacin, trospium, and fesoterodine. A new user is defined at the time of the first prescription of one of the medications of interest (prescription index date) as having no documented past exposure to the study drug that qualifies the subject for cohort entry. For each subject, follow-up will start on the date of the first prescription for a drug of interest and will finish at the earliest of the following events: end of the study period, death, disenrollment from the database, occurrence of an excluded diagnosis, or occurrence of a study endpoint.

Variables

Person-time will be classified based on individual OAB medication prescriptions.

The CV endpoints of interest will be acute myocardial infarction (AMI), stroke, CV mortality (comprised of coronary heart disease death and cerebrovascular disease death), and all-cause mortality. The composite endpoint major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or CV mortality—will also be examined.

Composite cancer endpoints will be evaluated separately for males and females. The cancers included in the composite endpoints are the 10 cancers with the highest incidence rates in the general population, excluding non-melanoma skin cancer:

- Males: prostate, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreas

- Females: breast, lung and bronchus, colon and rectum, melanoma of skin, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, corpus uteri, and pancreas

A broad range of characteristics, including demographics, characteristics that define elevated cancer risk, relevant diagnoses related to OAB, health care utilization, and use of other medications will be evaluated.

Data Source

In the UK, the CPRD contains prescriptions issued by the general practitioner (GP) and the medical information recorded by GPs as part of their routine clinical practice. The CPRD has approximately 5.1 million active subjects. Patients are representative of the whole UK population in terms of age and sex. For large subsets of patients, these data are linkable with hospitalization records, cancer registries, and national mortality data. Diagnoses and procedures are coded in Read codes, and hospitalization records are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). General practitioners may be contacted to provide additional information on their patients.

Study Size

The study is descriptive in nature and will be conducted in the cohort of new users of individual OAB medications during the study period.

Data Analysis

The cohorts will be defined following initiation of OAB treatment.

The data analysis will include the following activities:

- Users of OAB drugs will be characterized according to baseline covariates.
- Drug use patterns (e.g., discontinuation and switching between antimuscarinic drugs) will be evaluated.
- For a subset of cases identified via codes, study endpoints will be confirmed by review of medical records. Positive and negative predictive values of case-defining algorithms for CV endpoints will be estimated by using medical record review as the “gold standard.”
- The incidence rate of CV outcomes during periods of OAB treatment among new users of individual OAB medications will be estimated. Subgroup analyses will target the population aged 65 years or older and individuals with high CV risk.
- The incidence rate ratio of CV outcomes of each of the OAB medications compared with the most prevalent OAB medication in the CPRD, adjusted by all potential confounders, will be estimated.

- The incidence rate of each composite neoplasm outcome will be estimated following initiation of any OAB treatment among new users of OAB medications, stratified by sex. The incidence rate of each composite neoplasm outcome will also be estimated following initiation of OAB treatment among new users of each OAB medication while they are not exposed to other OAB medications (that is, exposed to a single OAB), stratified by sex.
- A wide range of potential confounders for CV and neoplasm outcomes will be defined, and their distribution and completeness of the information contained in the database will be described.

Milestones

- Final protocol submission to the FDA: March 31, 2013
- Assessment and summary report submission for the US and EU validation studies: March 2015

2 ROLES AND RESPONSIBILITIES

Astellas is the study sponsor. The three organizations designing and conducting the mirabegron post-authorization safety program are OptumInsight in the United States (US), RTI Health Solutions (RTI-HS) in Spain, and BIPS (Institute for Epidemiology and Prevention Research) in Germany. RTI Health Solutions is responsible for designing and conducting the study described in this protocol, using data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK).

Astellas will establish a scientific advisory board (SAB) that will include experts in oncology, urology, epidemiology, and statistics for observational studies. Following the initial meeting, it will meet regularly or on an as-needed basis to provide advice on the study design and protocol details.

This protocol has been developed by RTI-HS. Astellas has reviewed the protocol and provided input. Astellas has committed to set up contractual agreements with RTI-HS to implement the study, granting RTI-HS independent publication rights in line with the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice,[4] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct,[5] and the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[6]

3 PROPOSED STUDY TASKS AND MILESTONES

Task/Milestone	Responsible Party	Timing
Submission of study protocol to FDA	RTI-HS	March 2013
Seek RTI International IRB approval	RTI-HS	April 2013
Seek CPRD Independent Scientific Advisory Committee approval[a]	RTI-HS	April 2013
Start of data collection[b]	CPRD	June 2013
End of data collection[c]	CPRD	July 2013
Development of statistical analysis plan	RTI-HS	Sept 2013
Draft report of validation study results	RTI-HS	December 2014
Final report of validation study results	RTI-HS	February 2015
Submission of validation study report to FDA (regulatory milestone)	RTI-HS	March 2015

CPRD = Clinical Practice Data Link; FDA = Food and Drug Administration; IRB = institutional review board;; RTI = RTI International; RTI-HS = RTI Health Solutions; UK = United Kingdom.

[a] Delays in approval from the CPRD Independent Scientific Advisory Committee impact the rest of the timeline.

[b] Start of data extraction.

[c] Analytic set completely available.

4 BACKGROUND

4.1 Rationale

Mirabegron is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency, with a recommended starting dosage of 25 mg once daily. Astellas obtained marketing authorization for mirabegron on June 28, 2012, in the United States (US)[7] and on December 20, 2012, in the European Union (EU).

During the clinical program, mirabegron administered at the dose of 50 mg once daily was associated with an increase in pulse rate of approximately 1 beat per minute compared with placebo and a mean of 0.4 to 0.6 mm Hg change from baseline systolic blood pressure/diastolic blood pressure compared with placebo in patients with OAB.

During the development program, in a 52-week double-blind randomized trial (Study 178-CL-049), there was an imbalance in the number of neoplasms (malignant, benign, or unspecified) among patients randomized to mirabegron 100 mg (11 of 820; 1.3%) compared with those in the mirabegron 50 mg (1 of 812; 0.1%) or tolterodine (4 of 812; 0.5%) groups. In addition, in one of the six OAB 12-week phase 2/3 randomized double-blind studies (Study 178-CL-047), serious adverse events (SAEs) within the system organ class (SOC) of Neoplasms benign, malignant, and unspecified (including cysts

and polyps) were observed to be numerically higher in the mirabegron 50 mg (3 of 442; 0.7%) and mirabegron 100 mg (2 of 433; 0.5%) groups than in the placebo group (1 of 453; 0.2%). The numerical imbalance was not observed in the remaining five phase 2/3 studies of the same 12-week duration.

These effects were considered potential risks by the regulatory agencies that merited further consideration in a real-world setting. The FDA[8] and European Medicines Agency (EMA) each included a post-marketing (US)/post-approval (EMA) requirement to evaluate cardiovascular safety. The FDA also required a post-marketing commitment to evaluate cancer risks.[9] This post-authorization safety program is designed to address these concerns.

To prepare for a post-marketing safety assessment of cardiovascular (CV) and cancer risk associated with mirabegron use, a study has been designed to describe drug-use patterns among users of antimuscarinic drugs, to calculate background rates of CV and cancer outcomes in this population and to validate outcome-specific case-identification algorithms based on the medical or claims data recorded by the general practitioner (GP). Upon validation, these algorithms can be implemented in future cohorts that include mirabegron users to allow for an efficient and timely evaluation of cardiovascular and cancer risk associated with mirabegron as part of the required post-authorization study to be conducted in the US and the EU.

The present protocol describes the validation study that will be conducted in the CPRD.

4.2 Literature Review

Some studies on drug utilization have been identified, and key findings are summarized below as they are of relevance for the design of the post-approval safety program. However, none of the studies provides information on users of individual antimuscarinic drugs.

In a drug utilization study that used electronic medical records from the general population in the UK, adult female users of OAB drugs had a mean age of 63.9 years. This study was conducted in The Health Improvement Network (THIN) database, which partially overlaps with the CPRD in terms of contributing practices. In this study,[10] the mean time from diagnosis to first drug treatment was 28.7 months, and the mean (SD) number of treatment episodes per subject was 1.65 (1.31). Eleven percent of the study subjects had more than 3 treatment episodes during follow-up. Overall drug discontinuation at 6 months was 58.8%, although it varied by drug—53% for solifenacin and 89% for terodiline (an old OAB medication that has been withdrawn because of cardiotoxicity). At 12 months, overall drug discontinuation was 77.2%, lowest for tolterodine extended release (76%) and highest for terodiline (99%). Switching happened in 15.8% of the treatment episodes.

In a study using reimbursed prescriptions from Odense, Denmark, 66.2% of the individuals prescribed OAB drugs were women (mean age, 68.0 years) and 33.8% were men (mean age, 69.0 years).[11] All drugs had discontinuation rates over 50% at 6 months and over 75% at 12 months, with the exception of trospium chloride, which had a discontinuation rate of 64% at 12 months.

In a study performed in the HealthCore Integrated Research Database and GE Healthcare database, baseline cardiovascular comorbidity was higher in subjects with an OAB diagnosis or treated with OAB antimuscarinic drugs (39%) than in age- and sex-matched subjects without either OAB codes or OAB antimuscarinic treatment (21%).[12] Cardiovascular comorbidities with a higher prevalence in the OAB group included, among others, hypertension, diabetes, ischemic heart disease, and cardiac conduction disorders. In addition, the prevalence of use of non-OAB drugs with antimuscarinic effect was also higher in the OAB group: 33% vs. 17% for patients without OAB codes or OAB antimuscarinic treatment. Prevalence of cardiovascular comorbidity was similar in OAB patients treated with OAB antimuscarinic drugs (39%) and age- and sex-matched OAB patients with no such treatment (38%); use of non-OAB drugs with antimuscarinic effect was higher in treated subjects (37% vs. 29% for untreated subjects).

A related study, also in the US (GE Healthcare database), found that OAB patients treated with OAB antimuscarinics had baseline heart rate distributions similar to those with no such treatment.[13] In this study, treated OAB patients had a higher proportion of cardiovascular comorbidity (59% vs. 54% for untreated patients), including a higher proportion of hypertension, diabetes, and cerebrovascular disease. However, risk factors for cardiovascular conditions (e.g., age and sex) were not balanced among treated OAB patients (median age, 66 years; 17% men) and untreated OAB patients (median age, 59 years; 14% men).

Several algorithms for the case identification of cardiovascular endpoints recorded in the CPRD[a] have been evaluated in different studies. Studies have shown positive predictive values (PPV) of 82%,[14] 96%,[15] and 93%[16] for acute myocardial infarction (AMI); 76%[17] and 90%[18] for ischemic stroke; and 82%[19] and 100%[20] for hemorrhagic stroke.

Cancer diagnoses recorded in the CPRD have been found to be highly reliable. One study reported PPVs of 96% for the diagnosis of lung cancer, 92% for urinary tract cancer, 96% for gastroesophageal cancer, and 98% for colorectal cancer.[21] Another study reported, among CPRD practices with data linkage to the National Cancer Data Repository (NCDR), an 83.3% concordance between cancer diagnoses recorded in the CPRD for a cohort of patients with diabetes and matched patients without diabetes compared with cancer diagnoses recorded for the same patients in the NCDR (excluding non-melanoma skin cancer).[22] Older age was predictive of higher discordance in a

[a] The name of the database was General Practice Research Database (GPRD) at the time of many of these studies; we use CPRD here for consistency.

multivariable model. Using NCDR diagnoses as the reference, we estimate from data presented in this report that the sensitivities for diagnoses of various common cancers in the CPRD are breast, 97%; prostate, 99%; colorectal, 95%; lung, 91%; urinary tract, 95%; and melanoma, 96%. The investigators also used the linked Hospital Episode Statistics (HES) database to identify cancer cases and reported that 528 of the 5,797 cases recorded in the CPRD were confirmed in this additional data source, although they were not recorded in NCDR. Another study found that essentially all cases in the CPRD with a diagnostic code for esophageal cancer were confirmed to have had the disease[23]; moreover, where data were available to judge the time of clinical onset, the date was within 60 days of the date recorded in the electronic medical record in 89% of cases. Similarly, in a study of calcium channel blockers and risk of cancer, among cancer patients for whom additional information was obtained directly from the patient's GP, the diagnosis was confirmed in 95% of cases.[24] In another study using CPRD data, changes similar to those reported in national cancer statistics were observed in age-specific breast cancer incidence patterns after the introduction of a UK national screening program[25]; although this study was an ecological (time trend) analysis, the findings provide indirect support for the validity of breast cancer diagnoses in this data source. The risk of bladder cancer has also been studied in the CPRD in relation to several exposures including acetaminophen[26] and pioglitazone.[27]

5 RESEARCH OBJECTIVES, SPECIFIC AIMS, AND RATIONALE

The objectives of this study are as follows:

- To characterize users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium) with respect to selected covariates.
- To describe the patterns of usage of OAB medications, including duration of treatments, drug switching, and use of medications as add-on therapy.
- To assess or confirm the processes and algorithms used for the diagnosis of the CV and neoplasm endpoints of interest.
- To describe the availability of potential confounders in the CPRD.
- To estimate the incidence rates of CV events in new users of antimuscarinic drugs indicated for the treatment of OAB.
- To estimate the incidence rate ratio of CV outcomes in users of each of the OAB medications compared with tolterodine, a frequently used OAB medication across the populations of the research program.
- To estimate the incidence of two sex-specific multiple-cancer, composite endpoints (one for men and one for women), during the first year after start of treatment and during subsequent years, among new users of antimuscarinic drugs used in the treatment of OAB.

- To refine the study size and statistical power assessment for the post-marketing safety studies of mirabegron.

6 DATA SOURCE

6.1.1 Clinical Practice Research Datalink, United Kingdom

The Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD), contains the information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK (http://www.cprd.com/intro.asp). The CPRD covers approximately 8% of the UK population and includes approximately 5.1 million active users who are alive and currently contribute data to the database. The database includes approximately 900,000 individuals aged 65 years or older, of which 500,000 are women. Patients are representative of the whole UK population in terms of age and sex.

Core data include information on diagnoses, symptoms, referrals, tests ordered, test results, prescriptions issued, and additional clinical information. Prescriptions have fields for strength and dose. Drugs are classified following the British National Formulary, and medical data are coded in the Read coding system. The latter is very granular and is regularly updated in response to physician user requests. It has numerous codes for neoplasms and for overactive bladder diagnosis, signs, and symptoms.

The data are linkable, at least for a large subset of patients, through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA), with other health care data sets (e.g., hospitalization records, national mortality data, census data, cancer registry) via the patient's National Health Service (NHS) number, sex, date of birth, and postal code. Hospitalization records are coded in ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) codes.

6.2 Study Design Summary

Cohorts of patients who receive drugs used in the treatment of OAB will be drawn from the population during the study period of January 1, 2004, through December 31, 2012. The characteristics of the patients belonging to the overall cohort and to each cohort of new users of individual OAB medications will be described. The electronic algorithms used to identify potential cases from diagnosis codes corresponding to the endpoints of interest will undergo a validation process, the information available in the database on the major risk factors for CV endpoints and neoplasms that could act as potential confounders will be described, and the incidence rates of the endpoints in new users of the drugs of interest will be estimated.

6.3 Study Population

Subjects in the program will be required to meet *all* of the following inclusion criteria:

- Have at least 12 months of continuous enrollment in the database (thereby providing medical and prescription history data) before the first prescription or dispensing of an OAB drug of interest.
  - For most covariates (e.g., history of bilateral mastectomy, menopause status, use of hormone-replacement therapy), all available information without time limitation will be used, although the 12-month period prior to the cohort entry date will be used to estimate measures of health care utilization.
- Have a first recorded prescription or dispensing for oxybutynin, tolterodine, darifenacin, solifenacin, trospium, or fesoterodine.
- Be aged 18 years or older at the time of first prescription of a drug of interest.

Patients will be excluded if they meet *any* of the following criteria at any time prior to cohort entry:

- Had a diagnosis of cancer other than non-melanoma skin cancer.
- Had a diagnosis of human immunodeficiency virus (HIV) infection. These patients often receive health care through specialty clinics or separate health plans, and their health service use might not be fully captured in the data sources.

For other comorbidities, including previous CV events and those requiring treatment with potent immunosuppressants, rather than exclude patients, analyses will be stratified to include all patient populations in the study to maximize statistical power and to evaluate the effect modification of these risk factors. This strategy is in keeping with the spirit of the Food and Drug Administration (FDA) Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.[28]

A *new user* of any drug of interest will be a patient who receives a first prescription or dispensing for any OAB drug during the study period without a prescription or dispensing for the same medication in the previous 12 months. All new users of OAB medications of interest that meet the inclusion criteria will be included in the cohort.

6.4 Follow-up

Follow-up of eligible subjects will start on the date of the first prescription for an OAB medication (cohort entry date). For the analyses based on individual endpoints or composite endpoints (either CV or neoplasm), follow-up will finish at the earliest of the following dates:

- End of the study period
- Death

- Disenrollment from the database
- Occurrence of a diagnosis listed in the exclusion criteria
- For the analysis of a particular endpoint, occurrence of the endpoint or, in the case of composite endpoints, any of its components.
  - Patients may experience multiple endpoints (e.g., first a stroke and then cancer). Each of these events, and the associated person-time, will be captured.

6.5 Time at Risk and Exposure

6.5.1 Cardiovascular Study

To define time at risk, it is assumed that any cardiovascular effects of OAB medications will present shortly after first use, continue while patients continue the use, and decline after the medication is discontinued.

Each day of exposed person-time will be classified in mutually exclusive categories based on specific drug use and recency of use—current, recent, and past use. Patients will contribute person-time to different exposure categories if they switch treatment. Current use will include the days covered in the prescription plus 7 days, in the understanding that patients may forget doses and use the drug dispensed a few days beyond the days of supply noted in the prescription. Recent use will include the first 60 days after current use, and past use will include person-time of the end of recent use.

Exposure to each study drug will be defined according to the days of supply of each prescription. Days of supply will be ascertained from the prescription or dispensing information recorded in the databases. Dose of the medication will be ascertained from the dose field. In the event of missing values for the dose field, the dose will be estimated from descriptive analysis of the available recorded information (strength, number of units, amount of drug prescribed, etc.). The evaluation of various exposure metrics will allow for more complete ascertainment of risks associated with different profiles of use.

6.5.2 Neoplasm Study

It is assumed that effects of OAB medications on the incidence of neoplasms will continue for a long period of time after the medication is discontinued. Time at risk will be defined as starting with the first prescription for new use of any of the OAB drugs.

Follow-up time will extend beyond the end of exposure time, and exposure will be categorized in several ways, as follows;

- Duration of exposure in categories that will correspond to a course of treatment of 1 year, 2 years, and so on.

- Recency of use will also be considered in the exposure classification (i.e., recent use will be defined as any prescription within the previous year for the study drug to which a subject is accruing person-time, and past use will be defined as more than 1 year since the most recent prescription was issued).
- Further description of the exposure groups of interest is provided in the data analysis section. Cumulative exposure to study drugs will be defined, according to the days of supply of each prescription where possible, as the total amount of drug prescribed up to a given point in time, regardless of periods of discontinuation of the drug. Days of supply will be ascertained from the prescription or dispensing information recorded in the database. Dose of the medication will be ascertained from the dose field. In the event of missing values for the dose field, the dose will be estimated from descriptive analysis of the available recorded information (strength, number of units, amount of drug prescribed, etc.).

Patients who enter the OAB drug–exposed cohort will be considered “ever exposed” to OAB drugs. For the construction of user cohorts for single OAB medications, patients who enter the cohort of exposure to OAB drug A will be considered “ever exposed” to OAB drug A. Patients in the OAB drug A cohort who subsequently begin treatment with OAB drug B will have their person-time in the OAB drug A cohort censored at that time, and from the date of the first prescription of OAB drug B, their person-time will be entered into the cohort of those exposed to multiple OAB drugs (the multiple-exposure cohort).

6.6 Endpoints

6.6.1 Cardiovascular Endpoints

Each of the following individual study endpoints will be evaluated in primary analyses:

- AMI including out-of-hospital coronary heart disease deaths
- Stroke
- All-cause mortality
- CV mortality
  - Coronary heart disease death
  - Cerebrovascular disease death

The composite endpoint of major adverse cardiac events (MACE)—acute myocardial infarction, stroke, or cardiovascular mortality—will also be examined.

6.6.2 Neoplasm Endpoints

The neoplasms observed in the mirabegron clinical development program were those that occur commonly in the general population; therefore, the present study will focus on

a composite of the 10 most commonly occurring malignancies. Ranking cancers by the highest age-adjusted incidence rates among both sexes in the US Surveillance, Epidemiology, and End Results (SEER) data, 2005-2009,[29] these cancers (incidence rate per 100,000, adjusted to the 2000 US standard population) are prostate (69.4), breast (67.2), lung and bronchus (62.6), colon and rectum (46.3), melanoma of skin (21.0), urinary bladder (20.8), non-Hodgkin lymphoma (19.6), kidney and renal pelvis (15.1), corpus uteri (12.6), and pancreas (12.1).

Because several of these cancers occur exclusively (or nearly exclusively) in either males or females, the primary endpoints will be the composite sex-specific incidence rates, as shown in Table 1 (along with the US rates by sex and age):

Table 1. Incidence Rate for Neoplasm Endpoints per 100,000 Person-years in Subjects of All Ages and Those Aged 65 Years or Older, by Sex, United States

	All Ages[a]		Aged ≥ 65 Years[b]	
Type of Cancer	**Males**	**Females**	**Males**	**Females**
Colon and rectum	54	40.2	255.3	191.0
Pancreas	13.8	10.8	76.3	62.0
Lung & bronchus	76.4	52.7	435.8	289.6
Melanoma of the skin	27.2	16.7	125.6	46.4
Breast (female)	—	124.3	—	421.3
Corpus uteri	—	23.5	—	84.8
Prostate	154.8	—	742.2	—
Urinary bladder	37	8.9	222.4	51.1
Kidney and renal pelvis	20.7	10.5	91.2	44.3
Non-Hodgkin lymphoma	23.8	16.3	109.4	75.3
Total per 100,000	**407.7**	**303.9**	**2,058.2**	**1,265.7**

[a] SEER Cancer Statistics Review 1975-2009 Table 1.4. Incidence rates adjusted to 2000 US population. Available at http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=1&page=sect_01_table.04.html. Accessed on November 15, 2012.

[b] SEER website Fast Stats – Statistics stratified by age. Data for 2009. Available at: http://seer.cancer.gov/faststats/selections.php?#Output. Accessed on November 15, 2012.

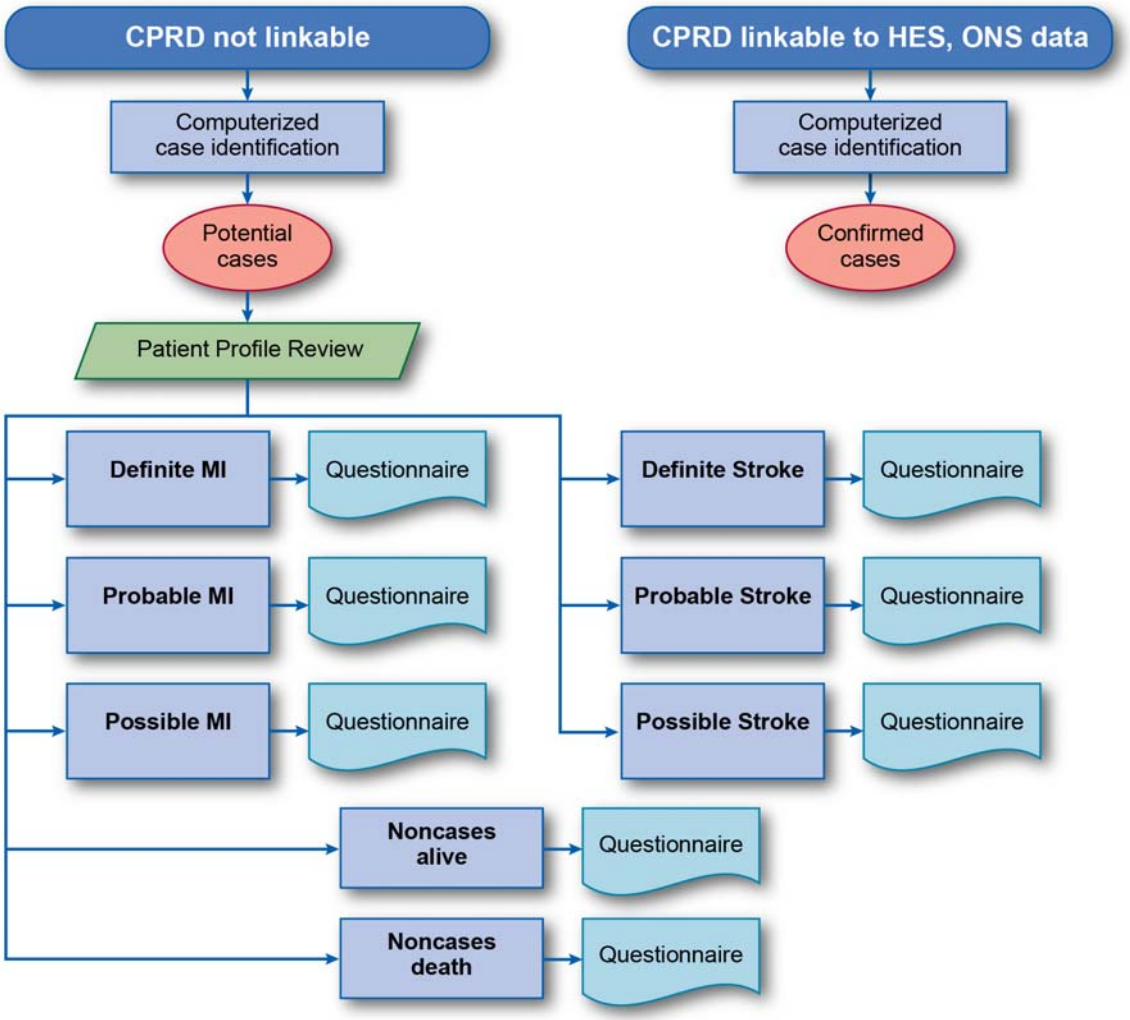
6.6.3 Endpoint Ascertainment and Validation

6.6.3.1 Cardiovascular Endpoints

For CV endpoints, Figure 1 diagrams the process for identifying and validating cases. In the CPRD, linkage with the NHS HES and Office for National Statistics (ONS) vital statistics is available for approximately 50% of the practices. In patients from these practices (DL practices), AMI and stroke events will be identified from linkage with HES

data, coded in ICD-10. Cause of death will be determined from linkage with ONS data, also coded in ICD-10.

Figure 1. Case Validation Process for Cardiovascular Cases in the CPRD



AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink; HES = hospital episode statistics; ONS = Office for National Statistics.

In data from the rest of the practices, with data not linkable (NDL), AMI and stroke events will be identified based on all of the clinical elements present in the database. The validation process for these events will have three steps. First, we will identify all potential cases using a computerized algorithm based on Read codes. Second, we will manually review the electronic patient profiles (a string of dated Read codes, prescriptions, and anonymized free-text comments written by the general practitioner) to classify potential cases into definite, probable, possible, and noncases based on the operational definitions outlined below. Last, we will randomly select cases from each category and send the GP for each selected case a questionnaire to confirm the occurrence of the event. Positive or negative predictive values, as appropriate, will be

calculated based on the responses in the questionnaires. More detail is provided in the following paragraphs. Published validation studies using similar approaches in the CPRD are briefly described in Appendix A.

Review of Patient Profiles of Potential Cases

Study physicians will review patient profiles to implement the operational definitions and classify study participants as definite, probable, or possible cases, or noncases, of AMI and stroke (separately for the two outcomes).

Definite, Probable, and Possible AMI Cases

A definite case of AMI will be one for which there is a code for AMI and 2 or more codes or key words in free-text comments within an appropriate time window of the AMI code:[30]

- Characteristic chest pain[31]
- Cardiac enzyme abnormal results (e.g., CPK [creatine phosphokinase], troponin)[32]
- Electrocardiogram with clinical signs of AMI[33]
- Arteriogram with a recent coronary occlusion
- Administration of thrombolytic therapy[34]
- Coronary revascularization procedure following AMI diagnosis
- Hospitalization
- Death

A probable case will be one with an AMI code and one of items in the list above.

A possible case will be one with an AMI code and no codes for the items above, or one with any of the items above (except hospitalization) but no AMI code.

Definite, Probable, and Possible Stroke Cases

A definite case of stroke will be one for which there is a code for stroke (not including transient ischemic attack [TIA]) and 2 or more of codes or key words in free-text comments:

- Diagnostic procedures with abnormal results (e.g., abnormal magnetic resonance imaging of brain)
- Hospitalization or referral to a neurologist
- Acute treatment: thrombolytic therapy or aspirin (ischemic stroke); embolization, clips, and other aneurysm treatments (subarachnoid hemorrhage and hemorrhagic stroke)
- Residual damage (e.g., hemiplegia, vascular dementia, aphasia)
- Physiotherapy (e.g., neurological physiotherapy)[35]

- Death

A probable case will be one with a stroke code and one of items in the list above.

A possible case will be one with a stroke code and none of the items listed.

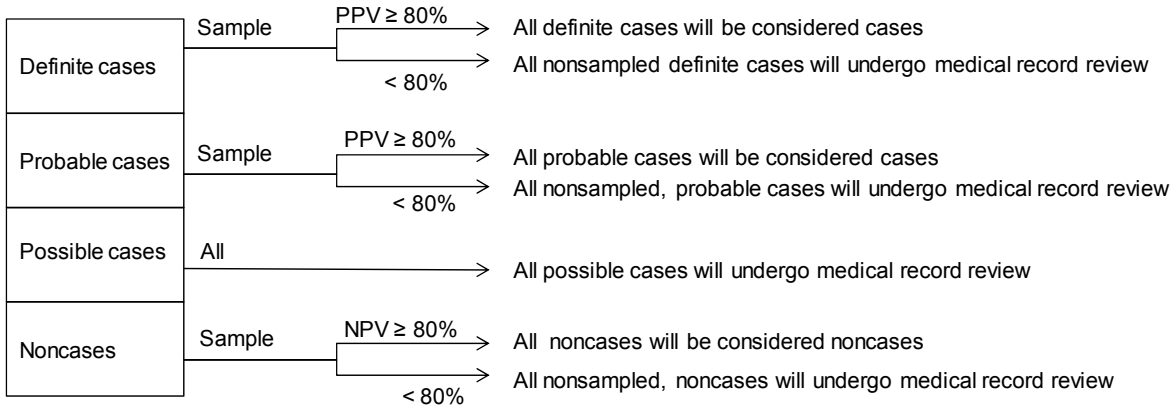
Case Confirmation With Questionnaires to General Practitioners and Calculation of Positive Predictive Values

Among subjects for whom linkage with the HES is not possible and who did not die before reaching the hospital after a potential AMI or stroke event, a random sample of definite, probable, and noncases will be validated. All cases classified as possible will be validated.

The validation process is achieved by asking the subject's GP to review medical records and charts and complete a questionnaire designed for the specific endpoint. For definite and probable cases and for noncases, the objective of the validation is to confirm that the algorithms are appropriately designed. In each of these categories, 150 subjects will be randomly identified, and the case status will be determined after medical records review. A probable or definite case will be considered to be a case if the PPV is at least 80%. Similarly, all noncases will be considered to be true noncases if the negative predictive value (NPV) is at least 80%. For possible cases, the objective of the validation is to assess whether a full patient medical chart review is needed for all subjects in this category for each endpoint. Therefore, all patients in this category will be sampled for validation. See Figure 2 for a summary of the criteria for case validation.

For patients who died, the diagnoses recorded on autopsy reports or death certificates, as available from the CPRD, will be used to determine the cause of death.

Figure 2. Case Validation Criteria in the CPRD



NPV = negative predictive value; PPV = positive predictive value.

Based on this assessment, the PPV will be calculated for the definite, probable, and possible cases as the number of confirmed cases among the sampled profiles in the

category divided by the total number of questionnaires returned to us in each category times 100 (to convert to a percentage). The NPV of the noncases will be estimated as the number of confirmed noncases among the sampled profiles in the category divided by the total number of questionnaires returned to us in each category times 100 (to convert to a percentage).

For the calculation of the incidence of the endpoints, if the PPV is at least 80% for the definite and probable case categories, all subjects in those categories will be considered cases. If the NPV of the noncases is 80% or above, all in the category will be considered noncases. If the predictive values do not meet these thresholds, all remaining cases in the category will be reviewed to confirm or exclude the outcome. All cases in the possible category will be validated and their case/noncase status confirmed.

6.6.3.2 Neoplasm Endpoints

Currently, 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 datasets via the patient's NHS number, sex, date of birth, and postal code. English practices altogether represent approximately 75% of the practices contributing to the CPRD; therefore, approximately half of the total CPRD practices have this link. (It is expected that as the CPRD expands over the next 2 years, there will be a further increase in the proportion of the covered population with linked information in these external data sources.) Practices are therefore divided into those with data linkage (DL) to NCDR and HES and those with no data linkage (NDL). To facilitate describing the study results and conducting sensitivity analyses in the main study, we will use the terminology explained in the following paragraphs to describe methods of screening and validation of neoplasm cases from several sources in the CPRD and linked data.

In NDL practices, patients in the CPRD initially identified by the presence in their electronic medical records of the appropriate clinical Read codes for each study malignancy (screening method 1 [SCR-1]) will be considered type 1 provisional cases (PROV-1). We will conduct further validation, blinded to study drug exposure, via electronic medical record review and review of free-text comments (validation method 1 [VAL-1]). Patients not detected as potentially having cancer by Read code screening will be considered not provisional cases (NO PROV).

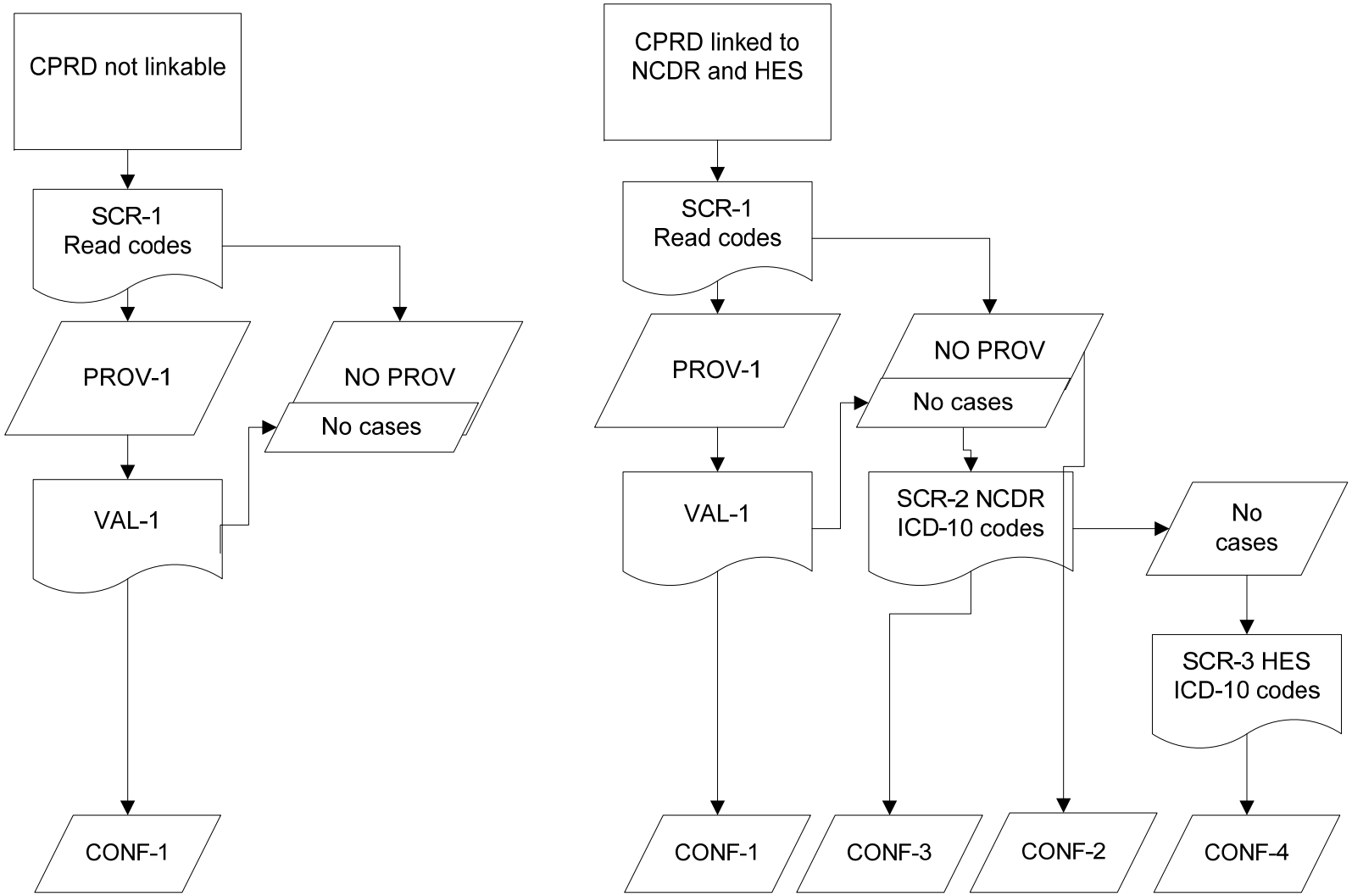
Provisional cases identified as above (PROV-1 cases) will be considered confirmed (type 1 confirmed cases [CONF-1]) if there is supportive evidence of a cancer diagnosis, in particular, a relevant pathology (morphology) Read code or evidence of appropriate cancer-specific therapy (surgery, radiation therapy, chemotherapy, hormonal therapy, or other targeted or biological therapy), within the period from 1 month before to 3 months after the first recorded clinical diagnostic code for the endpoint malignancy. Only surgical procedures that would be used to treat cancer will be considered confirmatory. For example, mastectomy will be considered sufficient evidence of a diagnosis of breast

cancer, but excisional biopsy (lumpectomy) will not be considered sufficient because it can be used as a diagnostic procedure or for treatment (therefore, some excisional biopsy specimens show no evidence of malignancy). Provisional cases will also be considered confirmed if subsequent clinical events (referrals, hospitalizations, or death) are associated with appropriate clinical Read codes for the cancer diagnosis.

In DL practices, because additional cases may be found in the NCDR data that are not found in the GP records,[36] we will use two methods for screening and case validation. We will first screen for cases using the same method as for the NDL practices (SCR-1) and validate cases using the same method as for the NDL practices (VAL-1), resulting in a set of cases from the DL practices designated as provisional (PROV-1). Among PROV-1 cases, those that can be confirmed according to the same methods as used in the NDL practices will be designated CONF-1. The incidence rates based on these cases should be comparable to those estimated from the NDL practices.

Because in the study of Boggon, et al. (2013)[36] approximately 6% of cases identified in NCDR using ICD-10 codes were not found in CPRD using Read codes, we will use an additional procedure (screening method 2 [SCR-2]) to identify additional cases in the DL practices. In this procedure, we will use ICD-10 codes to screen the NCDR data for cases that were not identified by SCR-1. Such additional cases will automatically be considered confirmed (CONF-2) because cancer registries perform independent case validation using standard procedures including review of pathology information. Also, in the DL practices, if after applying VAL-1 any remaining cases are confirmed using ICD-10 codes in the NCDR data (SCR-2), the designation of such cases will be changed to type 3 confirmed cases (CONF-3). Finally, if any remaining cases from DL practices are found to have confirmatory data in HES but not in NCDR (screening method 3 [SCR-3]), the designation of such cases will be type 4 confirmed cases (CONF-4).

Figure 3. Case Identification Diagram



CONF = confirmed cases; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; NCDR = National Cancer Data Repository; NO PROV = not a provisional case; PROV-1 = type 1 provisional cases; SCR = screening method; VAL = validation method.

A comparative endpoint analysis in addition to those described already will pool all CONF-1, CONF-2, CONF-3, and CONF-4 cases from both NDL and DL practices combined, (only the DL practices will contribute CONF-2, CONF-3, and CONF-4 cases). A separate comparative analysis will combine all CONF-1, CONF-2, CONF-3, and CONF-4 cases from DL practices with PROV-1 cases from NDL practices.

In applying the screening and validation processes described above, we will note the earliest date of diagnosis of the provisional and confirmed cancer cases based on all information available for each case and will exclude from the analysis any prevalent cases, that is, those whose earliest recorded diagnosis preceded their initiation of treatment for OAB.

A summary of studies with case validation of cancers identified by various algorithms, by cancer type, is shown in Table 2. Reported PPVs for studies in the CPRD (formerly GPRD) are all > 90%.

Table 2. Validation of Incident Cancers In Clinical Practice Research Datalink

Type of Neoplasm	Case Algorithm	Source of Cases	Gold Standard	Results
Incident lung cancer	Diagnosis code for lung cancer	GPRD	English Cancer Registry	PPV, 96%
Incident urinary tract cancer	Diagnosis code for urinary tract cancer	GPRD	English Cancer Registry	PPV, 92%
Incident colorectal cancer	Diagnosis code for colorectal cancer	GPRD	English Cancer Registry	PPV, 98%

GPRD = General Practice Research Database (now the Clinical Practice Research Datalink); PPV = positive predictive value.

Source: Dregan et al. (2012).[37]

6.7 Potential Confounding Factors

In the main analyses of the mirabegron implementation study, we will control for potential differences in distribution of determinants of CV endpoints or in cancer risk between users of antimuscarinic drugs. In the validation study, we will describe the study population.

The relevant confounding factors for CV disease, such as those outlined in Graham et al.,[38] include the following:

- Age
- Sex
- Geographic area of residence

- Characteristics that define high CV risk (e.g., history of cerebrovascular disease, coronary artery disease, angina, myocardial infarction, heart failure, arrhythmias, use of antiarrhythmic drugs, hypertension, use of antihypertensive drugs, hyperlipidemia, use of lipid-lowering drugs, diabetes mellitus)
- Relevant diagnoses related to OAB
- Use of OAB medications
- Health care utilization
- Smoking
- Obesity
- Alcohol/substance abuse
- Use of other medications (e.g., nitrates, other drugs used to treat angina, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEIs/ARBs], antiplatelets, nonsteroidal anti-inflammatory drugs [NSAIDs], estrogen, thyroid hormone replacement)
- Comorbidities (e.g., chronic obstructive pulmonary disease, dementia, gout, forms of arthritis, renal impairment, malignancy, peptic ulcer disease, organ transplantation)

Proxies for characteristics not captured in electronic data, such as occupational exposures or frailty, will be used whenever possible. To address time-varying confounding, the status information for important confounders (such as health care utilization) will be updated during follow-up for the analyses described in the data analysis section.

In addition to potential CV confounding factors, characteristics that define elevated risk of malignancies (e.g., *BRCA* mutations for breast cancer), use of other medications (e.g., potent immunomodulators), and comorbidities (e.g., chronic obstructive pulmonary disease, forms of arthritis, renal impairment) will be evaluated.

For most covariates (e.g., history of medical conditions, history of bilateral mastectomy, menopause status, use of hormone-replacement therapy), all available information without time limitation will be used, although to estimate measures of health care utilization the 12-month period prior to the cohort entry date will be used. In addition, comparing the time of enrollment prior to cohort entry by exposure level might be useful for better understanding whether or not this decision may introduce a problem.

Table 3 describes the patient characteristic variables available in the CPRD and its format.

Table 3. Description of Patient Characteristic Variables Available in the Clinical Practice Research Datalink and Available Validation Results

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source in the CPRD and Available Validation Results
Enrollment and disenrollment from data source, birth, cohort entry, cohort exit, death	Date	Specific date	GP electronic medical record
Cause of death	ICD-10 or other medical codes	Specific date	GP electronic medical records and linkage to ONS plus questionnaires
Duration of enrollment prior to cohort entry (days)	Number (start date of cohort minus date of enrollment in data source)	Specific period	GP electronic medical record
Duration of follow-up (days)	Number (date of cohort exit minus the date of cohort entry)	Specific period	GP electronic medical record
Demographics: age, sex	Age: numerical Sex: binary	Specific fields	GP electronic medical record
Socioeconomic characteristics: education, marital status, employment status, practice identification	Categorical: specific categories depend on the data structure	Baseline (any time before the cohort entry date)	Practice identification code, Index of Multiple Deprivation, GP electronic medical record
Genes: *BRCA1* and *BRCA2* mutations	Binary (yes or no for presence of either mutation)	Any time before or during the study period (this is not influenced by the exposure)	Read codes in GP electronic medical record
Functional stage (capabilities for living a normal daily life); proxy for frailty	Categorical	Baseline (most recent evaluation before the cohort entry date)	To be checked if reliably recorded in GP electronic medical record

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source in the CPRD and Available Validation Results
Smoking	Categorical: never, current, former, missing	Baseline (any time before the cohort entry date) and at event date	GP electronic medical record plus sample questionnaires; current smoking is more completely recorded than former smoking Validation study among subjects with inflammatory bowel disease in 1988-1997[39]; n = 150; 136 questionnaires returned: ▪ Ever-smoker: sensitivity and PPV = 86% (95% CI, 70%-95%) ▪ Current smoker: sensitivity = 78% (95% CI, 52%-94%); PPV = 70% (95% CI, 46%-88%) ▪ Former smoker: sensitivity = 53% (95% CI, 28%-77%; PPV = 60% (95% CI, 32%-84%) Rate of smoking in the CPRD as a percentage of the expected rate from a population-based survey: ▪ Current smokers: 79% ▪ Former smokers: 29%
Obesity/body mass index	Obesity: binary Body mass index: numerical Include a variable to denote missing	Baseline (any time before the cohort entry date)	GP electronic medical record plus sample questionnaires
Menopause	Binary	Any time before the study period and at event date	Read codes in GP electronic medical record plus sample questionnaires
Hypertension	Binary	Baseline (any time before the cohort entry date)	Read codes and prescriptions in GP electronic medical record
Dyslipidemia	Binary	Baseline (any time before the cohort entry date)	Read codes and prescriptions in GP electronic medical record
History of AMI, stroke, transient ischemic attack, coronary heart disease, heart failure, pulmonary artery disease	Binary	Baseline (any time before the cohort entry date)	Read codes and prescriptions in GP electronic medical record

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source in the CPRD and Available Validation Results
Diabetes without complications (diabetes with complications is included with the Charlson score)	Binary	Baseline (any time before the cohort entry date)	Read codes and prescriptions in GP electronic medical record
Family history of the individual cancers: Colon and rectum Pancreas Lung and bronchus Melanoma of the skin Breast (female) Corpus uteri Prostate Urinary bladder Kidney and renal pelvis Non-Hodgkin lymphoma	Binary	Any time before or during the study period (as this is not influenced by the exposure)	Read codes in GP electronic medical record
Comorbidities			
Alcohol abuse and related conditions	Binary	Baseline (any time before the cohort entry date) and time varying	Read codes in GP electronic medical record
Drug abuse	Binary	Baseline (any time before the cohort entry date) and time varying	Read codes in GP electronic medical record
Comorbidities included in the Charlson Index	Each comorbidity: binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Renal impairment	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Dialysis	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Fractures	Binary	Time varying and proxy of frailty	Read codes in GP electronic medical record
Gout	Binary	Baseline (any time before the cohort entry date)	Read codes and prescriptions in GP electronic medical record

Patient Characteristic	Type of Variable	Time Window of Assessment	Data Source in the CPRD and Available Validation Results
Arthritis	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Overactive bladder	Binary	Baseline (any time before the cohort entry date)	Read codes only (not drugs) in GP electronic medical record
Organ transplantation	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Polycystic ovary syndrome	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Endometrial polyps or other benign growths of the uterine lining	Binary	Baseline (any time before the cohort entry date)	Read codes in GP electronic medical record
Prescriptions Hormone-replacement therapy Tamoxifen use Thyroid hormone replacement Nitrates, digoxin, antidiabetic drugs, statins Non-aspirin NSAIDs Low-dose aspirin Antiplatelets (including aspirin in low doses) Immunosuppressive agents)	Binary	Baseline (any time before the cohort entry date), time varying	Prescriptions in GP electronic medical record
Health services utilization			
Outpatient visits	Numerical	Baseline (12 months)	GP electronic medical record
Hospitalizations	Numerical	Baseline (12 months)	GP electronic medical record
Nursing home stay	Numerical	Baseline and time varying	Read codes in GP electronic medical record
Sigmoidoscopies	Numerical	Baseline (12 months)	GP electronic medical record
Mammograms	Number	Time varying: per year, starting in the baseline period	GP electronic medical record

AMI = acute myocardial infarction; BRCA1 = breast cancer 1, early onset gene; BRCA2 = breast cancer 2, early onset gene; CPRD = Clinical Practice Research Datalink; GP = general practitioner; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NSAID = nonsteroidal anti-inflammatory drug; ONS = Office for National Statistics; PPV = positive predictive value.

7 STUDY SIZE

The study is descriptive in nature and will include all new users of the antimuscarinic drugs of interest during the study period.

Table 4 shows the number of prescriptions issued in the CPRD through June 2011. Oxybutynin and tolterodine are the most frequently prescribed antimuscarinic drugs, in agreement with a prior drug utilization study in the UK in the population of THIN.[40]

Table 4. Prescriptions for Selected Antimuscarinic Drugs Through June 2011, Clinical Practice Research Datalink, United Kingdom

Drug name	Number of Prescriptions
Oxybutynin	1,492,008
Tolterodine	1,160,936
Solifenacin	377,998
Trospium	141,580
Fesoterodine	20,727
Darifenacin	4,716

8 DATA MANAGEMENT

We will apply to the CPRD for the data. All data management and analysis will be performed in SAS software (SAS Institute, Inc. Cary, North Carolina).

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures will be followed, with periodic backup of files to tape. Standard procedures to restore files in the event of a hardware or software failure will be in place.

9 DATA ANALYSIS

9.1 Characterization of Users of OAB Medications

- Characterization of users of OAB medications (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium) with respect to a series of selected covariates
- Description of the above patients stratified by the ability to link their data to the Hospital Episode Statistics (HES) data and to the cancer registry

9.2 Drug Prescription Patterns Description

- Description of the patterns of usage of OAB medications, including dose, duration of treatment, drug switching, and use of medications as add-on therapy

9.3 Validation of the Endpoints and Confounders

- Calculation of the predictive value of the case-finding strategies used for CV endpoints
- Description of the results of the case-finding strategies used for cancer endpoints
- Description of cancer endpoints separately for practices with external data linkage to the cancer registry and hospital episode statistics (DL) and those with no data linkage (NDL)
- Description of the results of the confounding variables obtained through questionnaires and how they compare with the information that is present in the CPRD.

9.4 Cardiovascular Study

The cohort will be established using the CV inclusion and exclusion criteria.

Patient baseline characteristics will be assessed through analysis of data in the period prior to the cohort entry date. Baseline characteristics of interest will include age and sex, comorbidities related to OAB, other comorbidities, and specific medication and health care services use. Comparisons of these baseline characteristics, including potential CV confounders, across drug-use groupings will be presented. De novo use and previous use of antimuscarinic medications will be quantified.

Based on results of the outcome validation, the most appropriate outcome definition (e.g., definite cases only, definite plus probable cases) will be used in all subsequent analyses. Tables will summarize enrolled person-time and frequency of events. Crude and age-sex-adjusted incidence (absolute risk) will be calculated for each outcome for the overall cohort of patients treated with antimuscarinic drugs and for each of the subcohorts of new users of individual drugs (current use of individual drugs in monotherapy or current use of combination therapy).

A variety of stratified analyses will be conducted using standard methods including Mantel-Haenszel. Groups for stratified analysis will include patients aged 65 years or more, individuals with risk factors for CV disease, and patients with CV comorbidity of variable severity. Analyses that are stratified by prior use of antimuscarinic drugs will be performed to address drug switching over the course of the study.

The impact of various intervals of time since exposure (e.g., recent use or past use) on the estimates of interest will be evaluated.

The incidence rate ratio of CV outcomes of each of the OAB medications compared with tolterodine, adjusted by all potential confounders, will be estimated.

The adjusted incidence rate ratio of each of the CV outcomes that are components of the MACE for each of the OAB will be calculated, and the homogeneity of the rate ratios of the MACE components will be evaluated.

9.5 Neoplasm Study

The cohort will be created using the neoplasm inclusion and exclusion criteria.

Patient baseline characteristics will be assessed through analysis of data in the period prior to the cohort entry date. Baseline characteristics of interest will include age and sex, comorbidities related to OAB, other comorbidities, and specific medication and health care services use. Comparisons of these baseline characteristics, including potential cancer confounders, across drug-use groupings will be presented. De novo use and previous use of antimuscarinic medications will be quantified.

The occurrence of the composite cancer outcomes, by sex, will be estimated. The study report will summarize in each exposure category the number of enrolled patients, person-time, and frequency of events. Crude and age-adjusted incidence (absolute rate) will be calculated for each of the sex-specific composite cancer outcomes for the cohort of patients ever treated with any OAB, ever treated with each individual antimuscarinic drug, and ever treated with each individual drug alone.

Analyses will be performed on several distinct but overlapping groups of cases. Endpoint analysis 1 will include only CONF-1 cases from NDL and DL practices combined. Endpoint analysis 2 will use all CONF-1 cases from NDL and DL practices combined plus all remaining PROV-1 cases from both groups of practices. If most initially designated PROV-1 cases are subsequently confirmed as CONF-1 cases, the results of these two analyses will be closely similar; however, if a large proportion of PROV-1 cases cannot be confirmed, analysis 1, which will be restricted to CONF-1 cases, may be less affected by potential case misclassification than analysis 2, which will include both CONF-1 and PROV-1 cases. However, analysis 1 will likely yield less precise effect estimates than analysis 2 due to the smaller number of cases included.

Among the DL practices, the difference between the initial number of CONF-1 cases and the final number of CONF-1, CONF-2, CONF-3, and CONF-4 cases combined will be used to provide an estimate of the additional number of cases that could be expected in the NDL practices if NCDR and HES data had been available for these practices. In analysis 3, the CONF-1 rate estimates from the NDL practices will be adjusted to account for the additional expected cases when rates are estimated for the study population as a whole. Incidence rates for individual cancers will also be analyzed, although these estimates will be less precise than the incidence rates for the composite cancer endpoint. Incidence rates for individual cancers will be analyzed for males and females combined when appropriate. Patients who are not susceptible to developing an individual cancer type will not be included in the cancer type-specific analyses; for example, women who are known to have undergone prophylactic bilateral mastectomy will not be included in an analysis of breast cancer alone, and women who are known to have had a hysterectomy will not be included in an analysis of uterine cancer alone.

If information on a particular covariate is available in the CPRD, patients will be assumed to have the factor only if there is evidence for its presence (i.e., values for covariates will not be considered missing and will not be imputed). The only exception to this principle will be when “missing” is one of the possible values recorded for the variable (e.g., for smoking), in which case the value as listed within the database will be retained in the analysis as one of the possible values (e.g., smoking status will be “smoker,” “nonsmoker,” “former smoker,” or “missing”).

Additional details of the statistical analyses will be described in the statistical analysis plan.

10 QUALITY ASSURANCE

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the statistical analysis plan, abstraction forms, and study reports will undergo quality-control review, senior scientific review, and editorial review. Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)*.[41] The EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies*, echoes this approach.[42]

At RTI-HS, an independent Office of Quality Assurance (OQA) will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry, data transfer, and institutional review board (IRB) documentation. Such audits will be conducted by the OQA according to established criteria in standard operating procedures and other applicable procedures.

11 STRENGTHS AND LIMITATIONS

The main strength of this study is that it will draw from all available data sources in addition to the traditional GP electronic medical records and GP questionnaires (i.e., HES data, cancer registries death certificates) to address current gaps in knowledge, in particular, among users of OAB medications. This approach will maximally inform the mirabegron post-approval study protocols. In addition, this study can result in useful background incidence and validation data for the mirabegron post-approval cardiovascular and neoplasm studies, for which the computer programs generated for the present study can be adapted.

Due to the structure of the UK health care system, supported through taxes and managed by the government, the turnover in the system is typically low, thus ensuring that sufficient follow-up time will be accrued for endpoints to occur. However, follow-up may not be long enough for some malignancies with a long latency (5-10 years). If the lookback period before cohort entry is not long enough to find a previous diagnosis of AMI, stroke, or cancer recorded, it is possible that some of the assumed incident events are actually prevalent/recurrent events. For cancer endpoints, the probability that this occurs depends on the type of cancer and decreases with longer lookback periods. To minimize this, we will look not only for disease codes but also for codes for personal history of the endpoints. Another important limitation will be related to the identification of exposure. The record of a prescription issued does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over-the-counter or provided as samples by the physician will not be captured. During hospitalizations and nursing home stays, completeness of data on exposure, confounders, and possible outcomes may be affected.

12 PROTECTION OF HUMAN SUBJECTS

12.1 Europe, RTI Health Solutions

12.1.1 Approval by the RTI International IRB

RTI International holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organization to

review and approve human subjects protocols through the RTI International institutional review board (IRB) committees. RTI-HS will obtain approval from the RTI International IRB for the study.

12.1.2 Approval by the CPRD

RTI-HS will seek approval from the CPRD's Independent Scientific Advisory Committee (ISAC). This will require that RTI-HS prepare several documents, including a version of the present protocol adapted to ISAC's required format. Proposed questionnaires to be used for validation must be appended to the protocol. Historically, the approval process takes 6-8 weeks and may involve revisions of the submitted documents to address concerns expressed by ISAC members.

13 OTHER GOOD SCIENTIFIC PRACTICE

The study will be conducted in accordance with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[43] the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*[44] and guidelines for study conduct and reporting put forth in the FDA draft guidance document *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets*.[45] The ENCePP *Checklist for Study Protocols*[46] will be completed, and the study will be registered in the ENCePP study registry.[47]

The study will comply with the definition of the noninterventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline *Pharmacovigilance Planning E2E*[48] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*,[49] and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012.[50]

A scientific advisory board (SAB) will provide advice on study design, analysis, and case validation strategies and on an as-needed basis, should specific concerns arise. Dr. C Chapple (University of Sheffield and Royal Hallamshire Hospital, UK) and Prof. Noel Weiss (University of Washington, Department of Epidemiology and Fred Hutchinson Cancer Research Center, US) have agreed to be on the SAB for this study.

14 ADVERSE EVENT REPORTING

For studies in which the research team uses data only from automated health care databases, according to the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,

> *"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."*[51]

Thus, reporting of individual cases will not be required and the analysis of adverse reactions will be based upon aggregated data that are presented in the final study report.

According to the new EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*,

> *"For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report."*[52]

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach.[53] The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.

15 COMMUNICATION PLAN

Study protocols and study status and progress reports will be included in regulatory communications in line with regulatory requirements and the following milestones:

- Final protocol submission to the FDA: March 2013
- Assessment and summary report submission to FDA: March 2015
- Communications to be agreed with the EMA

Astellas has committed to set up contractual agreements with RTI- HS to implement the study, granting RTI-HS independent publication rights in line with the ISPE *Guidelines for Good Pharmacoepidemiology Practices (GPP)*,[54] ENCePP *Code of Conduct*,[55] and the International Committee of Medical Journal Editors *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[56] Study results will be published and communication in appropriate scientific venues, e.g., ISPE conferences, will be

considered. The appropriate STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist[57] will be followed for study reporting.

16 PROPOSED RESOURCES TO CONDUCT THE STUDY

16.1 RTI

The project will be led by an epidemiologist at the Director level, who will oversee the implementation of the project and documents and will be in charge of communication with research partners and Astellas, along with an epidemiologist at the Vice President level. A senior research epidemiologist will be assigned to the project and be in charge of the general implementation and drafting of new protocols, the statistical analysis plan, and study results reports. A hematologist/oncologist, an internal medicine specialist, and a cardiologist at the Director level in the epidemiology group will provide clinical expertise. Analyses of CPRD data will be performed at RTI by the senior research epidemiologist and a senior statistician.

Two statistician-programmers will work on the project.

Programming written by one programmer will be independently reviewed by a different programmer, with oversight by a senior statistician.

17 AMENDMENTS

N/A

18 APPENDIX A: VALIDATION STUDIES CONDUCTED IN THE CPRD

Acute Myocardial Infarction

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value (95% CI)
Varas-Lorenzo C, Garcia-Rodriguez LA, Perez-Gutthann S, et al. Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation. 2000;101(22):2572-78	1991-1995	▪ 50-74 years old at cohort entry ▪ Female	Baseline: ▪ Cardiovascular or cerebrovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases Censor if in follow-up: ▪ Cardiovascular or cerebrovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases	81.56 (79.31-83.62)
García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation. 2004;109(24):3000-6	1997-2000	▪ 50-84 years old on January 1, 1997 ▪ 2 years of enrollment with a general practitioner ▪ 1 year since first prescription	Baseline: ▪ Cancer ▪ Subjects 70 years old and older with scarce contact with general practitioner Censor if in follow-up: ▪ Cancer ▪ 85 years old	95.92 (91.71-98.33)
Hammad TA, McAdams MA, Feight A, et al. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008;17(12):1197-201	1997-2004	▪ 40-84 years old at cohort entry ▪ GPRD quality-related criteria ▪ 1 year of baseline information	Baseline: ▪ Prior AMI	92.60 (88.30-95.70)

AMI = acute myocardial infarction; CI = confidence interval; GPRD = General Practice Research Database.

Stroke

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Arana A, Varas C, González-Pérez A, Gutiérrez L, Bjerrum L, García Rodríguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6	1991-1997	▪ 50-59 years old at cohort entry ▪ Females	Baseline: ▪ Cardiovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases Censor if in follow-up: ▪ Cardiovascular diseases ▪ Neoplasms ▪ Coagulopathies ▪ Vasculitis ▪ Alcohol-related diseases ▪ 70 years old	Ischemic stroke: 76% Hemorrhagic stroke: 100%
Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):579-85	2000-2004	▪ 40-84 years old in 2000-2004 ▪ 2 years of enrollment with general practitioner	Baseline: ▪ Cerebrovascular diseases ▪ Cancer Censor if in follow-up: ▪ Cancer ▪ 85 years old	First recorded ischemic stroke: 90.2% (95% CI, 78.6-96.7)

Reference	Study Period	Inclusion Criteria	Exclusion Criteria	Positive Predictive Value
Gaist D, Wallander MA, González-Pérez A, García-Rodríguez LA. Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):176-82.	2000-2008	▪ 20-89 years old ▪ Enrollment status, permanent or dead ▪ 2 years of enrollment with general practitioner ▪ 1 year since the first computerized prescription ▪ At least 1 visit to general practitioner in the previous 2 years	Baseline: ▪ A diagnosis of intracerebral hemorrhage or subarachnoid hemorrhage before cohort entry ▪ 70+ years old at the start of follow-up with follow-up longer than 1 year and no records in THIN during follow-up Censor if in follow-up: ▪ 90 years old Computer-identified cases were discarded after manual review if: ▪ They were secondary to traumatic injury ▪ They were ischemic instead of hemorrhagic ▪ Not first episode ▪ The patient had cancer or subdural hemorrhage ▪ The episode took place while the patient was hospitalized	Subarachnoid hemorrhage: 91% Intracerebral hemorrhage: 73% Analyses modifying some parts of the outcome definition are also presented; lower confirmation rate in some groups of patients receiving anticoagulant therapy

PPV: positive predictive value.

19 REFERENCES

[1] Letter from Victoria Kusiak, MD, of the FDA to Judy Kannenberg, MBA, RAC, of Astellas Pharma Global Development, Inc., June 28, 2012.

[2] Letter from FDA: Advice DEpi 6 15 12 PMR, NDA 202611 Myrbetriq (mirabegron) 25 mg extended release tablets. Postmarketing Requirement Recommendations, 15 June 2012.

[3] Astellas. Research report: Mirabegron and Neoplasms (New Drug Application 202611, August 26, 2011), Astellas Pharma Global Development, Inc., Northbrook, IL

[4] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). April 2007. http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed October 3, 2012.

[5] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies. November 21, 2011. Available at: http://www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf. Accessed March 6, 2013.

[6] International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: http://www.icmje.org/urm_main.html Accessed March 6, 2013.

[7] Letter from Victoria Kusiak, MD, of the FDA to Judy Kannenberg, MBA, RAC, of Astellas Pharma Global Development, Inc., June 28, 2012.

[8] Letter from FDA: Advice DEpi 6 15 12 PMR, NDA 202611 Myrbetriq (mirabegron) 25 mg extended release tablets. Postmarketing Requirement Recommendations, 15 June 2012.

[9] Astellas. Research report: Mirabegron and Neoplasms (New Drug Application 202611, August 26, 2011), Astellas Pharma Global Development, Inc., Northbrook, IL

[10] Gopal M, Haynes K, Bellamy SL, Arya LA. Discontinuation rates of anticholinergic medications used for the treatment of lower urinary tract symptoms. Obstet Gynecol. 2008 Dec;112(6):1311-8.

[11] Brostrøm S. Hallas J. Persistence of antimuscarinic drug use. Eur J Clin Pharmacol. 2009 Mar;65(3):309-14.

[12] Andersson KE, Sarawate C, Kahler KH, Stanley EL, Kulkarni AS. Cardiovascular morbidity, heart rates and use of antimuscarinics in patients with overactive bladder. BJU Int. 2010 Jul;106(2):268-74. doi: 10.1111/j.1464-410X.2009.09073.x. Epub 2009 Nov 17.

[13] Asche CV, Kim J, Kulkarni AS, Chakravarti P, Andersson KE. Presence of central nervous system, cardiovascular and overall comorbidity burden in patients with overactive bladder disorder in a real-world setting. BJU Int. 2012 Feb;109(4):572-80. doi: 10.1111/j.1464-410X.2011.10436.x. Epub 2011 Jul 20.

[14] Varas-Lorenzo C, García-Rodríguez LA, Perez-Gutthann S, Duque-Oliart A. Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation. 2000 Jun 6;101(22):2572-8.

[15] García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation. 2004 Jun 22;109(24):3000-6.

[16] Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008 Dec;17(12):1197-201.

[17] Arana A, Varas C, González-Pérez A, Gutiérrez L, Bjerrum L, García Rodríguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6.

[18] Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):579-85.

[19] Gaist D, Wallander MA, González-Pérez A, García-Rodríguez LA. Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):176-82.

[20]Arana A, Varas C, González-Pérez A, Gutiérrez L, Bjerrum L, García Rodríguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6.

[21] Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. Cancer Epidemiol 2012 Oct;36(5):425-9.

[22] Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):168-75.

[23] Walker AM. Identification of esophageal cancer in the General Practice Research Database. Pharmacoepi Drug Saf. 2011 Nov;20(11):1159-67.

[24] Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel blockers and risk of cancer. Lancet. 1997 Feb 22;349(9051):525-8.

[25] Kaye JA, Derby LE, Kaye JA, Derby LE, del Mar Melero-Montes M, Quinn M, et al. The incidence of breast cancer in the General Practice Research Database compared with national cancer registration data. Br J Cancer. 2000 Dec;83(11):1556-8.

[26] Kaye JA, Myers MW, Jick H. Acetaminophen and the risk of renal and bladder cancer in the General Practice Research Database. Epidemiology. 2001 Nov;12(6):690-4.

[27] Wei L, Macdonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. Br J Clin Pharmacol. 2013 Jan;75(1):254-9.

[28] US Food and Drug Administration. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets (draft guidance). United States Food and Drug Administration; February 2011. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf. Accessed March 6, 2013.

[29] Surveillance, Epidemiology and End Results. SEER Cancer Statistics Review 1975-2009 (vintage 2009 populations). Table 1.4. Age-adjusted SEER incidence and US death rates and 5-year relative survival (percent) by primary cancer site, sex, and time period. Available at: http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php. Accessed August 8, 2012.

[30] Varas-Lorenzo C, García-Rodríguez LA, Perez-Gutthann S, Duque-Oliart A. Hormone replacement therapy and incidence of acute myocardial infarction. A population-based nested case-control study. Circulation. 2000 Jun 6;101(22):2572-8.

[31] E.g., Read code G33z400 (in use as of May 2012)

[32] E.g., Read codes starting in 44H (in use as of May 2012)

[33] E.g., Read codes starting with 323 (in use as of May 2012)

[34] E.g., Read codes starting in 7929 and in 7L10 (in use as of May 2012)

[35] E.g., Read code 6ZI.13 (in use as of May 2012)

[36] Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiol Drug Saf. 2013 Feb;22(2):168-75.

[37] Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. Cancer Epidemiol. 2012 Oct;36(5):425-9.

[38] Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010 Jul 28;304(4):411-8.

[39] Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. Pharmacoepidemiol Drug Saf. 2004 Jul;13(7):437-41.

[40] Gopal M, Haynes K, Bellamy SL, Arya LA. Discontinuation rates of anticholinergic medications used for the treatment of lower urinary tract symptoms. Obstet Gynecol. 2008 Dec;112(6):1311-8.

[41] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed March 6, 2013.

[42] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. July 9, 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed March 6, 2013.

[43] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed March 6, 2013.

[44] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). July 25, 2011. Available at: http://www.encepp.eu/standards_and_guidances/index.shtml. Accessed March 6, 2013.

[45] US Food and Drug Administration. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data sets (draft guidance). United States Food and Drug Administration; February 2011. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf. Accessed March 6, 2013.

[46] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). July 25, 2011b. Available at: http://www.encepp.eu/standards_and_guidances/index.shtml. Accessed March 6, 2013.

[47] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Electronic register of studies. Version 3.0.46. 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed March 6, 2013.

[48] ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Pharmacovigilance planning. E2E. Nov 2004. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed March 6, 2013.

[49] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. June 22, 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed March 6, 2013.

[50] European Commission. Implementing Regulation (EU) No 520/2102 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. 2012. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed March 6, 2013.

[51] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). April 2007. http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed March 6, 2013.

[52] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. June 22, 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed March 6, 2013.

[53] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. July 9, 2012. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed March 6, 2013.

[54] International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). April 2007. http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed March 6, 2013.

[55] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies. November 21, 2011. Available at: http://www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf. Accessed March 6, 2013

[56] International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: http://www.icmje.org/urm_main.html Accessed March 6, 2013.

[57] STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE checklists. 2007. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed March 6, 2013.