SPD555-802: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort

Protocol

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APPROVAL PAGE

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LIST OF ABBREVIATIONS

5-HT_4	5-hydroxytryptamine receptor 4
AMI	acute myocardial infarction
BIPS GmbH	Leibniz Institute for Prevention Research and Epidemiology
CABG	coronary artery bypass graft
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CHD	coronary heart disease
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CT	computed tomography
CV	cardiovascular
EBM	Einheitlicher Bewertungsmaßstab
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
GI	gastrointestinal
GP	general practitioner
GPP	*Guidelines for Good Pharmacoepidemiology Practices*
GPRD	General Practice Research Database
hERG	human ether-a-go-go-related gene
HES	Hospital Episode Statistics
HR	hazard ratio
IBS	irritable bowel syndrome
ICD-10	*International Statistical Classification of Diseases and Related Health Problems , 10th Revision*
ICD-10-CM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*
ICD-10-GM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification*
IRB	institutional review board
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee

ISD	Information Services Division
ISPE	International Society for Pharmacoepidemiology
MACE	major adverse cardiovascular event
MREC	Medical Research Ethics Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMR	nuclear magnetic resonance (image)
ONS	Office for National Statistics (United Kingdom)
OOH	out-of-hospital
OPS	Operationen- und Prozedurenschlüssel
PEG	polyethylene glycol 3350
PPV	positive predictive value
RR	relative risk or risk ratio
SAP	statistical analysis plan
SCD	sudden cardiac death
SHI	statutory health insurance
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

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ABSTRACT

Title: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort

Version 2.0, 14 May 2014

Patricia Tennis, PhD, RTI Health Solutions Epidemiology

Rationale and background: Prucalopride is a 5-hydroxytryptamine receptor 4 (5-HT_4) agonist that is currently available in the European Union (EU) and other regions for the treatment of chronic constipation in women in whom laxatives have been ineffective. No signal for increased risk of adverse cardiovascular (CV) events has been observed for prucalopride during extensive nonclinical and clinical CV investigations or as a result of safety monitoring during the entire clinical development program and postmarketing period. However, given the prior experience with other 5-HT_4 agonists, the United States Food and Drug Administration (FDA) has expressed interest in having additional information about CV safety for any members of this drug class (FDA, 2011), including prucalopride.

Research question and objectives:

The primary objective of this study is to estimate, in real-world settings, the adjusted incidence rate ratio (IRR) and 95% confidence interval (CI) for major adverse cardiovascular events (MACE)—defined as the composite of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, and in-hospital cardiovascular death—in initiators of prucalopride versus initiators of polyethylene glycol 3350 (PEG), both indicated for chronic constipation, adjusting for CV risk factors and other confounders.

Secondary objectives are as follows:

- Estimate incidence rates for MACE and for its individual components in the prucalopride and PEG cohorts
- Estimate adjusted IRRs for the individual components of MACE for the prucalopride cohort compared with the PEG cohort

Study design: This study will consist of multiple observational (noninterventional) population-based cohort substudies of patients initiating prucalopride compared with patients initiating PEG, in four data sources. The frequency of MACE and the adjusted IRR will be calculated.

Population: The study will be implemented in four administrative health care data sources in two countries: in the United Kingdom (UK), two data sources derived from electronic medical records from general practices, the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN); also in the UK, the Information Services Division (ISD) of Scotland, an administrative health care data source; and in Germany, the German

Pharmacoepidemiological Research Database (GePaRD), constructed from claims of statutory health insurance agencies.

The prucalopride cohort will be formed by patients who have a dispensing or prescription for prucalopride, at least 12 months of data in the data source prior to the first dispensing or prescription, and no evidence of prior use of prucalopride in the data source. The first prescription of prucalopride will be the index prescription, prescribed or dispensed on the index date.

The PEG cohort will be selected from patients who have a dispensing or prescription for PEG, at least 12 months of data in the data source prior to the first dispensing or prescription, and no evidence of prior use of PEG in the data source. The first prescription for PEG will be the index prescription, prescribed or dispensed on the index date. Up to 5 PEG initiators will be selected for each prucalopride initiator, matched by age category, sex, and calendar year of first prescription of prucalopride or PEG. Currently, PEG is the most commonly prescribed medication for chronic constipation in the EU.

For this study, new users are individuals starting a study medication for the first time, although they may have had the other study medication in the past. Switching from one study medication to another, if both meet the definition of new use, is permitted in this study. Individuals in the PEG cohort who switch to prucalopride will enter the prucalopride cohort at the time of the switch; members of the prucalopride cohort who switch to PEG will be eligible to be selected for the PEG cohort.

Variables: The primary endpoint, MACE, will comprise the first occurrence of any of its individual components during follow-up.

Time at risk from current use for prucalopride initiators and PEG initiators is defined as the duration of the prucalopride or PEG prescription or dispensing plus 7 days. For the primary analysis, follow-up will end at the earliest of death, first occurrence of an outcome of interest, switch to other study medication, termination of enrollment in the health plan system, or end of study period.

Data sources: Prucalopride or PEG exposure will be ascertained from general practitioner (GP) prescriptions in CPRD and THIN data and by outpatient dispensings in ISD Scotland and GePaRD data. Cardiovascular risk factors and other covariates will be identified from the available health care utilization codes before the index date.

The cardiovascular endpoints of interest will be identified by applying existing diagnosis code algorithms from published pharmacoepidemiologic studies to hospital admission and discharge diagnosis codes in the data. In the UK, validation of outcomes will be conducted by obtaining, as available, copies of relevant medical reports from GP records, linkage to Hospital Episode Statistics discharge diagnoses, linkage to Office for National Statistics death records, and GP questionnaires.

Study size: A prucalopride cohort size of 10,950 should be sufficient to reach, with 80% probability, an IRR upper bound of the 95% CI less than 3 (null hypothesis) under the alternative hypothesis that IRR is 1.

Data analysis: For each cohort, the prevalence of baseline risk factors for MACE will be described. Incidence rates of each outcome of interest will be calculated for the prucalopride and PEG cohorts, and IRRs will be estimated.

Within each data source, propensity scores will be developed by modeling use of prucalopride against CV risk factors that could be confounders. After stratifying cohort-specific incidence rates by propensity score decile and by data source, the coordinating center will conduct an overall analysis combining the results across all data sources to calculate overall summary incidence rate and IRR estimates. Overall incidence rates will be age- and sex-standardized to the distribution of person-years in the prucalopride cohort across all data sources by age category and sex. Overall IRRs will be standardized to the distribution of propensity score deciles in the prucalopride cohort across all data sources.

Milestones:

- Ethical approvals
- Annual monitoring of prucalopride initiators
- Pilot phase report, including descriptive analyses and adjusted IRR analysis
- Report of study results

1. RATIONALE AND BACKGROUND

1.1 Rationale

Prucalopride is a 5-hydroxytryptamine receptor 4 (5-HT_4) agonist that is currently available in the European Union (EU) and other regions for the treatment of chronic constipation in women in whom laxatives have been ineffective.

In general, 5-HT_4 receptor agonists have the potential to treat disorders of motility throughout the gastrointestinal (GI) tract, including but not limited to, delayed gastric emptying and colonic dysmotility (Gershon and Tack, 2007). Several 5-HT_4 receptor agonists have been developed for the treatment of chronic constipation and other GI disorders. First-generation 5-HT_4 agonists, cisapride and tegaserod, are nonselective and interact with other receptors in a concentration range relevant for their interaction with the 5-HT_4 receptor.

- Cisapride was withdrawn from the United States (US) market in 2000 due to its association with QT interval prolongation, torsade de pointes and other ventricular arrhythmias, and sudden death, especially when used in conjunction with other QT-prolonging drugs and/or CYP3A4 inhibitors in subjects with pre-existing cardiac conditions. These events are likely due to cisapride's affinity for the *hERG* (human ether-a-go-go-related gene) channel, which is within the range of 1-5 times human plasma levels, or a concentration ratio ≤ 5 between its 5-HT_4 receptor-mediated effects and its inhibitory effect on the delayed rectifier potassium current (IK_r) (Mohammad et al., 1997; Potet et al., 2001).

- Tegaserod was withdrawn from the US market in 2007 (available for restricted emergency use) due to a possible association with ischemic cardiovascular (CV) side effects in an analysis of 29 randomized controlled clinical studies with tegaserod use of up to 3 months duration (13 [0.1%] of 11,614 subjects treated with tegaserod had an ischemic CV side effect compared with 1 [0.01%] of 7,031 subjects treated with placebo). However, note that subsequent to the removal of tegaserod from the US market, 2 published epidemiological studies indicated that there was no increased risk of CV ischemic events associated with tegaserod use (Anderson et al., 2009; Loughlin et al., 2010).

Prucalopride is a newer generation, highly selective 5-HT_4 agonist with high affinity for the 5-HT_4 receptor. The product has been shown to have high receptor specificity, i.e., in vitro affinity for other receptors was only detected at concentrations exceeding its 5-HT_4 receptor affinity by at least 150-fold. Substantial safety margins for prucalopride over effects on the *hERG* channel contrast strongly with those for cisapride, which has significant functional activity at the *hERG* channel in the therapeutic range. No signal for increased risk of adverse CV events has been observed for prucalopride during extensive nonclinical and clinical CV investigations or as a result of safety monitoring during the entire clinical development program and postmarketing period.

However, given the prior experience with other 5-HT_4 agonists, the US Food and Drug Administration (FDA) has expressed interest in having additional information about CV safety for any members of this drug class (FDA, 2011), including prucalopride. To provide the FDA the required additional assurance of the CV safety profile of prucalopride, the sponsor proposes to conduct a noninterventional pharmacoepidemiology safety study in a number of countries in the EU where prucalopride is currently marketed.

The endpoint "major adverse cardiovascular events" (MACE) has been defined within the context of evaluating CV safety within randomized clinical studies. For the purposes of this noninterventional study, MACE will be defined as the composite of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, and in-hospital cardiovascular death.

The purposes of this proposed study are as follows:

- To estimate the incidence of MACE among initiators of prucalopride in comparison to the incidence among a cohort of initiators of another prescription medication for chronic constipation, polyethylene glycol 3350 (PEG), and

- To evaluate whether prucalopride initiators are at increased risk of MACE after controlling for known CV risk factors and other potential confounding factors.

To accrue a sufficient number of prucalopride initiators to address the study objectives, the study will be implemented in multiple European health care data sources according to a common core protocol. Among the several European data sources that are available and appropriate for this type of pharmacoepidemiology safety study, most are based on public insurance claims data and therefore represent only dispensing of prescription medications that are reimbursed by public insurance. Although prucalopride is approved in more than 50 countries, it is currently reimbursed in only a few. In some countries (e.g., Germany), reimbursement is limited to certain subpopulations. The following data sources are planned for this study:

- The Clinical Practice Research Datalink (CPRD), which is compiled from electronic medical records of United Kingdom (UK) general practitioners (GPs) where the GPs act as coordinators of patient health care
- The Health Improvement Network (THIN) is also compiled from electronic medical records of UK GPs
- The Information Services Division (ISD) of Scotland health care administrative data
- The German Pharmacoepidemiological Research Database (GePaRD), compiled from statutory health insurance (SHI) claims in Germany.

In addition to these data sources, it is anticipated that upon FDA approval of prucalopride, this study will be extended to US data sources. A protocol amendment or separate protocol will be developed at that time. It is expected that a large number of additional prucalopride initiators will be identified in the US data sources because a previous study in a similar indication

conducted with one of these data sources was able to identify large numbers of relevant subjects (Loughlin et al., 2010).

Currently, an ongoing study monitors utilization of prucalopride in the THIN and CPRD data sources as part of a European Medicines Agency (EMA) postapproval commitment; however, the number of prucalopride users accrued in that monitoring study will not be sufficient to address this study's objectives.

1.2 Background

In the UK, patients with chronic constipation are most commonly diagnosed by GPs. Patients are referred to specialist gastroenterologists if malignancy is suspected, further testing is required to clarify cause, or if patients do not respond to diet changes, lifestyle advice, and laxatives. Elderly patients may also be diagnosed by and/or referred to geriatricians, often for assessment of other comorbidities. Common therapies include lactulose, Dulcolax (bisacodyl), Fybogel (ispaghula husk), Senokot (senna), and Movicol (PEG), with the latter being the most common prescription medication for constipation. Although the National Institute for Health and Care Excellence (NICE) recommends that prescribing should be initiated by GPs for cost containment, in reality, most prucalopride prescriptions are initiated in secondary care by gastroenterologists and, less frequently, by geriatricians or colorectal surgeons, and repeat prescriptions are followed up in primary care. NICE guidance recommends prucalopride as an option for the treatment of chronic constipation only for women who have had treatment with at least two laxatives from different classes at the highest tolerated recommended doses for at least 6 months, have not received adequate relief, and for whom invasive treatment for constipation is under consideration.

In Germany, patients are most commonly diagnosed by primary care practitioners and internal medicine physicians. Patients are referred to specialist gastroenterologists if they are nonresponsive to diet changes, lifestyle advice, and laxatives and if malignancy is suspected or further testing is required to clarify cause. German reimbursement authorities classify prucalopride similar to laxatives, resulting in restricted reimbursement—that is, no reimbursement for any idiopathic chronic constipation and limited reimbursement for selected cases in secondary chronic constipation. Therefore, prucalopride prescribing is predominantly initiated by specialist gastroenterologists but with repeat prescriptions written in primary care.

The approved dosage in the EU is 2 mg once daily. It is recommended that elderly individuals start with 1 mg per day and increase to 2 mg if needed.

1.3 Principles of Using Population-Based Health Care Databases

According to the FDA Guidance on conducting and reporting pharmacoepidemiologic safety studies (FDA, 2013), "Recent technological advances now allow investigators to efficiently assemble electronic healthcare data and, relative to alternative approaches, rapidly conduct pharmacoepidemiologic studies of drug safety issues in real-world healthcare settings and with large numbers of patients. In addition, innovative statistical methods allow investigators

to study complex drug safety questions previously considered too difficult to examine outside of a clinical trial setting."

The data sources selected for this proposed study (i.e., CPRD, THIN, ISD Scotland, and GePaRD) have all been used to evaluate drug safety in the real-world health care setting (including studies using multiple data sources) and to support postmarketing regulatory commitments with both the FDA and the EMA (for example, http://sos-nsaids-project.org/?q=home; http://www.safeguard-diabetes.org/). Pharmacoepidemiology FDA-sponsored studies have also frequently been performed with the General Practice Research Database (GPRD), the predecessor to the CPRD (Hammad et al., 2008a; Hammad et al., 2008b; Kornegay et al., 2002).

Population-based health care data sources, which include information from usual health care utilization, have been used for several decades to evaluate the frequency and risk factors of outcomes among users of medications of interest compared with users of other medications. Compared with randomized studies, database studies offer increased generalizability, study size, and diversity of subjects that reflect how the medications are being used in clinical practice, although they may be more affected by misclassification of exposure and outcome.

Methods to reduce the bias of effect estimates derived from such studies focus on minimizing the differences in the study groups being compared. To reduce bias in estimates of the effect of a specific medication of interest, factors that are associated with exposure *and* with the outcome are made comparable across the study groups (that is, they are controlled in the analysis). Factors not associated with the outcome of interest (here CV outcomes), even if different among the exposure groups of interest (prucalopride initiators compared with PEG initiators), will have no direct impact on the estimate of the association between prucalopride and cardiovascular outcomes (in this study, the incidence rate ratio [IRR]).

There is little evidence that chronic constipation is associated with increased risk of adverse CV outcomes. One observational study in postmenopausal women who were ineligible for or unwilling to participate in the Women's Health Initiative clinical studies attempted to evaluate this question. Participating women reported through annual mail surveys. The authors observed a small increased risk of CV outcomes, which was attributed to residual confounding related to self-reporting of CV risk factors (Salmoirago-Blotcher et al., 2011). The study described in this protocol will stratify results by propensity scores in the analysis stage to simultaneously adjust for the impact of multiple CV risk factors.

Loughlin et al. (2010) evaluated the risk of stroke and acute coronary syndrome, myocardial infarction, and coronary revascularization among users of tegaserod in a study using a US health insurance claims database. The authors compared the experience of tegaserod users and nonusers with similar gastrointestinal diagnoses, matched to the tegaserod users by propensity score. The majority of tegaserod users were female (89%) and aged younger than 55 years (77%). Differences in baseline disease characteristics between the tegaserod users and potential comparators prior to matching were removed by the propensity score matching. The incidence of CV events (stroke and acute coronary syndrome, myocardial infarction, and coronary revascularization) among tegaserod users was 4.8 per 1,000 person-years, and

incidence of stroke was 0.72 per 1,000 person-years. Incidence of both types of events was similar among tegaserod users and matched comparators. In the tegaserod cohort relative to the comparator cohort, the results indicated no increased risk of CV outcomes (adjusted hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.73-1.23) or stroke (adjusted HR, 0.90; 95% CI, 0.46-1.77). Medical records for validation were obtained for 84% of identified cases.

This approach, including use of matching and analytical methods for removing confounding, is used commonly for the quantification of increased risk among users of medications in real-world settings. This population-based approach to evaluating the medication of interest by including diverse practices and patients is useful for obtaining large numbers of patients, desired precision of outcome frequencies, and broad understanding of the safety profile in diverse types of patients in general health care systems.

This study protocol describes the planned study design and data sources. A separate document, the statistical analysis plan (SAP), provides further detail on the methods applied to conduct the analyses. A third document, the data development plan, will describe all the codes planned to be used to identify diagnoses, medications, and procedures specified in the analysis plan, by data source, and any unique differences for specified data sources. A fourth document, the validation plan, will describe in detail the process of obtaining, sharing, reviewing, and adjudicating any information for case categorization.

2. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to estimate, in real-world settings, the adjusted IRR and 95% CI for MACE—defined as the composite of hospitalization for AMI, hospitalization for stroke, and in-hospital cardiovascular death—in initiators of prucalopride versus initiators of PEG, both indicated for chronic constipation, adjusting for CV risk factors and other confounders.

Secondary objectives are as follows:

- Estimate incidence rates for MACE and for its individual components in the prucalopride and PEG cohorts
- Estimate adjusted IRRs for the individual components of MACE for the prucalopride cohort compared with the PEG cohort

2.1 Specific Aims

The study will be conducted using selected electronically available administrative health care data sources. From each data source, this study will assemble a study cohort of patients initiating (newly dispensed or prescribed) prucalopride and a study cohort of patients initiating PEG, matched by age category, sex, and calendar year of the index date (the date of the first prucalopride or PEG prescription).

The study aims to estimate the upper bound of the two-sided 95% CI for the adjusted IRR for MACE in prucalopride initiators versus PEG initiators. A prucalopride cohort size of 10,950 should be sufficient to reach, with 80% probability, an upper bound of the 95% CI of the IRR of less than 3 if the true IRR is 1.0. Following US marketing approval, a separate study or an extension to Study SPD555-802 could be implemented in the US, enabling a cohort size of over 27,490, which would be sufficient to establish with 80% probability an upper 95% CI of the IRR of less than 2 if the true IRR is 1.0.

3. RESEARCH METHODS

3.1 Study Design

This study will consist of multiple observational (noninterventional) population-based cohort substudies of patients initiating prucalopride compared with patients initiating PEG, matched by age category, sex, and calendar year of the index date, in four data sources. The frequency of MACE and the adjusted IRR (95% CI) will be calculated.

This study will follow a new-users (initiators) design (Ray, 2003). For this study, new users are individuals starting a study medication for the first time and may have had the other study medication in the past. Switching from one study medication to another, if both meet the definition of new use, is permitted in this study. Information on risk factors before the start of each exposure of interest will allow control for potential confounders at the start of treatment. The new-user design also averts survival bias due to underascertainment of events related to the start of treatment. Where possible, subjects will be followed until 7 days after the estimated end of use of prucalopride or PEG.

The main composite cardiovascular endpoint of interest will be based on the classical MACE endpoint ascertained in randomized clinical studies. Definition of this endpoint will follow the FDA recommendations for clinical studies in the draft *Standardized Definitions for End Point Events in Cardiovascular Trials* (Hicks et al., 2012), but will be adapted to the noninterventional setting and the availability of information in each data source selected for study implementation. This composite cardiovascular endpoint will be composed of (1) hospitalization for nonfatal AMI, (2) hospitalization for nonfatal stroke, and (3) in-hospital cardiovascular death. Individual components of this endpoint will also be evaluated. A sensitivity analysis will include out-of-hospital coronary and cerebrovascular deaths in addition to MACE.

Propensity scores will be used to combine multiple potential confounders into a single score, and all derived incidences will be adjusted for propensity score category.

The study will be implemented across four substudies in the following health care data sources: in the UK, two data sources derived from electronic medical records from general practices, the CPRD and THIN; also in the UK, ISD Scotland, an administrative health care data source; and in Germany, the GePaRD, constructed from claims of SHI agencies. The coordinating center will work with the research center conducting each substudy following

this common protocol and SAP to conduct analyses and generate outputs from each data source.

3.1.1 Study Tasks

The following steps will be required to complete this study:

- Ethics review will be implemented.
- The coordinating center will conduct the combined descriptive analysis.
- The accumulating number of prucalopride initiators in the data sources will be monitored annually.
- Pilot phase. The collaborating research centers conducting the substudies will review patterns of use of prucalopride and PEG and, if needed, the coordinating center, with input from all collaborating research centers, will revise and amend the protocol and analysis plan definitions, including criteria for the PEG cohort and variables to be included in the propensity score analysis. Collaborating research centers will obtain source documents for outcome validation as applicable. The coordinating center will coordinate and pool the number of events to help determine the timing of the analysis for the study report.
- Study report. Collaborating research centers will conduct data source–specific analyses, including validation of newly identified cases of the outcomes of interest. The coordinating center will conduct the combined analysis, estimate the adjusted IRR and 95% CI, and develop the study report of results.

3.2 Population

3.2.1 Data Sources

To increase study size (Section 3.6), the study will be implemented in multiple health care data sources according to a common core protocol. At present, the data sources planned for this study are from the UK (CPRD, THIN, ISD Scotland; see Section 3.2.1.1) and Germany (GePaRD; see Section 3.2.1.2).

The feasibility of including additional data sources continues to be investigated.

3.2.1.1 United Kingdom

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Those records are available for research purposes in two main data sources: the CPRD (formerly the GPRD) and THIN. These two data sources have similar information recorded by GPs; there is an overlap of general medical practices and patients between the CPRD and THIN, and combining CPRD and THIN data will increase the size relative to the CPRD alone by approximately 27% (Cai et al., 2012). ISD Scotland data will be drawn from routinely collected national administrative data on hospital diagnoses and prescriptions; study-specific additional clinical information can be requested. Approximately 10% to 15% of

CPRD and THIN practices are in Scotland and will have to be excluded from the CPRD and THIN analyses.

CPRD

The CPRD (http://www.cprd.com/intro.asp) contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The CPRD has information on 5.4 million individuals (active contributors), which represents approximately 9% of the UK population. These data are linkable, at least partially, with other health care data sets (e.g., hospitalization and national mortality data). Updated, valid, linked data are available through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency.

Detailed information on prescriptions written by the GPs, including prescribed dose and duration, is automatically recorded in the database. Read codes are used for recording clinical diagnoses by GPs. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Information on specialist visits and hospitalizations are routinely forwarded to the GP, who enters that information into the medical record. The CPRD also includes information recorded by GPs on patient demographics and lifestyle factors (although not complete for all patients).

Approximately 65% of the English practices have consented to have their patient information linked to other health care data sets, such as Hospital Episode Statistics (HES) and the national death register at the Office for National Statistics (ONS), via the patient's National Health Service (NHS) number, sex, date of birth, and postal code. English practices represent approximately 75% of all practices contributing to the CPRD; therefore, approximately half of the total CPRD practices have this link. Linkage to HES enables access to the hospitalization data, that is, admission date, discharge diagnosis, and procedure codes. Linkage to the national death register at ONS can be used to ascertain death and causes of death and to validate the mentions of death in the GP records. Death rates by age group and various causes of death, including ischemic heart disease, are comparable between linked CPRD data and official rates for England and Wales, and the subset of linked CPRD practices seems to be a representative sample of the general population (Setakis et al., 2010). Data in HES and ONS are updated every 6 months, but the lag-time can be more than 1 year.

Research at the CPRD requires approval from the CPRD Independent Scientific Advisory Committee (ISAC).

THIN

Data from THIN are available through Cegedim Strategic Data (CSD). Established in 2002, THIN now collects data from 570 practices, covering 6% of the general population, with more than 65 million patient-years of experience (CSD Medical Research, 2012). Eleven million individual patients are represented in the data; of those, approximately one-third are active at any one time. THIN records information on all services provided by the GP. As with the CPRD, information on specialist visits and hospitalizations are routinely forwarded to the GP, who enters that information into the medical record.

All practices record information received on hospital admissions, discharge diagnoses, medications, outpatient specialist visits, and fact of death. For some of the practices, THIN offers additional hospital episode data linked to the general practice patients, but currently very few practices participate in this process. When a drug is prescribed, a computer record is immediately created and added to the data source.

THIN supplies de-identified data for approved drug safety and epidemiological studies. Such research needs to be approved by the South East Multicentre Research Ethics Committee (http://www.thin-uk.com/contributing_data.htm).

ISD Scotland

The Scottish record linkage system (ISD Scotland) contains electronic coded information on all outpatient prescriptions and all nonpsychiatric hospitalizations in Scotland. The following information, among others, is included in the hospitalization data: birth date, age, sex, main condition, reason for admission, other conditions present, investigative procedures and treatments, and admission and discharge dates (http://www.datadictionary.scot.nhs.uk/SMR-Datasets/SMR-Validation-Section/General-Clinical-Data-Section/Main-Condition.asp; accessed May 24, 2013). Outpatient diagnoses are not available, except by accessing individual GP medical records on an ad hoc basis. Case validation for hospitalizations can be obtained by accessing the original case records. The fact and date of death and underlying cause of death can be identified by linkage to the national death register.

Prescriptions issued by the GP and dispensed by pharmacies are contained in the prescription database. They are entered into the system by the GP, pulled down by the pharmacist from the cloud computing system, and then dispensed; if the prescription is handwritten or the practice is not yet set up to utilize the cloud computing system, then the pharmacist enters it into the prescription database. All prescriptions are centrally scanned. In Scotland, all community prescribing is done by GPs; this may be done on the advice of a specialist (Strom, 2006). Each record contains the strength, number dispensed, and patient instructions.

3.2.1.2 Germany: GePaRD

The GePaRD is a population-based database compiled from health insurance claims submitted to SHI agencies in Germany (Jobski et al., 2012; Kraut et al., 2010; Pigeot and Ahrens, 2008). Ninety percent of the population in Germany is insured with the SHI agencies. The GePaRD covers more than 15 million SHI members from all regions of Germany, approximately 17% of the German population [population data from Eurostat (2012)]. Membership in SHI agencies is fairly stable over time. The GePaRD includes the following types of data from all patients enrolled in one of the SHI agencies: demographics; hospital diagnoses and dates; ambulatory care diagnoses and procedures by calendar quarter (coded in the *International Classification of Diseases and Related Health Problems, 10th Revision, German Modification* [ICD-10-GM]); and ambulatory prescriptions, including date of prescription and date of pharmacy dispensing. Although information on dose is not directly available, prescribed quantity and central pharmaceutical number, linkable to packaging size and strength, is recorded for each medication.

ICD-10-GM is used for coding diagnoses, and OPS (Operationen- und Prozedurenschlüssel) codes are used for surgical and diagnostic procedures. Types of treatments and diagnostic procedures are registered according to EBM (Einheitlicher Bewertungsmaßstab) codes, developed for payment of physicians for the outpatient treatment of German SHI patients.

Studies are conducted in collaboration with the Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany; SHI and health ministry approval is needed for the study.

German reimbursement authorities classify prucalopride together with laxatives, resulting in restricted reimbursement—that is, no reimbursement for any idiopathic chronic constipation and limited reimbursement for selected cases in secondary chronic constipation in patients with cancers, megacolon, diverticulosis, diverticulitis, mucoviscidosis, and neurogenic paresis of the bowel; before diagnostic interventions; during use of phosphate-binding medication for chronic insufficiency of the kidney and opiate and opioid therapy; and in terminal life phase. Hence, the study population from German data sources may represent only a subset of the general chronic constipation population.

3.2.1.3 Summary of Data Sources

Table 1 presents a summary of planned populations and data sources in which the substudies will be implemented. The following research centers will conduct the substudies:

- CPRD: RTI Health Solutions
- THIN: CEIFE (Centro Español de Investigación Farmacoepidemiológica)
- ISD Scotland: University of Dundee
- GePaRD: Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH)

All research centers have been involved in the development of this protocol and will collaborate with the coordinating center in implementing the study in each of the respective above-described data sources. As with all studies conducted with GePaRD data, approval by the statutory health insurance providers (SHIs) that contribute data to the GePaRD must be obtained before the study is initiated.

Table 1: Main Features of Selected European Data Sources

Feature	CPRD	THIN	ISD Scotland	GePaRD
Data type	Primary health care electronic medical record database plus partial linkage to HES and other data	Primary health care electronic medical record database plus partial linkage to HES and other vital statistics data[a]	Administrative medical records of the national health insurance system	SHI claims
Population covered in current year	5.4 million	3.7 million	5.2 million	15 million
Proportion of the country's population covered by the data source	8.6% of UK	5.9% of UK	100% of Scotland	17% of Germany
Representativeness of patients	Representative of sex and age of UK population	Representative of sex and age of UK population	Covers entire population of Scotland	Representative of sex and age of German population
Data on outpatient medications (e.g., prucalopride, use of antidiabetics, antihypertensives)	Yes, prescription date and substance for outpatient prescription medications prescribed by the GP	Yes, prescription date and substance for outpatient prescription medications prescribed by the GP	Yes, dispensing date and substance for outpatient prescription medications issued by a GP, dispensed by pharmacies, and covered by national insurance	Yes, dispensing date and substance for outpatient prescription medications dispensed and covered by the SHI
Dose	Prescribed dose	Prescribed dose	Based on date of prescription, date of dispensing, prescribed quantity, packaging size, and strength	Based on date of prescription, date of dispensing, prescribed quantity, packaging size, and strength
Duration	Indicated in the written prescription	Indicated in the written prescription	Based on prescribed quantity, packaging size, and strength	Based on prescribed quantity, packaging size, and strength
Drug dictionary codes/therapeutic classification	Multilex/British National Formulary	Multilex/British National Formulary	ATC	ATC

Table 1: Main Features of Selected European Data Sources

Feature	CPRD	THIN	ISD Scotland	GePaRD
Type of prescriptions	Any prescribed by GP	Any prescribed by GP	All dispensings in community pharmacies for prescriptions issued by a GP for covered medications	All reimbursable outpatient pharmacy dispensings for covered medications
Clinical indication (i.e., constipation vs. not)	Diagnosis associated with new courses of medications, but completeness is variable Computerized free-text information is available for review	Diagnosis associated with new courses of medications, but completeness is variable Computerized free-text information is available for review	Available only by accessing individual GP medical records on an ad hoc basis	Not specifically, based on proxies; when mentioned as outpatient diagnosis
Outpatient diagnosis (e.g., comorbidities such as diabetes and hypertension)	Yes, also date of GP visit	Yes, also date of GP visit	Available only by accessing individual GP medical records on an ad hoc basis	Yes, by calendar quarter
Hospitalization date and diagnosis	Date of hospitalization and diagnosis recorded by GPs and partial linkage to HES (admission and discharge)	Date of hospitalization and diagnosis recorded by GPs and partial linkage to HES (admission and discharge)	Date and reason for admission Main condition	Main admission and discharge diagnoses for all; if available, additional main diagnoses, secondary diagnoses and ancillary diagnoses
Disease and procedure codes dictionary	Read codes ICD-10-CM codes (HES)	Read codes	ICD-10	ICD-10-GM; OPS and EBM for therapeutic and diagnostic procedures
Lifestyle risk factors (e.g., smoking, high body mass index)	Yes, but completeness is variable	Yes, but completeness is variable	Yes, obtained from GP records on an ad hoc basis; completeness may be variable	No
Data availability	Since 1987 Current linkage to HES/ONS for ~55% of practices	Since 1980	Variable, by region	Since 2004

Table 1: Main Features of Selected European Data Sources

Feature	CPRD	THIN	ISD Scotland	GePaRD
Fact of death	Yes, as recorded by GPs and partial linkage to ONS	Yes, as recorded by GPs, minimum linkage to ONS	Yes, through linkage to ONS	Yes
Cause of death	Yes, as recorded by GPs and partial linkage to ONS	Yes, as recorded by GPs, minimum linkage to ONS	Yes, through linkage to ONS	No
Approximate time lag for data entry after health care use	6-12 weeks HES/ONS data: 1+ year	6 months	6 months	1.8-2.0 years
Frequency of updates	3-4 updates per year HES/ONS data: 2 updates per year	Continuously	Continuously	Annually; participating SHIs provide data at different times
Overlap with other study data sources	~10% in Scotland ~53% are also THIN practices	~15% in Scotland ~66% are also in CPRD	Not estimated	Not applicable
Approval process for database research	Independent Scientific Advisory Committee approval of protocol is required	South East Multicentre Research Ethics Committee approval is required	Reviews by Multicentre Research Ethics Committee and by a Caldicott Guardian are requested	Approvals by SHI and the German Federal Insurance Authority are required

ATC = Anatomical Therapeutic Chemical; CPRD = Clinical Practice Research Datalink; EBM = Einheitlicher Bewertungsmaßstab (codes); GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; HES = Hospital Episode Statistics (database); ICD-10 = *International Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*; *and Related Health Problems;* ICD-10-GM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification*; ISD = Information Services Division (Scotland); ONS = Office for National Statistics (UK); OPS = Operationen- und Prozedurenschlüssel (Germany); SHI = statutory health insurance provider (Germany); THIN = The Health Improvement Network (UK); UK = United Kingdom.

a Ongoing development of linkage to HES and other data sources; such linkage is expected to expand over the next 2 years.

The study period will start at the time of first availability of prucalopride within each country. The end of the study period will vary by data source, depending on the lag time for capturing medication and outcomes. Each included patient will be required to have a minimum of 12 months of medical history available in the data source prior to the index date for assessment of patient characteristics that could act as potential confounders.

3.2.2 Study Cohorts: Selection Criteria

The prucalopride cohort will be formed by patients who have a dispensing or prescription for prucalopride, at least 12 months of data in the data source prior to the first dispensing or prescription, and no evidence of prior use of prucalopride in the data source. The first prescription of prucalopride will be the index prescription, prescribed or dispensed on the index date.

The PEG cohort will be selected from patients who have a prescription or dispensing for PEG, at least 12 months of data in the data source prior to the first dispensing or prescription, and no evidence of prior use of PEG in the data source. The first prescription for PEG will be the index prescription, prescribed or dispensed on the index date. Up to 5 PEG initiators will be selected for each prucalopride initiator, matched by age category, sex, and calendar year of first prescription of prucalopride or PEG. Currently, PEG is the most commonly prescribed medication for chronic constipation in the EU.

Other alternative therapies—lubiprostone, licensed in the UK but not launched, and linaclotide, launched in the UK and Germany in May 2013—would not yield sufficient numbers of patients for a comparator cohort.

The inclusion criteria are as follows:

- Prescribed or dispensed prucalopride or PEG.
- Have at least 12 months of data in the data source prior to the index date.
- In the CPRD or THIN, must be registered with the participating GP at least 12 months before cohort entry.

The exclusion criteria are as follows:

- Individuals with less than 1 year of data available prior to the index date.
- Individuals aged less than 18 years at the time of first prucalopride or PEG prescription or dispensing
- Individuals whose first prucalopride or PEG prescription or dispensing is for 4 or fewer days; these patients may be receiving treatment for acute constipation or procedural preparation.

Because all populations are of interest, regardless of cardiovascular risk profiles, patients with prior history of the events of interest will be included in the study cohorts. PEG cohort

members will be matched to the prucalopride cohort members by sex, 5-year age category, and calendar year of index date, in a ratio of up to 5 PEG initiators to 1 prucalopride initiator. PEG initiators will be matched to prucalopride initiators by applying greedy matching techniques within each category. New users are individuals starting a study medication for the first time, although they may have had the other study medication in the past. Switching from one study medication to another, if both meet the definition of new user, is permitted in this study. Individuals in the PEG cohort who switch to prucalopride will enter the prucalopride cohort at the time of the switch; members of the prucalopride cohort who switch to PEG will be eligible to be selected for the PEG cohort.

Preliminary data from THIN show that from January 2010 through September 2012, there were 376 prucalopride initiators and more than 149,000 users of PEG (see Annex 1; data on file, Shire). Among the 376 prucalopride initiators aged 18 years and older, approximately 15% had no recorded constipation diagnosis ever before initiating prucalopride, and 43% had no recorded constipation diagnosis in the year before initiating prucalopride; therefore, to enable inclusion of all prucalopride patients, a diagnosis of constipation will not be used as an inclusion criterion for this study. The large number of PEG initiators will make it quite feasible to select and match to the prucalopride initiators on sex, age category, and calendar year of index date. The 5:1 matching ratio will be used instead of a lower ratio because the pool of patients exposed to PEG is large and the larger ratio will result in better precision around the estimates.

During the pilot phase, the number of individuals excluded and reasons for exclusion will be tabulated, and the comparability of the prucalopride and PEG cohorts will be evaluated. If the frequency of codes for constipation, irritable bowel syndrome (IBS), colonoscopy, and other gastrointestinal morbidities differs substantially between the two cohorts, an alternative exclusion and/or matching strategy to make the cohorts more similar may be considered.

3.3 Exposure Assessment

Time at risk is designed and defined for acute outcomes. **Time at risk from current use** for prucalopride initiators and PEG initiators is defined to start on the day of prescription or dispensing and continue through the days of supply of prucalopride or PEG plus 7 days. Overlapping time at risk from current use for consecutive prescriptions of the index medication will be concatenated, with the overlapping time counted only once. For consecutive prescriptions of the index medication separated by gaps of 7 days or less, time at risk from current use will include the gaps between prescriptions.

For consecutive prescriptions of the index medication separated by gaps greater than 7 days between the end of days' supply of one prescription and the start of the next prescription, time at risk from current use will include the first 7 days of the gap. Time at risk from current use will begin again if a patient re-starts a drug after a gap in use greater than 7 days. A sensitivity analysis will define the time at risk from current use as the duration of the prescription plus 30 days.

For the primary analysis, time at risk from current use will be cumulative across all prescriptions of the index medication (e.g., time at risk from current use will begin again if a patient re-starts a drug after a gap in use of more than 7 days).

Accrual of time at risk of current use for a study medication will be terminated if there is a prescription or dispensing for the other study medication. Time at risk will no longer accrue beyond the date of any of the following criteria:

- 7 Days after the end of the last prescription/dispensing for the index medication
- Death
- First occurrence of the endpoint under evaluation during the time at risk
- Termination of enrollment in the health plan or system
- End of study period

Use of nonstudy medications (including those for constipation) will not affect analysis of prucalopride use and PEG use. Use of only nonstudy medication will be irrelevant to exposure to the study drugs.

Sensitivity analyses relating to exposure definitions are the following:

- To explore the impact of a longer extension of the period of time at risk, the end of time at risk will be calculated at the end of the last prescription plus 30 days.
- To explore potential impact of channeling bias, individuals with a prescription for either prucalopride *or* PEG in the 12 months prior to the index date will be excluded. It is expected that many if not most of those prescribed prucalopride will have previously been prescribed PEG because the Summary of Product Characteristics states that prucalopride "is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief" (Shire Pharmaceuticals, 2009).
- To explore the impact of potential depletion of susceptibles during follow-up after the first treatment episode (e.g., individuals at risk of an event might discontinue treatment early; therefore, individuals who continue treatment may have lower risk), a sensitivity analysis will be performed on MACE risk (MACE only) at treatment initiation. For this analysis, exposure time at risk will be limited to the first treatment episode (i.e., up to the first gap longer than 7 days), follow-up will be censored at the first medication switch (in addition to other proposed censoring criteria), and no switching between cohorts will be permitted.

If a subject switches from one study medication (medication A) to the other study medication (medication B) for the first time ever, overlap of exposure may occur. Individuals who switch from PEG to prucalopride will enter the prucalopride cohort. Individuals who switch from prucalopride to PEG are eligible to be selected for the PEG cohort. Overlapping exposure, that is, simultaneous exposure to both medications that meets the criteria for current exposure, is not included in the primary analysis, nor is switching to a nonstudy medication. A sensitivity analysis will include the person-time and events during overlapping exposures in

both study cohorts.The start date of the overlap will be the first prescription or dispensing date of the second study medication; the end date will be the earlier of the following: 7 days after the estimated end date for the last prescription of medication A or 7 days after the first prescription or dispensing date for medication B.

Time at risk from past use includes all person-time after the index date that is not considered time at risk from current use. Follow-up during gaps in treatment (i.e., from the end of the time at risk from current use associated with a given prescription until next prescription or dispensing date) will be considered time at risk from past use. Time at risk from past use will start on the day after the end of time at risk from current use and will end at the earliest of the following termination criteria:

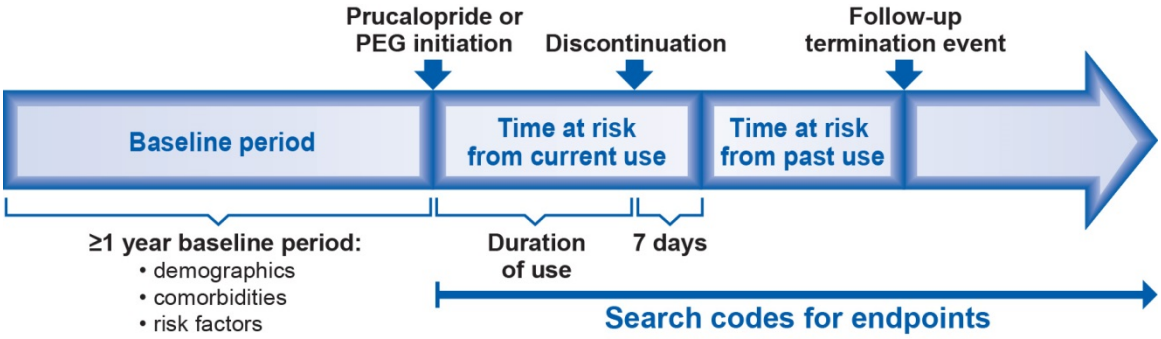
- Prescription for the other study medication
- Death
- First occurrence of the endpoint under evaluation
- Termination of enrollment in the health plan or system
- End of study period

An additional sensitivity analysis will include all observation time meeting criteria for time at risk from current use or time at risk from past use.

Discontinuation of use is defined as the estimated end of the last prescription or dispensing of index medication, i.e., without the 7-day extension considered time at risk from current use. Use of another medication for constipation does not affect the estimated time of discontinuation.

Figure 1 summarizes the time periods of patient observation, including those for calculating time at risk from current use of a study medication.

Figure 1: Patient-Level Observation Period Definitions



PEG = polyethylene glycol 3350.

3.4 Study Endpoints

3.4.1 Primary Composite Cardiovascular Endpoint in all Data Sources

The main composite cardiovascular endpoint of interest, MACE, will include the first occurrence of any of the following individual components during the follow-up:

- Hospitalization for nonfatal AMI or
- Hospitalization for nonfatal stroke or
- In-hospital cardiovascular death

Due to the lack of information on cause of out-of-hospital deaths and lack of information on outpatient diagnoses in some of the selected data sources, endpoints will include only hospitalizations for AMI and for stroke, and cardiovascular deaths will be assessed from hospital discharge diagnoses. This approach follows FDA recommendations for consistent classification, that is, that the ascertainment of homogenous events across all selected data sources is preferable to defining endpoints based on the maximum available information in each data source.

Because the vast majority of individuals with AMIs and stroke events are hospitalized for diagnosis and clinical management, and specific hospital discharge codes have a high positive predictive value (PPV) (see details in Section 3.4.4), many database studies conducted in North America and Europe have historically ascertained these events through hospitalizations.

3.4.2 Exploratory Endpoint in Selected Data Sources

Approximately one-third of individuals with AMIs and stroke events will die suddenly before being hospitalized. Therefore, in data sources with information available on cause of death for out-of-hospital deaths (CPRD, THIN, ISD Scotland), sensitivity analyses (see Section 3.8.3). will include an exploratory composite endpoint comprised of MACE plus out of hospital CV deaths. This endpoint has been extensively used in prior pharmacoepidemiology studies (García Rodríguez et al., 2004; Graham et al., 2005; Ray et al., 2009; Roumie et al., 2008b; Varas-Lorenzo et al., 2009) for regulatory submissions.

3.4.3 Endpoint Identification

For the assessment of each individual endpoint, only the first event of that specific endpoint occurring during follow-up will be included. For assessment of the composite endpoints, only the first of any of the individual components occurring during follow-up will be included. Table 2 summarizes the individual components that will be included in each of the composite cardiovascular endpoints of interest and the data sources within which each can be ascertained.

Table 2: Summary of Endpoints and Data Sources With Relevant Information

Individual Endpoints and Data Source		
Hospitalizations	In-hospital cardiovascular deaths	Out-of-hospital deaths (for sensitivity analyses)
1. Nonfatal AMI 2. Nonfatal stroke	3. Death due to AMI 4. Sudden cardiac death 5. Death due to heart failure 6. Death due to stroke 7. Cardiovascular procedure–related death 8. Death due to cardiovascular hemorrhage 9. Other cardiovascular causes	10. Deaths with underlying CHD cause, including AMI and SCD 11. Deaths with underlying cerebrovascular disease cause
Databases: CPRD, THIN, ISD Scotland, GePaRD	Databases: CPRD, THIN, ISD Scotland, GePaRD	Databases: CPRD, THIN, ISD Scotland

Composite Endpoints[a]	
Primary cardiovascular endpoint: • MACE endpoint (1-9)	Exploratory endpoint for sensitivity analysis: composite of the primary cardiovascular endpoint (MACE, 1-9) and OOH CV deaths (10-11)

AMI = acute myocardial infarction; CHD = coronary heart disease; CPRD = Clinical Practice Research Datalink; CV = cardiovascular; GePaRD = German Pharmacoepidemiological Research Database; ISD = Information Services Division; MACE = major adverse cardiovascular event; OOH = out-of-hospital; SCD = sudden cardiac death; THIN = The Health Improvement Network.

a Numbers in parentheses indicate the individual endpoints in the upper portion of the table that make up the composite endpoint.

3.4.4 Case Ascertainment

The following steps will be performed to identify the endpoints of interest:

1. Each data source will be searched for electronic codes that indicate the possibility of an endpoint of interest (Table 3).
2. For GePaRD patients and for CPRD and THIN patients linkable to HES, those potential events ascertained through hospital discharge diagnoses will be considered confirmed if the primary hospital discharge diagnosis codes are consistent with the codes listed in Table 3 and the admission code does not indicate a noncardiovascular reason for admission. For ISD Scotland and linkable CPRD and THIN patients, in-hospital CV death will be considered confirmed if cause-of-death codes from the national death register are consistent with the codes in Table 3.
3. For patients in ISD Scotland, CPRD, and THIN whose data are not linkable to HES or ONS, further clinical and other information for case validation will be obtained via (1) local investigator clinical review of electronic patient profiles (e.g., database listings of outpatient visits, procedures, and medications) and (2) questionnaires sent to the GP. The GP may provide clinical data required to classify the event or may simply confirm that the event occurred and that appropriate testing or intervention was performed. For CPRD and THIN, in the past it has been possible to also examine free-text comments that sometimes contain referral reports and autopsy reports; these have been obtained by applying for the conduct of a search with prespecified terms. Availability of free-text comments throughout the study period is currently uncertain. In the event that free text is not available for research, additional questionnaires to be completed by the GP may be required.
4. A committee of 3 clinicians blinded to exposure will review all available information for each potential event and classify the event as a confirmed, probable, or possible case or a nonevent.

Table 3 presents descriptions of the algorithms for case finding of each endpoint. The algorithm to be applied for each endpoint is based on information from prior published and validated case ascertainment algorithms to maximize case ascertainment sensitivity while retaining those with a high PPV.

Table 3: Summary of Case Finding Algorithms for Each of the Endpoints of Interest

Hospitalizations for AMI	Hospitalizations for Stroke
Case finding: ICD-10 hospital discharge codes for all data sources	
(Joensen et al. (2009); Pajunen et al. (2005))	(Andrade et al. (2012); Flynn et al. (2010); Kirkman et al. (2009); Kokotailo and Hill (2005); Krarup et al. (2007); Roumie et al. (2008a))
• I21, Acute myocardial infarction	• I60, Subarachnoid hemorrhage • I61, Intracerebral hemorrhage • I63, Cerebral infarction • I64, Stroke, not specified as hemorrhage or infarction
Hospitalizations for AMI	**Hospitalizations for Stroke**
Case finding for THIN, CPRD (without HES linkage): Read codes, electronic patient profiles, free-text search	
(Fireman et al. (2012); García Rodríguez et al. (2004); Hammad et al. (2008b); McAlpine et al. (1998); Varas-Lorenzo et al. (2000))	(Andersohn et al. (2006); Arana et al. (2006); Gaist et al. (2013); Ray et al. (2009); Roumie et al. (2008a); Ruigómez et al. (2010))
AMI/chest pain Read code with hospitalization and documentation that any of the following occurred:[a] • Record of ECG or location of infarction • Death within 1 month • Coronary revascularization procedure (i.e., CABG or stent) • Positive cardiac enzymes recorded • Thrombolytic therapy	Stroke Read code AND hospitalization and any of the following [a] : • Record of CT, NMR, EEG, or location of infarction • Death within 1 month • Stroke-related surgery/procedure • Thrombolytic therapy • Evidence of residual damage – Paresis, numbness – Speech, vision, swallowing problems – Rehabilitation or physiotherapy

Table 3: Summary of Case Finding Algorithms for Each of the Endpoints of Interest

In-hospital deaths, by cause of death[b]	
Case finding: ICD-10 codes to be applied to all data sources	
Hicks et al. (2012)	
AMI	Stroke
I21, I22, I23, I24.1, I51.0-I51.3	I60-I61, I63-I64, I69.0-I69.1, I69.3-I69.8, G45
SCD	Cardiovascular procedures
I46.1-I46.9, I47.0-I47.2, I49.0, R96.1, R98	List of codes to be developed according to each database dictionary
Heart failure	Cardiovascular hemorrhage
I50, J81, I11.0; I13.0, I32.0	I31.2, I62, I69.2; I71.1; I71.3; I71.5; I71.8
Other cardiovascular causes	
I00-I09, I10, I11.9, I15, I30-I43, I20, I25, I26, I30, I33-I39; I40-I41; I42-I43; I44-I45; I47.1, I47.9; I49.1-I49.9; I51.0-I51.9; I70-I79; R57.0	
Coronary and cerebrovascular deaths out of the hospital, for sensitivity analyses	
Case finding: underlying cause of death by ICD-10 in CPRD (ONS) and ISD Scotland (mortality registry) and Read codes in CPRD and THIN (ICD-10 codes to be mapped to Read codes)	
AMI/CHD death, including SCD	Stroke deaths
Chung et al. (2010)	Muller-Nordhorn et al. (2008)
I10, I11.9, I20-I24, I25, I42.8-I42.9, I46, I47.0-I47.2, I49.0, I49.8-I49.9, I51.6, I51.9, I70.9, R96.1, R98	I60-I69, G45, R96.0, R96.1, R98

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD= coronary heart disease; CPRD = Clinical Practice Research Datalink; CT = computed tomography; ECG = electrocardiogram; EEG = electroencephalogram; HES = Hospital Episode Statistics; ICD-10 = I*nternational Classification of Diseases and Related Health Problems, 10th Revision*; ISD = Information Services Division; NMR = nuclear magnetic resonance (image); ONS = Office for National Statistics (United Kingdom); SCD = sudden cardiac death; THIN = The Health Improvement Network.

[a] Exact time windows will be determined after patient profiles have been reviewed.

[b] Codes were selected by study investigators based on diagnoses listed in Hicks et al. (2012).

Note: When a fourth digit is not specified for an ICD-10 code, all subcategories of that code are included.

Definitions and more information on data source–specific case ascertainment processes for each outcome can be found in Annex 2:

- Hospitalizations for nonfatal AMI
- Hospitalizations for nonfatal stroke
- In-hospital cardiovascular deaths
- Out-of-hospital cardiovascular and cerebrovascular deaths

3.4.5 Case Validation Process

Validation of MACE as defined for this study is not of significant concern because the PPV for cardiovascular disease codes is documented to be high in Europe and North America, independent of the health care system, up to 96% for AMI (Kiyota et al., 2004; Varas-Lorenzo et al., 2008) and up to 80% for stroke (Roumie et al., 2008a). Nevertheless, in data sources where medical record review is feasible in this study (CPRD, THIN, ISD Scotland), validation via medical record review or linkage to the HES and ONS will be conducted for all identified potential cases.

The following sections describe the processes available to obtain additional information on the endpoints of interest, by data source. After available information has been requested, all available information on each potential case will be compiled. A common validation plan will be developed in collaboration with participating research centers.

3.4.5.1 United Kingdom

In the UK (CPRD, THIN, and ISD Scotland), the GPs work within the NHS and are the first point of contact for the patients enrolled into their practices. Therefore, the GP is informed of all visits to the hospital, including emergency department visits and visits to specialists. As with emergency department visits, it is expected that information from patients who attend chest pain units would be reported to the GP and entered into the patient GP record, which makes up the data for CPRD and THIN.

CPRD/THIN

Potential study cases linkable to HES and ONS will be confirmed according to the prespecified set of ICD codes and criteria for case ascertainment. HES in England provides reliable ascertainment of hospital admissions for ischaemic heart disease (ICD-10 codes I20-I25), cerebrovascular disease (G45, I60-I69), or venous thromboembolism (I26, I80-I82) (Wright et al., 2012). For 89% of HES-ascertained myocardial infarction (I21-I22) and for 89% of HES-ascertained stroke (both overall [I60-I64] and by subtype), the specific CV diagnoses of interest in HES were confirmed by GPs. Only 1 of 864 women with no HES record of hospitalization was reported to have been admitted, according to the GP record. These events will be identified by using specific ICD codes validated in other data sources (Roumie et al., 2008a; Varas-Lorenzo et al., 2008).

For potential study cases in the CPRD or THIN not linkable to HES and ONS, we will follow a sequential approach in several steps.

1. Using Read codes, we will apply previously validated algorithms to identify acute cardiovascular events of interest and CV deaths. The PPV of the Read/OXMIS codes for AMI has been reported to be approximately 93% (95% CI, 90%-96%) (Hammad et al., 2008b). For ischemic stroke, the PPV has been reported to be approximately 86% (95% CI, 79%-91%) using THIN (Ruigómez et al., 2010).
2. Manual review of patient profiles will follow to classify potential events and causes of cardiovascular deaths in the following categories according to the level of certainty:

confirmed, probable, and possible cases and noncases. Patient profiles are chronological listings of the diagnoses, clinical tests, procedures, and medications recorded in the electronic database. As is typical for such studies, a clinician investigator blinded to the exposures of interest will review and screen all the patient profiles, including available free-text annotations, to screen out obvious noncases.

3. Additional linkage to more detailed free text surrounding the potential event date, which frequently contains original clinical and laboratory reports, will be requested. In the CPRD and THIN, the review of free-text comments improves validity (Ruigómez et al., 2010). For deaths, the free-text information can be used to retrieve causes of death and relevant clinical history recorded by the GPs. If free text is not available, this step will be omitted.
4. For each potential case that has passed the initial clinical screening, questionnaires will be sent to the GP. Previous pharmacoepidemiologic studies of AMI and stroke in the CPRD and THIN have conducted partial or overall validation of these endpoints through questionnaires sent to the corresponding GPs for access to information related to the event of interest, including hospital discharge letters (Andersohn et al., 2006; Arana et al., 2006; García Rodríguez et al., 2004; Varas-Lorenzo et al., 2000).
5. For fatalities, autopsy reports or death certificates, as available from the GPs, will be used to determine the cause of death. Death certificates can be obtained by special request for those fatal cases with recorded unavailable/unknown cause of death; these usually require 4 to 8 weeks for retrieval, with a response rate of approximately 80%.

ISD Scotland

All potential cases will be identified via the hospitalization discharge diagnosis codes and linkage to the national death register. Original hospital records will be obtained to validate the outcomes in accordance with the criteria listed in Table 3 and reviewed by a clinical cardiologist for evaluation of potential cases.

During the conduct of a large randomized study of pravastatin versus placebo conducted in western Scotland, outcome data were collected prospectively by clinical investigators and by record linkage to ISD Scotland (The West of Scotland Coronary Prevention Study Group, 1995). The record linkage system identified 94% of events reported by investigators (1,043 of 1,109) and investigators ascertained 88% of events identified through the record linkage system (1,043 of 1,180). Among the 58 deaths reported by investigators, all were identified by the record linkage system and 56 were matched by cause of death.

More specific publications have shown algorithms based on one of the hospitalization codes to be applied in this study have high PPV (92%) (McAlpine et al., 1998). For stroke, the PPV was 90% or better over the three events evaluated: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (Flynn et al., 2010).

3.4.5.2 Germany (GePaRD)

Hospitalization data are complete in the GePaRD. Cardiovascular endpoints, including hospital deaths, will be identified and ascertained by the following steps:

1. Potential cases will be identified using the ICD-10-GM codes.
2. Demographics and comorbidities of AMI and stroke patients will be examined and checked for consistency of health care use with the endpoint suggested by the diagnosis code(s).
3. Patient profiles of all potential cases will be examined and checked for plausibility. This review will include inpatient and outpatient diagnoses (ICD-10-GM codes), inpatient procedures and therapies (OPS codes), and outpatient services and procedures (EBM codes). The main discharge diagnosis will be used to identify AMI and stroke because this code indicates the reason for the hospitalization episode. For stroke, imaging and/or surgical procedures (hemorrhagic stroke) in the hospital will also be used to ascertain acute events. This approach has been used successfully in a study on anticoagulants and hemorrhagic stroke (Behr et al., 2010).

In this data source, fact and date of out-of-hospital deaths are available but not cause of death. Only hospital deaths (occurring within 30 days after hospital discharge) by cardiovascular cause, identified by discharge diagnosis, will be ascertained.

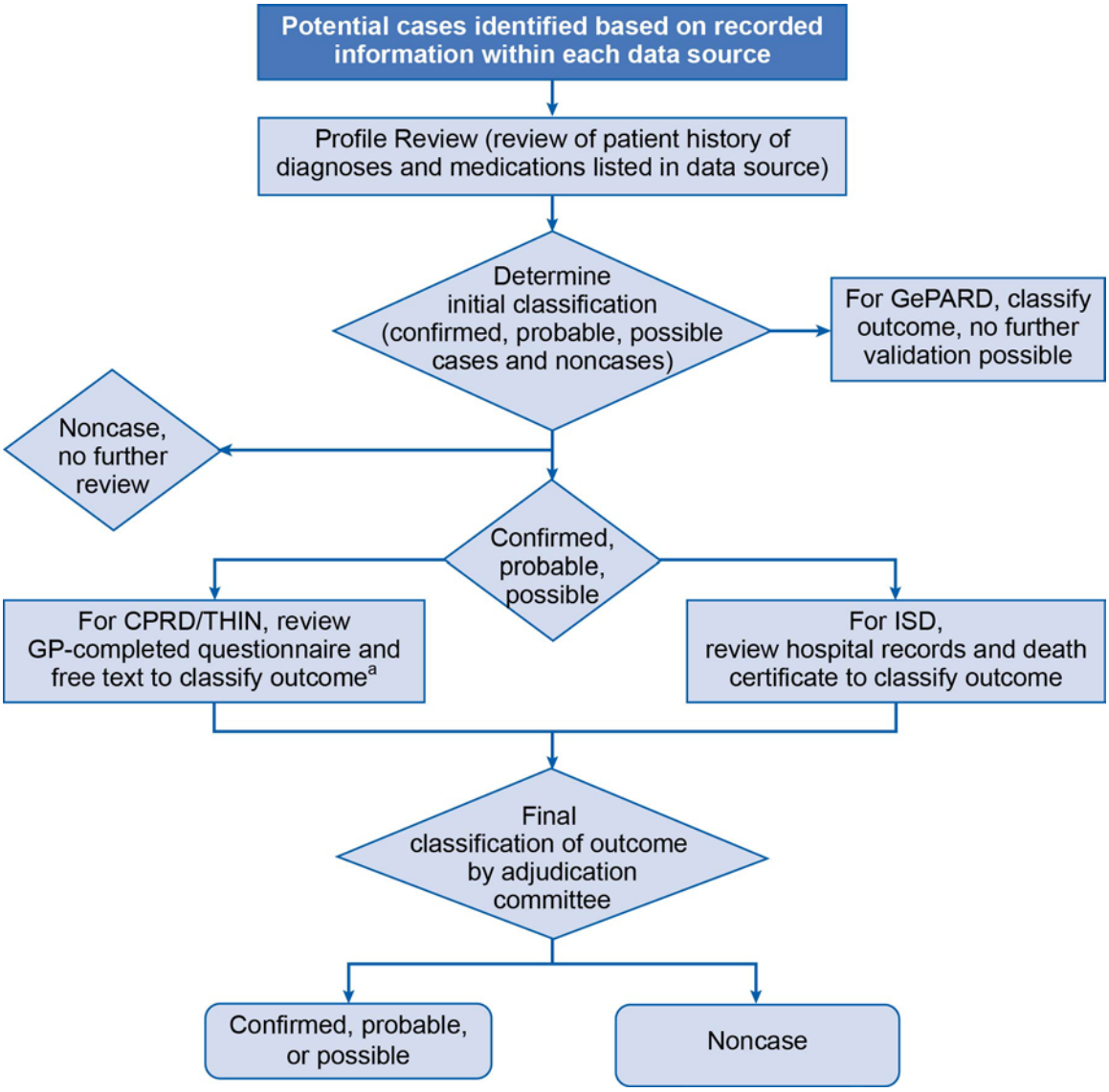
In the GePaRD, validation of events through review of medical sources (i.e., hospital charts) is not possible. Benchmarking of the age-stratified incidence of cardiovascular outcomes in European data sources used in the European Commission Framework Programme VII Safety of Non-Steroidal Anti-Inflammatory Drugs project yielded event rates in the GePaRD similar to those in other European data sources (for example studies, see the project's publications page, http://www.sos-nsaids-project.org/?q=content/publications).

3.4.6 Final Case Adjudication Process

The case adjudication process will be described in detail in the validation plan. In summary, a common set of criteria for clinical review and classification of each identified potential event will be developed, with more details for the criteria listed in Table 3. All information for each potential case, including patient database profiles, free-text entries, completed GP questionnaires, and electronic copies of other medical records, will be blinded to exposure, and all identifying information will be redacted. Three clinical reviewers with experience in evaluating endpoints for population-based health care database studies will review all available event-related information and adjudicate each potential case. The reviewers will discuss together and classify the potential cases they did not agree on during the initial classification.

Figure 2 provides an overview of the validation process for potential cases that cannot be linked to HES or ONS.

Figure 2: Case Validation Process for Potential Cases That Cannot be Linked to National Hospital Files or to National Death Files



CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; ISD = Information Services Division.

[a] If free text is not available, this step will be omitted.

3.5 Other Variables

The availability of data on other variables to characterize study subjects will vary by data source. Outpatient diagnoses will be available for the CPRD and THIN before the index date and for the GePaRD before the calendar quarter of the index date. In general, in database analyses, the absence of information, such as an outpatient diagnosis, is classified as the absence of the condition. All subjects without a dispensing for a medication are considered

unexposed, and all subjects without a diagnosis are considered as not having the condition. The following variables of interest will be used in analyses:

- Demographic variables on the index date
  - Age (based on date of birth)
  - Sex
- Exposure characteristics
  - Number of prescriptions or dispensings of prucalopride and of PEG
  - Duration of use of prucalopride and of PEG
- Diagnoses and medication use that indicated the presence of cardiovascular risk factors at any time in the data source on or before cohort entry date
  - Procedures and outpatient diagnoses or inpatient procedures and diagnoses that indicate a history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, or coronary or cerebrovascular revascularization
  - Outpatient or inpatient, when available, medications that indicate history of cardiovascular disease (e.g., thrombolytics, anticoagulants)
  - Hyperlipidemia (defined via outpatient or inpatient diagnosis code or dispensing for lipid-lowering medication)
  - Hypertension (defined via outpatient or inpatient diagnosis code or dispensing for antihypertensive medications)
  - Obesity (defined via outpatient or outpatient diagnosis codes and recorded weights and heights or body mass index [in the CPRD and THIN only, albeit inconsistently])
  - Diabetes (defined via outpatient or inpatient diagnosis codes or antidiabetic medications)
  - Chronic renal injury (defined via outpatient or inpatient diagnosis codes)
  - Smoking (recorded in the CPRD and THIN only, albeit inconsistently)
  - Smoking-related disease (e.g., outpatient diagnosis or inpatient diagnosis code for chronic obstructive pulmonary disease)
  - History of cancer diagnosis (excluding non-melanoma skin cancer) or treatment
  - Indicators of cardiovascular risk factors on or before cohort entry
- Measures of gastrointestinal disease
  - Number of medical visits with constipation listed as a diagnosis before the index date
  - Patterns of use of specific medications often prescribed for constipation before the index date
  - Presence and number of other outpatient and inpatient gastrointestinal diagnoses before the index date

  - Number of IBS diagnoses on or before the index date
  - Colonoscopy or similar procedure during the first 21 days of follow-up
- Prescription or dispensing for opioid medications in 6 months before cohort entry
- History of chronic opioid use (more than 1 prescription or dispensing for and opioid in the 12 months before cohort entry)
- Prescription or dispensing for diuretic in 6 months before cohort entry
- Any hospitalization, regardless of diagnosis, of more than 7 days' duration in the 14 days before cohort entry (because constipation is related to long periods of immobility)
- Surrogates for general health, e.g., number of outpatient visits in the last 12 months and number of hospitalizations in the last 12 months
- Socioeconomic status or deprivation measures (Townsend index, or geographic code linkable to Townsend index), available in the UK

3.6 Study Size and Statistical Power

The study size will be driven by the number of prucalopride initiators and duration of exposure that will be available in the selected data sources during a defined study period. Table 4 describes published MACE rates from the planned data sources. Prucalopride initiators already identified in THIN in the UK suggest that the study cohorts will be predominantly women aged younger than 60 years. Given the published background rates in this demographic group (Table 4), the incidence rate can be expected to be approximately 1 per 1,000 person-years for AMI and approximately 0.5 per 1,000 person-years for stroke.

Table 4: Published Rates of Study Endpoints in the Data Sources to be Included in the Study

Data Source and Reference	Outcome	Population	Rate per 1,000 Person-years
ISD Scotland			
(1)	AMI incidence in record linkage system, 2011-2012	Females aged 45-64 years	1.2
(2)	Cerebrovascular disease incidence in record linkage system, 2011-2012	Females aged 45-64 years	1.5
(3)	Coronary heart disease deaths (location unspecified), 2011	Females aged < 75 years; lower age limit unspecified	0.22

Table 4: Published Rates of Study Endpoints in the Data Sources to be Included in the Study

Data Source and Reference	Outcome	Population	Rate per 1,000 Person-years
CPRD			
Walters et al. (2008) comparator cohort matched to subjects with panic disorder	AMI incidence	Females (age) • 16-39 years • 40-49 years • 50-59 years • 60-69 years • ≥ 70 years	 0.05 0.4 1.4 4.8 9.9
		Males (age) • 16-39 years • 40-49 years • 50-59 years • 60-69 years • ≥ 70 years Overall	 0.3 1.9 4.5 9.4 15.2 2.1
Varas-Lorenzo et al. (2000)	AMI incidence	Women, aged 50-74 years • Never HRT users • Ever HRT users	 1.8 1.2
	Transient ischemic attack (58% of cases), ischemic stroke, hemorrhagic stroke	Women (age) • 50-59 years • 60-69 years Overall women	 0.7 2.3 1.3
Walters et al. (2008)	In-hospital coronary heart disease death	Females (age) • 16-39 years • 40-49 years • 50-59 years • 60-69 years • ≥ 70 years Males (age) • 16-39 years • 40-49 years • 50-59 years • 60-69 years • ≥ 70 years Overall	 0.02 0.15 0.5 2.7 8.9 0.07 0.6 1.6 5.4 15.6 1.4

Table 4: Published Rates of Study Endpoints in the Data Sources to be Included in the Study

Data Source and Reference	Outcome	Population	Rate per 1,000 Person-years
THIN			
Schink et al. (2011)	Stroke (hospitalization or outpatient diagnosis)	All ages and sexes, standardized (includes children)	1.2
GePaRD			
Schink et al. (2011)	Stroke (hospitalization or outpatient diagnosis)	All ages and sexes, standardized (includes children)	1.8
Behr et al. (2010)	Intracerebral hemorrhage (hospitalization diagnosis)	Females (age) • < 55 years[a] • 55-64 years • 65–74 years Males (age) • < 55 years[a] • 55-64 years • 65-74 years	 0.047 0.23 0.48 0.068 0.46 0.90

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; HRT = hormone-replacement therapy; ISD = Information Services Division; THIN = The Health Improvement Network.

(1) Source: http://www.isdscotland.org/Health-Topics/Heart-Disease/ (accessed May 12, 2013). Heart Disease Statistics Update. Year Ending March 31, 2012. Publication date–December 18, 2012. Table IC2.

(2) Source: http://www.isdscotland.org/Health-Topics/Stroke/ (accessed May 23, 2013) Stroke Statistics Update. Year Ending March 31, 2012, Publication date–December 18, 2012. Table IS1.

(3) Source: http://www.isdscotland.org/Health-Topics/Heart-Disease/ (accessed June 7, 2013). Heart Disease Statistics Update. Year Ending March 31, 2012. Publication date–December 18, 2012. Table MC2.

a Lower age limit unspecified.

To estimate the expected power, we used an expected incidence for the primary combined cardiovascular endpoint (MACE) of 2 per 1,000 person-years. Table 5 shows the number of prucalopride initiators and the person-years needed to have 80% power to reject various hypotheses regarding the risk ratio (RR) at the two-sided alpha = 0.05 level if the true RR is 1.0. The number of prucalopride initiators was based on an average current use follow-up time for prucalopride initiators of 130 days. Calculations were made using the formulas in Episheet (Rothman, 2011). A cohort size of 10,950 prucalopride initiators should be sufficient to provide 80% power to reject the hypothesis that the RR is greater than 3 assuming the true RR is actually 1.0.

With the specified data sources, it is estimated that there will be 5,035 prucalopride initiators available for the pilot phase and 11,150 available for the study report (see Annex 3). After completion of this analysis, it is Shire's intention to submit the results with the prucalopride New Drug Application. The collaboration will continue to investigate the inclusion of

additional data sources to increase the statistical power (decrease the standard error of the RR) of the study.

Future analyses and the ability to add US data sources post approval will result in a study size greater than 27,490, which is expected to establish that the IRR is less than 2.0 (see Annex 4). As previously mentioned, it is expected that a large number of additional prucalopride initiators will be identified in the US data sources.

Table 5: Number of Prucalopride Initiators and Total Number of Events (Both Treatments) Needed for the Primary Analysis to Have 80% Power to Reject Various Hypotheses Regarding the RR at the Two-Sided Alpha = 0.05 Level; Incidence of Combined Endpoints in the PEG Cohort is 2 per 1,000 Person-years, Assuming the True RR is 1.0

	Hypotheses				
	RR ≥ 1.5	**RR ≥ 2**	**RR ≥ 2.5**	**RR ≥ 3**	**RR ≥ 4**
Number of prucalopride initiators	80,270	27,490	15,720	10,950	6,880
Expected total number events (both treatments)	343	117	67	47	29
Minimum number of person-years	28,589	9,791	5,599	3,900	2,450

PEG = polyethylene glycol 3350; RR = risk ratio.
Matching ratio of 5:1 PEG to prucalopride; average duration of current use time at risk = 130 days.
For alternative scenarios, please see Annex 4.
Note that number of events depends on number of subjects and duration of follow-up.

3.7 Data Collection and Management

In accordance with local privacy laws, all research centers hold the patient-level data. This means that patient-level data from THIN, GePaRD, and ISD Scotland will be held outside the coordinating center and cannot be provided to another party for combining results across all data sources.

Each research center will create the patient-level analysis variables from the health care data available by following the protocol and SAP. Research center–specific differences in local diagnosis and medication codes will be documented in a data development plan. Research centers will generate tabulated output without patient-specific data in a format specified in the SAP, and this output will be provided to the coordinating center via secure electronic data transfer. The coordinating center will combine research center–specific estimates into pooled estimates in accordance with the SAP.

Routine procedures at each research center will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programs. Each data source custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures.

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 select study staff. A mechanism for FDA staff to analyze anonymized data will be made available at each research site.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research center to restore files in the event of a hardware or software failure.

3.8 Data Analysis

Database-specific analyses implemented by collaborating research centers will be conducted using SAS version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) for the CPRD and GePaRD data; Stata 12 (StataCorp LP, College Station, Texas) will be used for THIN data. All analyses implemented by the coordinating center will use SAS version 9.3 or higher.

3.8.1 Descriptive Analyses

Descriptive analyses will be included in the pilot and study reports. The number of excluded prucalopride subjects and reasons for exclusion will be enumerated. Within each data source, the following characteristics of all variables of interest (see Section 3.5) will be described for each cohort: (1) for categorical variables, the proportion within each level; (2) for continuous variables, the mean and standard deviation, minimum, maximum, median, and quartiles. (See Section 3.8.2.4 for a description of the combined descriptive analyses.)

3.8.1.1 Characterization of MACE Cases

The numbers of patients identified as individuals falling into each category of the endpoints of interest will be summarized. Categories of interest are the final case classification and sources of information utilized to reach the classification (e.g., HES linkage, ONS linkage, patient profiles only, or original GP or hospital records). Recent history, i.e., shortly before the event, of cardiovascular risk factors will also be characterized.

3.8.2 Primary Analysis

3.8.2.1 By Data Source and by Endpoint

For the primary analyses, only confirmed MACE cases will be included. Secondary outcomes of interest are confirmed individual components of MACE: hospitalization for AMI, hospitalization for stroke, and in-hospital cardiovascular death.

Within each data source and for each endpoint, the crude incidence rate within the prucalopride and PEG cohorts will be derived as follows:

$$\frac{\text{Number of cases occurring during time at risk from current use}}{\text{Total time at risk from current use (person-years)}}$$

All IRRs will be calculated as follows:

$$\frac{\text{Incidence rate in prucalopride cohort}}{\text{Incidence rate in PEG cohort}}$$

Using 10-year age groups, incidence rates will be calculated within age-sex strata and standardized to the age-sex distribution of prucalopride patients across all data sources. Age-sex standardized exposure-specific incidence rates (95% CI) (equations 15-1 and 15-7) and IRRs (95% CI) (equations 15-6 and 15-11) shown in Rothman et al. (2008) will also be stratified by presence versus absence of at least one cardiovascular risk factor, including history of cardiovascular disease (including all MACE component endpoints), hypertension, smoking, hyperlipidemia, diabetes, aged more than 55 years, and body mass index greater than 30 kg/m^2. Counts of total MACE events and of each MACE type will also be tabulated among these strata.

The overall standardized incidence rate ratio will be standardized to the distribution of person-years among each data source–specific propensity score decile in the prucalopride group, as shown in equation 15-6 in Rothman et al. (2008). Confidence intervals will be the asymptotic Wald limits, as shown in equation 15-11 in Rothman et al. (2008).

3.8.2.2 Confounding

In general, confounding will be controlled through (1) matching during specification of the PEG cohort and (2) the use of exposure propensity scores. Exposure propensity scores estimate the probability that a given patient will receive a treatment conditional on measured covariates and can serve as a summary confounder variable. Because exposure propensity scores focus on the indication for use and nonuse of medications, they can be useful to control for confounding by indication. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small, because rather than having to model the events with many variables, one can instead model the exposure, which may have ample data to accommodate a rich model (Cepeda et al., 2003). This advantage may be important in this study, given the low number of expected events for the study endpoints. Data aggregated by strata of propensity scores estimated in each data source will be used to estimate overall effects across all of the data sources.

The propensity scores, which are based on the values at treatment initiation of the covariates (e.g., age, sex, comorbidities, and surrogates for cardiovascular risk), will estimate the probability that each patient initiates prucalopride rather than PEG. Matching variables, particularly categorical ones, may be included in the model. The propensity score will serve as a within–data source variable that summarizes the confounding from a large set of variables. Propensity scores will be estimated using multiple logistic regression models. Interaction terms will be explored. Covariates to be used for the estimation of propensity scores are those related to the probability of receiving treatment and those possibly associated with the risk of study outcome. Age will be included as a continuous variable.

To identify confounders to be included in the modeling to assess propensity scores within each data source, the IRR will be calculated controlling for each potential confounder one at a time. A change of less than 10% in the IRR will serve as an indicator that confounding for that variable is of negligible importance in the data. Variables with a greater than 10% change in the IRR will be included in the propensity score model. Each research center will independently develop a fitted propensity score model and estimate a propensity score for each patient. In cohort studies, such as the study described in this protocol, balance is achieved on the matched variables. However, the matched sets do not need to be retained in analysis, and statistical methods that account for the matched sets are not required (Rothman et al., 2008). Once the sample for the comparator group, i.e., the PEG cohort, is selected, the matched sets are no longer kept as sets. In cohort studies, ignoring the matched sets does not introduce bias, and propensity scores are derived ignoring the sets.

To remove patients for whom there are no comparable patients in the other cohort, the distributions of propensity scores in prucalopride and PEG patients will be examined. Patients with extreme or nonoverlapping propensity scores (i.e., ranges in the upper or lower tails of the propensity score distribution within which only patients taking prucalopride or patients taking PEG fall) will be excluded. As matching is not retained in the development of the propensity score, trimming may affect one cohort more than the other; the overall ratio of prucalopride-to-PEG numbers could change in either direction. However, it is typically the case that only a small number of subjects have non-overlapping propensity scores; thus, the 1:5 ratio will be minimally affected. The effect and appropriateness of trimming will be reviewed at the analysis stage, though few patients are expected to be affected. Any patients removed from analyses in this manner will be examined separately.

The ultimate goal is to stratify person-time and endpoint counts for each cohort into deciles of propensity scores defined by the distribution of propensity scores for the prucalopride cohort. To check that the covariables are balanced within each data source–specific propensity score decile, the distribution of each variable within each propensity score decile will be compared between the cohorts. In addition, standardized mean differences between exposure groups within each propensity score decile (Austin, 2008), will be derived. Adjoining deciles may be collapsed as appropriate. The methods for evaluating deciles and collapsing them into less granular strata are addressed in the SAP. If the cohorts are found to be unbalanced, the propensity score modeling will be updated.

According to a simulation performed by Brookhart et al. (2006), variables that are unrelated to the exposure but are related to the outcome should always be included in a propensity score model to increase the precision without increasing bias. Propensity scores aim to achieve balance across several variables simultaneously. The matching variables (age, sex, year) are just a few components of the propensity score. Balance across the overall propensity score may not exactly replicate balance across the matching variables. Thus, even though the matching variables may be balanced because of the matching, they may become unbalanced upon controlling for other factors in the propensity score. Therefore, these variables will be kept in the propensity score model.

3.8.2.3 Estimation, by Data Source

Each research center will apply the study definitions to calculate person-time of exposure and number of events associated with each exposure category and endpoint definition. Using these data in conjunction with propensity scores, each research center will create an exposure summary table containing the essential data for measuring the effect of exposure on the study outcomes while adhering to the restrictions that are imposed on the release of individual-level data from each data source. The basic approach is for each research center to create tables with cross-classifications of subject, person-time counts, and case counts stratified by exposure category, endpoint, and deciles of propensity scores. Deciles are used to minimize potetential confounding within percentile groupings and can be combined if stratum sizes become too small. To estimate overall measures of effect, the coordinating center will combine these stratified data. Specification of the exact output tables to be provided by the coordinating center will be included in the SAP.

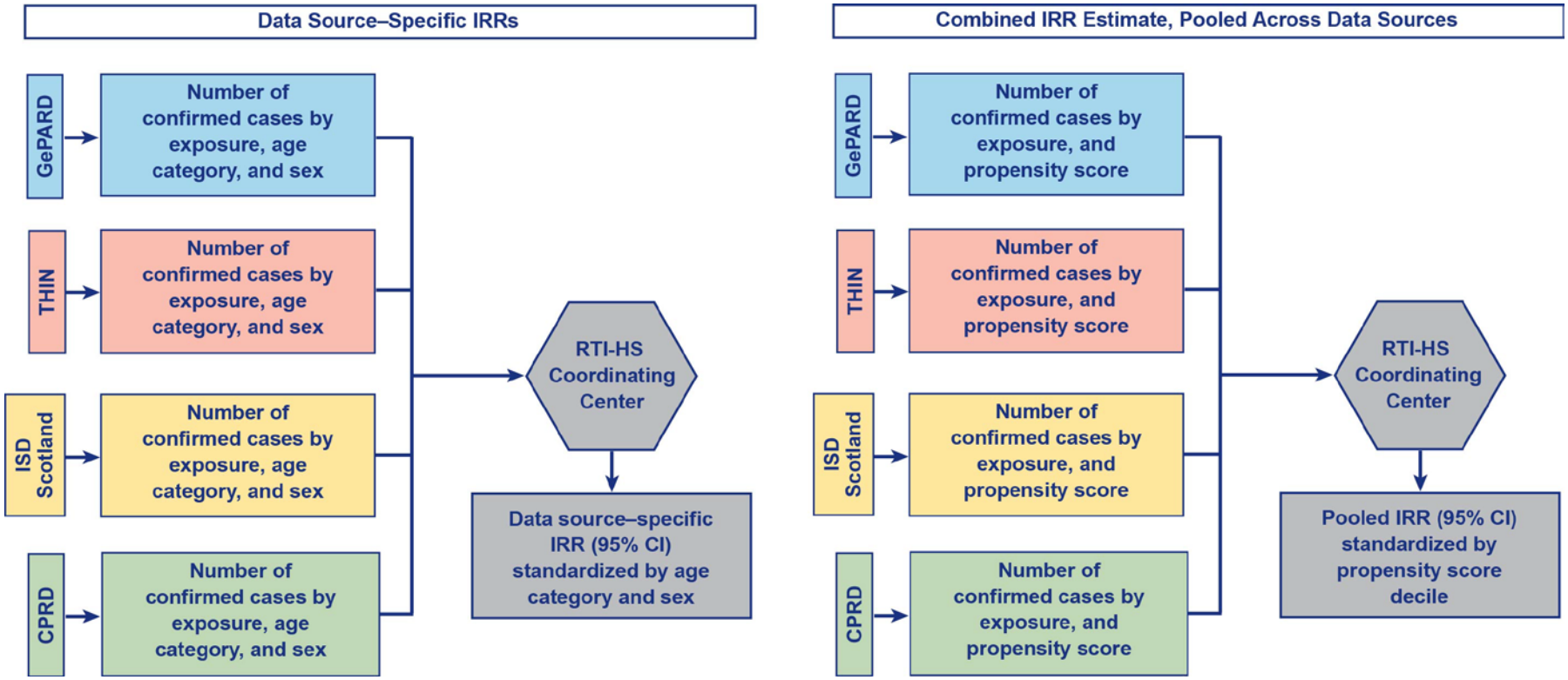
3.8.2.4 Combining Estimates Across Data Sources

Figure 3 diagrams the roles of the research centers and the coordinating center. After receiving the site-specific, propensity-score stratified tables from each research center, the coordinating center will conduct an analysis of the data from each individual data source and an overall analysis combining the data across all data sources. The overall analysis will be designed to estimate the effect of the exposure while controlling for confounding. Adjustment of the IRR for the prucalopride cohort versus the PEG cohort will be implemented after stratifying cohort-specific incidence rates by propensity score decile. Standardization is implemented by weighting the stratum-specific estimates to the distribution of person-time across deciles of propensity scores of the exposed cohort as the reference—equation 15-6 in Rothman et al. (2008). The data source will be retained as a stratification variable, and the effect within each data source will be estimated. This approach will be used to simultaneously adjust for the multiple variables that were used to estimate the propensity scores, which is particularly useful when the number of events is small relative to the number of covariates.

Although repeated analyses, a pilot phase and a study report, are planned, no adjustments in type I error for multiple analyses over time will be implemented.

This approach has been used in other noninterventional studies conducted in multiple data sources (Mines et al., 2014; Rassen et al., 2010; Roberts, 2012; VIVUS Inc., 2012).

Figure 3: Roles of Research Centers and Coordinating Center



CI = confidence interval; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; IRR = incidence rate ratio; ISD = Information Services Division (Scotland); RTI-HS = RTI Health Solutions; THIN = The Health Improvement Network.

3.8.3 Sensitivity/Exploratory Analyses

3.8.3.1 Impact of Exposure Time

Sensitivity analyses will be conducted for each outcome of interest by lengthening the definition of current exposure to end 30 days after the estimated end of the last dispensing or prescription for prucalopride or PEG (primary analysis has an exposure that extends to 7 days after the estimated end of the last dispensing or prescription). Accordingly, discontinuation will be redefined by assuming that each dispensing lasts until the specified extended duration (30 days) after each dispensings' days' supply.

To explore the impact of potential depletion of susceptibles during follow-up after the first treatment episode (e.g., individuals at risk of an event might discontinue treatment early; therefore, individuals who continue treatment may have lower risk), a sensitivity analysis will be performed on MACE risk (MACE only) at treatment initiation. For this analysis, exposure time at risk will be limited to the first treatment episode, which will end at any gap longer than 7 days; follow-up will be censored at the first medication switch (in addition to other proposed censoring criteria); and no switching between cohorts will be permitted.

Another sensitivity analysis will define follow-up observation time as including time at risk from past use of prucalopride or PEG in addition to time at risk from current use.

Overlapping exposure, that is, simultaneous exposure to both medications that meets the criteria for current exposure, is not included in the primary analysis. A sensitivity analysis will include the person-time and events during overlapping exposures in both study cohorts.

3.8.3.2 Impact of Outcome Categories

A sensitivity analysis that expands the MACE endpoint to include probable cases, in addition to confirmed cases, of AMI, stroke, and in-hospital cardiovascular death will be conducted.

Primary analyses will be conducted by including only outcomes that can be ascertained in all of the data sources, that is, all endpoints except out-of-hospital CV deaths. Thus, for the exploratory analysis, cardiovascular deaths that occur out of the hospital will be included in an exploratory endpoint for the data sources for which these events can be ascertained (see Table 2 for specification of data sources by endpoint).

3.8.3.3 Impact of Cancer

Patients with cancer may be at increased risk of cardiovascular outcomes due to chronic opioid use, antineoplastic treatments, and/or terminal status. Therefore, a sensitivity analysis after excluding individuals with a diagnosis of cancer (except for non-melanoma skin cancer) will be implemented.

3.8.3.4 Potential Channeling

To assess the potential impact of channeling bias, a sensitivity analysis to exclude individuals with a prescription for either prucalopride *or* PEG in the 12 months prior to the index date will be implemented.

3.8.3.5 Unmeasured Confounding

It is possible that final relative risk estimates in any study could be confounded by variables that could not be measured or could not be measured accurately in one or more cohorts. This is often a concern in studies based on secondary data. To assess the potential impact of unmeasured confounding on the results in this study, a bias analysis will be implemented (Savitz and Barón, 1989). In this analysis, a range of plausible hypothetical values for the prevalence of the unknown confounder among the exposed and among the unexposed and for the IRR of the unknown confounder and the outcome of interest (e.g., 2 to 3) is applied to assess the hypothetical potential impact of an unknown confounder on the overall IRR. Such analyses show the magnitude of the difference in the prevalence of a confounder between exposed and unexposed groups and the strength of relationship between the confounder and the outcome that are needed to substantially influence the study result.

3.8.4 Content of Reports

The report of results from the pilot phase will include descriptive analyses to assess the feasibility of exposure and other definitions. It will also include preliminary analyses for the study objectives, using the patients accumulated to date, that is, estimates of the pooled adjusted incidence rates and IRRs for the primary and secondary endpoints and selected sensitivity analyses. The pilot report will be used to determine the timing of the full study report.

The full study report will describe the cohorts and the results of all analysis. All pooled IRRs will be standardized for propensity score category and data source. All sensitivity analyses will be included.

4. QUALITY ASSURANCE AND QUALITY CONTROL

The standard operating procedures of each research center 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.

All 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 SAP, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

At the coordinating center, an independent Office of Quality Assurance in RTI Health Solutions (RTI-HS) performs audits and assessments that involve various aspects of projects, including but not limited to documentation of education and training, data entry, data transfer, and RTI International institutional review board (IRB) approval. Such audits are conducted according to established criteria in standard operating procedures and other applicable procedures. Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices* (GPP) (ISPE, 2007).

Each of the research centers will follow its own quality and audit trail procedures, which may vary among the research centers.

4.1 Limitations of the Research Methods

As with any database study, the actual study size will be determined by the utilization of the drug of interest and the inclusion/exclusion criteria. Additional rounds of analyses can be implemented as the available number of patients increases, and we will continue to evaluate the feasibility of extending the study to other data sources. Study size also depends on reimbursement status for data sources that rely on insurance claims.

The rate of MACE in the population treated for chronic constipation (predominantly younger women) is expected to be low. By using multiple data sources, we intend to accrue patient experience more quickly than would be possible using a single data source. There will be some heterogeneity across data sources, which may impact the precision of estimates. The study population size may also limit the ability to evaluate differences in risk across patient subgroups.

Because of the serious nature and clinical guidelines for the management of the acute cardiovascular events of interest, hospitalization is expected for most of the nonfatal events under study. The selected data sources for this study have been shown to reliably capture and classify cardiovascular hospitalizations, as described in Sections 3.4.4 and 3.4.5. All data sources will be able to capture conditions and deaths that occur in a hospital.

Some of the planned data sources for this study cannot ascertain causes of out-of-hospital death; therefore, such out-of-hospital deaths will not be included in the primary endpoint for homogeneity purposes. Historically, many data source studies of major cardiovascular events have been conducted without ascertaining out-of-hospital deaths due to this limitation. However, a sensitivity analysis is planned in which three of the four data sources will incorporate relevant out-of-hospital deaths in the combined endpoint. The inclusion of these deaths in the evaluation will be relevant if the exposure is associated with the severity of the cardiovascular event. Therefore, in this analysis, underascertainment of the outcomes of interest will be minimized.

It has been shown that, in general, misclassification of outcomes that do not differ by exposure (i.e., prucalopride initiators compared with PEG initiators) will underestimate the incidence ratio. However, the impact is expected to be small because the validation studies of

these outcomes have shown that identification of the cardiovascular outcomes of interest are quite reliable in the planned data sources.

Determination of severity or duration of constipation would be a challenge. Clinical data on constipation are frequently not available in automated health databases, and patients may treat themselves with over-the-counter medications for long periods of time. The identification of chronic constipation among patients would require the use of an algorithm with less-than-perfect sensitivity and specificity. Therefore, if chronic constipation or severe chronic constipation is independently associated with an increased risk of cardiovascular outcomes, the study may not be able to fully control for these conditions. Although one published article suggests that constipation may be associated with factors that are associated with MACE (Salmoirago-Blotcher et al., 2011), there is little evidence that chronic constipation is independently associated with an increased risk for MACE. The matching and propensity score approaches will limit the effect of any confounding.

Information on cardiovascular risk factors is limited to information recorded in the electronic medical record. For many patients, that information will be comprehensive, including factors such as smoking. For other patients, less information will be available, owing to the nature of the data source (e.g., claims only) or the total time a patient's information is in the data source. Use of over-the-counter medications will not be captured. There is no reason to believe that completeness of historical information would differ between the two study cohorts; therefore, any misclassification would not be differential.

Determining exposure duration in an accurate manner can be a challenge with secondary health care data. In UK data sources, where the research data are captured through GP prescribing, any prescribing by a specialist is not captured. Thus, if an individual receives a prescription through a specialist, that exposure would not be captured in this study. However, commonly, specialists will write the first prescription and future prescribing is transferred to the GP. Once a prescription or dispensing appears in the data, we assume the patient takes the product as prescribed. However, we have no direct measure of patient adherence. It is possible that patients in either cohort will stop medication prematurely and/or reserve medication to take at a later time, resulting in misclassification of exposure. Therefore, we extend the time at risk to 7 days following the end of the prescription period to account for possible variation in adherence and will evaluate in sensitivity analyses a longer period (30 days after the end of the prescription period).

5. PROTECTION OF HUMAN SUBJECTS

This is a retrospective, noninterventional study and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. No patient-level data will be shared outside of each research center. Each research center will ensure independent institutional review board, ethics committee, and/or other required committee approval of the study protocol in accord with applicable national and local regulations. In addition, RTI Health Solutions as the

coordinating center will obtain approval from the RTI International IRB. RTI Health Solutions will use only aggregated data from the research centers in the pooled analyses.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

The study will comply with the nature of noninterventional (observational) studies referred to in the International Conference on Harmonisation harmonized tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).

5.1 RTI International

RTI International, of which RTI Health Solutions is a division, 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 its IRB committees. RTI International currently has three IRB committees available to review research protocols. One IRB committee is constituted to review medical research; two of its members are MDs. All three IRBs have been audited by the FDA and are fully compliant with applicable regulatory requirements. RTI Health Solutions will obtain approval for the study from the RTI International IRB.

5.2 CPRD

The final study protocol and proposed questionnaires to be used for validation will be submitted to the ISAC specified on the CPRD website (http://www.cprd.com/ISAC). The CPRD requires that any study using CPRD data that will be published or for which results will be communicated to third parties must receive ISAC approval before proceeding. ISAC is responsible for reviewing protocols for scientific quality but may recommend that study-specific Medical Research Ethics Committee (MREC) approval be sought if ethical issues arise in relation to an individual study. Separate MREC approval will be required for any study that includes any form of direct patient involvement (http://www.cprd.com/ISAC/otherinfo.asp).

5.3 THIN

The protocol will require review approval by the South East Multicentre Research Ethics Committee (http://www.thin-uk.com/contributing_data.htm) in the UK.

5.4 ISD Scotland

The protocol must be reviewed by an MREC and by a Caldicott Guardian (an individual appointed by the government) to judge whether the research is in the public interest.

5.5 GePaRD

For the GePaRD, access to the data is possible only in the context of approved projects, and preliminary investigations regarding the number of prescriptions of a specific drug or the number of patients diagnosed with a specific disease are not allowed. Approval is needed from the four SHI agencies providing data to the GePaRD. A summary of the protocol will be provided to the SHI agencies, outlining the public health importance of the research question. In Germany, scientific research based on health insurance data is regulated by the Code of Social Law, and individual studies must be approved by the Federal Ministry of Health. Given that this study is based on pseudonymous data, no informed consent is required.

6. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from ISPE (2007, Section VI) and the EMA *Guideline on Good Pharmacovigilance Practices* (EMA, 2012b, Section VI:C.1.2.1), noninterventional studies, such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of adverse events/reactions.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The common study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Reports, and other regulatory milestones and requirements.

In its GPP, ISPE contends that “there is an ethical obligation to disseminate findings of potential scientific or public health importance” (ISPE, 2007, Section V); for example, results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (2010). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2007). The Consolidated Standards of Reporting Trials statement (Moher et al., 2001) refers to randomized studies but provides useful guidance applicable to nonrandomized studies as well. The research team has agreed to publish the full results from this study, and communication via appropriate scientific venues, such as ISPE, will be considered.

The sponsor and the investigator have agreed on a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The sponsor will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication (EMA, 2012a, Section VIII.B.7).

8. OTHER GOOD RESEARCH PRACTICE

This study adheres to ISPE GPP (2007) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2013).

The study will be conducted in accordance with the FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets* (FDA, 2013).

9. RESOURCES REQUIRED

The following investigators will coordinate and lead the overall program of substudies:

- Patricia Tennis, PhD, RTI Health Solutions, Principal Investigator
- Elizabeth Andrews, PhD, RTI Health Solutions, Coinvestigator
- Susana Perez-Gutthann, MD, PhD, RTI Health Solutions, Coinvestigator

The following investigators will lead a substudy at their respective research centers:

- Dr. Luis Alberto García Rodríguez, CEIFE, principal investigator of the THIN study
- Professor Tom McDonald, Medicines Monitoring Unit, University of Dundee, principal investigator for the ISD Scotland study
- Patricia Tennis, PhD, RTI Health Solutions, principal investigator for the CPRD study
- Tania Schink, MPH, BIPS GmbH, principal investigator for the GePaRD study

The principal investigators for the substudies conducted with THIN, ISD Scotland, CPRD, and GePaRD data have all conducted research with these data in the past (see curriculum vitae in the Annex 5). Patricia Tennis, Elizabeth Andrews, and Susana Perez-Gutthann have conducted research with THIN and CPRD data.

RTI Health Solutions epidemiologists will author all study documents (e.g., protocol, SAP, study reports), which the principal investigators at the research centers will review before finalization. RTI-Health Solutions epidemiologists will coordinate all activities for the program of substudies.

10. REFERENCES

Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. Stroke. 2006 Jul;37(7):1725-30.

Anderson JL, May HT, Bair TL, Muhlestein JB, Horne BD, Carlquist JF. Lack of association of tegaserod with adverse cardiovascular outcomes in a matched case-control study. J Cardiovasc Pharmacol Ther. 2009 Sep;14(3):170-5.

Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:100-28.

Arana A, Varas C, Gonzalez-Perez A, Gutierrez L, Bjerrum L, Garcia Rodriguez LA. Hormone therapy and cerebrovascular events: a population-based nested case-control study. Menopause. 2006 Sep-Oct;13(5):730-6.

Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. Pharmacoepidemiol Drug Saf. 2008 Dec;17(12):1218-25.

Behr S, Andersohn F, Garbe E. Risk of intracerebral hemorrhage associated with phenprocoumon exposure: a nested case-control study in a large population-based German database. Pharmacoepidemiol Drug Saf. 2010 Jul;19(7):722-30.

Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol. 2006 Jun 15;163(12):1149-56.

Cai B, Xu W, Bortnichak E, Watson DJ. An algorithm to identify medical practices common to both the General Practice Research Database and The Health Improvement Network database. Pharmacoepidemiol Drug Saf. 2012 Jul;21(7):770-4.

Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol. 2003 Aug 1;158(3):280-7.

Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):563-72.

Cross E, How S, Goodacre S. Development of acute chest pain services in the UK. Emerg Med J. 2007 Feb;24(2):100-2.

CSD Medical Research. Statistics [Internet]. Cegedim Strategic Data; 2012. Available at: http://csdmruk.cegedim.com/our-data/statistics.shtml. Accessed June 4, 2013.

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

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

ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 2). EMA/95098/2010 Rev.2. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; June 18, 2013. Available at: http://www.encepp.eu/standards_and_guidances/index.shtml. Accessed March 8, 2013.

Eurostat. Population data for Germany. 2012. Available at: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1. Accessed February 7, 2013.

FDA. FDA gastrointestinal diseases advisory committee briefing document: evaluation of cardiac safety and serotonin receptor (5HT4) agonists, Statistical considerations for CV safety studies. Food and Drug Administration Center for Drug Evaluation and Research; November 17, 2011. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM279736.pdf. Accessed June 4, 2013.

FDA. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. US Department of Health and Human Services, Food and Drug Administration; May 2013. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf. Accessed June 4, 2013.

Fireman B, Toh S, Butler MG, Go AS, Joffe HV, Graham DJ, et al. A protocol for active surveillance of acute myocardial infarction in association with the use of a new antidiabetic pharmaceutical agent. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:282-90.

Flynn RW, MacDonald TM, Murray GD, Ferguson C, Shah K, Doney AS. The Tayside Stroke Cohort: exploiting advanced regional medical informatics to create a region-wide database for studying the pharmacoepidemiology of stroke. Pharmacoepidemiol Drug Saf. 2010 Jul;19(7):737-44.

Gaist D, Wallander MA, Gonzalez-Perez A, Garcia-Rodriguez 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.

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

Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology. 2007 Jan;132(1):397-414.

Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005 Feb 5-11;365(9458):475-81.

Hammad TA, Graham DJ, Staffa JA, Kornegay CJ, Dal Pan GJ. Onset of acute myocardial infarction after use of non-steroidal anti-inflammatory drugs. Pharmacoepidemiol Drug Saf. 2008a Apr;17(4):315-21.

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. 2008b Dec;17(12):1197-201.

Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, et al. Standardized definitions for cardiovascular and stroke end point events in clinical trials. Standardized Data Collection for Cardiovascular Trials Initiative; November 9, 2012. Available at: https://www.cardiac-safety.org/think-tanks/ecrf-forms-for-posting/Draft%20Definitions%20for%20Testing%20November%209-%202012%20with%20MI%20Preamble%20CLEAN.pdf Accessed May 23, 2013.

ICH. Pharmacovigilance planning. E2E. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2004. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed March 8, 2013.

ICMJE. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. International Committee of Medical Journal Editors; April 2010. Available at: http://www.icmje.org/urm_main.html. Accessed March 8, 2013.

ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. International Society for Pharmacoepidemiology; 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed March 8, 2013.

Jobski K, Schmid U, Behr S, Andersohn F, Garbe E. 3-year prevalence of alcohol-related disorders in German patients treated with high-potency opioids. Pharmacoepidemiol Drug Saf. 2012 Oct;21(10):1125-9.

Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. Journal of Clinical Epidemiology. 2009 Feb;62(2):188-94.

Kirkman MA, Mahattanakul W, Gregson BA, Mendelow AD. The accuracy of hospital discharge coding for hemorrhagic stroke. Acta Neurol Belg. 2009 Jun;109(2):114-9.

Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J. 2004 Jul;148(1):99-104.

Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. Stroke. 2005 Aug;36(8):1776-81.

Kornegay CJ, Vasilakis-Scaramozza C, Jick H. Incident diabetes associated with antipsychotic use in the United Kingdom general practice research database. J Clin Psychiatry. 2002 Sep;63(9):758-62.

Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28(3):150-4.

Kraut AA, Schink T, Schulze-Rath R, Mikolajczyk RT, Garbe E. Incidence of anogenital warts in Germany: a population-based cohort study. BMC Infect Dis. 2010;10:360.

Loughlin J, Quinn S, Rivero E, Wong J, Huang JQ, Kralstein J, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. J Cardiovasc Pharm T. 2010 Jun;15(2):151-7.

McAlpine R, Pringle S, Pringle T, Lorimer R, MacDonald TM. A study to determine the sensitivity and specificity of hospital discharge diagnosis data used in the MICA study. Pharmacoepidemiol Drug Saf. 1998 Sep;7(5):311-8.

Mines D, Tennis P, Curkendall SM, Li DK, Peterson C, Andrews EB, et al. Topiramate use in pregnancy and the birth prevalence of oral clefts. Pharmacoepidemiol Drug Saf. 2014 Apr 1.

Mohammad S, Zhou Z, Gong Q, January CT. Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol. 1997 Nov;273(5 Pt 2):H2534-8.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001 Apr 14;357(9263):1191-4.

Muller-Nordhorn J, Binting S, Roll S, Willich SN. An update on regional variation in cardiovascular mortality within Europe. Eur Heart J. 2008 May;29(10):1316-26.

Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Raiha P, Karja-Koskenkari P, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2005 Apr;12(2):132-7.

Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008 Mar;17(3):215-23.

Potet F, Bouyssou T, Escande D, Baró I. Gastrointestinal prokinetic drugs have different affinity for the human cardiac human ether-à-gogo K(+) channel. J Pharmacol Exp Ther. 2001 Dec;299(3):1007-12.

Rassen JA, Avorn J, Schneeweiss S. Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple health care utilization databases. Pharmacoepidemiol Drug Saf. 2010 Aug;19(8):848-57.

Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003 Nov 1;158(9):915-20.

Ray WA, Varas-Lorenzo C, Chung CP, Castellsague J, Murray KT, Stein CM, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes. 2009 May;2(3):155-63.

Roberts MD. Qnexa (phentermine/topiramate). NDA 22580. Presented at the US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee Meeting; 2012. Silver Spring, MD. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM293905.pdf. Accessed March 7, 2014.

Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

Rothman KJ. Episheet—spreadsheets for the analysis of epidemiologic data. October 25, 2011. Available at: http://www.epidemiolog.net/studymat/. Accessed 8 March 2013.

Rothman KJ. Epidemiology: an introduction. 2nd edition. New York, NY: Oxford University Press; 2012.

Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet. 2005 Nov 19;366(9499):1773-83.

Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf. 2008a Jan;17(1):20-6.

Roumie CL, Mitchel EF, Jr., Kaltenbach L, Arbogast PG, Gideon P, Griffin MR. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. Stroke. 2008b Jul;39(7):2037-45.

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.

Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2013 Jul;44(7):2064-89.

Salmoirago-Blotcher E, Crawford S, Jackson E, Ockene J, Ockene I. Constipation and risk of cardiovascular disease among postmenopausal women. Am J Med. 2011 Aug;124(8):714-23.

Savitz DA, Barón AE. Estimating and correcting for confounder misclassification. Am J Epidemiol. 1989 May;129(5):1062-71.

Schink T, Herings R, Lucchi S, Picelli G, Romio S, Schade R, et al. A comparison of incidence rates of stroke estimated from different data sources in the SOS project. Presented at the 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2011. Chicago, USA. Available at: http://www.sos-nsaids-project.org/public-dissemination-activities/ICPE2011_7_poster_stroke_Schink_disclaimer.pdf. Accessed July 2, 2013.

Setakis E, Gallagher A, Williams TW, van Staa TP. Linking UK death certificate data to UK primary care data (GPRD) to obtain cause of death (abstract). Pharmacoepidemiol Drug Saf. 2010;19:S83.

Shah AD, Martinez C. A comparison of the cause of death recorded in the General Practice Research Database with national mortality statistics in England and Wales (abstract). Pharmacoepidemiol Drug Saf. 2004;13:S2.

Shire Pharmaceuticals. Annex I. Summary of product characteristics. Resolor (prucalopride). 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001012/WC500053998.pdf. Accessed March 7, 2014.

STROBE. Checklist. Strengthening the Reporting of Observational Studies in Epidemiology; 2007. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed 8 March 2013.

Strom BL, editor. Pharmacoepidemiology, Fourth Edition. Chichester, UK: John Wiley & Sons, Inc; 2006.

The West of Scotland Coronary Prevention Study Group. Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. J Clin Epidemiol. 1995 Dec;48(12):1441-52.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012 Oct 16;126(16):2020-35.

Varas-Lorenzo C, Garcia-Rodriguez 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.

Varas-Lorenzo C, Castellsague J, Stang MR, Tomas L, Aguado J, Perez-Gutthann S. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. Pharmacoepidemiol Drug Saf. 2008 Aug;17(8):842-52.

Varas-Lorenzo C, Castellsague J, Stang MR, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. Pharmacoepidemiol Drug Saf. 2009 Nov;18(11):1016-25.

VIVUS Inc. VI-0521 (QNEXA®) advisory committee briefing document. NDA 022580. Presented at the US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee Meeting; February 22, 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292317.pdf. Accessed March 7, 2014.

Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J. 2008 Dec;29(24):2981-8.

Wright FL, Green J, Canoy D, Cairns BJ, Balkwill A, Beral V. Vascular disease in women: comparison of diagnoses in hospital episode statistics and general practice records in England. BMC Med Res Methodol. 2012;12:161.

ANNEX 1 Selected Characteristics of Prucalopride and PEG Users in THIN (CEIFE 10 June 2013)

Table 1-1: Characteristics of Users of Prucalopride Aged 18-59 Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=19		N=357		N=376	
	n	%	n	%	n	%
Follow-up time (since first prescription in study period to last entry)[a]						
Up to 1 year	9	47.4%	224	62.7%	233	62.0%
1-2 years	10	52.6%	123	34.5%	133	35.4%
3+ years	0	0.0%	10	2.8%	10	2.7%
Duration of treatment						
<=13 days	0	0.0%	8	2.2%	8	2.1%
14-27 days	2	10.5%	14	3.9%	16	4.3%
28-89 days	12	63.2%	185	51.8%	197	52.4%
90-129 days	1	5.3%	33	9.2%	34	9.0%
>=130 days	4	21.1%	117	32.8%	121	32.2%
Indication (A. based on codes recorded ever before)[b]						
Only constipation	12	63.2%	175	49.0%	187	49.7%
IBS + constipation	2	10.5%	126	35.3%	128	34.0%
IBS unspecified	0	0.0%	18	5.0%	18	4.8%
other	5	26.3%	38	10.6%	43	11.4%
Indication (B. based on codes recorded in year prior)[b]						
Constipation only in the year prior	8	42.1%	175	49.0%	183	48.7%
IBS with constipation in year prior	0	0.0%	30	8.4%	30	8.0%
IBS unspecified in the year prior	0	0.0%	3	0.8%	3	0.8%
Other	11	57.9%	149	41.7%	160	42.6%

Table 1-1: Characteristics of Users of Prucalopride Aged 18-59 Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=19		N=357		N=376	
	n	%	n	%	n	%
Number of constipation codes on or in 12 months before the first prescription date						
0	11	57.9%	163	45.7%	174	46.3%
1	4	21.1%	75	21.0%	79	21.0%
2	3	15.8%	55	15.4%	58	15.4%
3+	1	5.3%	64	17.9%	65	17.3%
Duration of treatment among those with >=1 constipation code on or in 12 months before the first prescription date						
<=13 days	0	0.0%	6	3.1%	6	3.0%
14-27 days	1	12.5%	8	4.1%	9	4.5%
28-89 days	5	62.5%	98	50.5%	103	51.0%
90-129 days	1	12.5%	19	9.8%	20	9.9%
>=130 days	1	12.5%	63	32.5%	64	31.7%

IBS = irritable bowel syndrome.

[a] Information available until 30 September 2012.

[b] Indication was assigned based on codes recorded ever before (A). or codes recorded in the year prior (B) and categorized in the following groups:

1. Constipation (if the patient had a code for constipation in the past and no code for IBS).

2. IBS with constipation (if the patient had a code for constipation and a code for IBS in the past. or a code of IBS and >3 Rx of laxatives in year prior. that may indicate constipation as well).

3. IBS unspecific (a prior code for IBS with no constipation code. or no frequent use of laxatives).

4. Other indications (the remaining cases).

Table 1-2: Characteristics of Users of PEG Aged 18-59 Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=54,234		N=95,079		N=149,313	
	n	%	n	%	n	%
Follow-up time (since first prescription in study period to last entry)[a]						
Up to 1 year	17,989	33.2%	31,846	33.5%	49,835	33.4%
1-2 years	17,258	31.8%	30,295	31.9%	47,553	31.8%
3+ years	18,987	35.0%	32,938	34.6%	51,925	34.8%
Duration of treatment						
<=13 days	5,591	10.3%	9,555	10.0%	15,146	10.1%
14-27 days	10,560	19.5%	18,481	19.4%	29,041	19.4%
28-89 days	25,666	47.3%	46,453	48.9%	72,119	48.3%
90-129 days	3,138	5.8%	5,264	5.5%	8,402	5.6%
>=130 days	9,279	17.1%	15,326	16.1%	24,605	16.5%
Indication (A. based on codes recorded ever before)[b]						
Only constipation	25,175	46.4%	40,062	42.1%	65,237	43.7%
IBS + constipation	2,702	5.0%	11,595	12.2%	14,297	9.6%
IBS unspecified	1,136	2.1%	4,237	4.5%	5,373	3.6%
Other	25,221	46.5%	39,185	41.2%	64,406	43.1%
Indication (B. based on codes recorded in year prior)[b]						
Constipation only in the year prior	17,294	31.9%	28,469	29.9%	45,763	30.6%
IBS with constipation in year prior	254	0.5%	1,184	1.2%	1,438	1.0%
IBS unspecified in the year prior	219	0.4%	1,004	1.1%	1,223	0.8%
Other	36,467	67.2%	64,422	67.8%	100,889	67.6%

Table 1-2: Characteristics of Users of PEG Aged 18-59 Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=54,234		N=95,079		N=149,313	
	n	%	n	%	n	%
Number of constipation codes on or in 12 months before the first prescription date						
0	36,797	67.8%	65,947	69.4%	102,744	68.8%
1	14,511	26.8%	24,436	25.7%	38,947	26.1%
2	2,113	3.9%	3,403	3.6%	5,516	3.7%
3+	813	1.5%	1,293	1.4%	2,106	1.4%
Duration of treatment among those with >=1 constipation code on or in 12 months before the first prescription date	N=17,437		N=29,132		N=46,569	
<=13 days	1,988	11.4%	3,096	10.6%	5,084	10.9%
14-27 days	3,436	19.7%	5,835	20.0%	9,271	19.9%
28-89 days	8,102	46.5%	14,296	49.1%	22,398	48.1%
90-129 days	1,091	6.3%	1,691	5.8%	2,782	6.0%
>=130 days	2,820	16.2%	4,214	14.5%	7,034	15.1%

IBS = irritable bowel syndrome; PEG = polyethylene glycol 3350.

[a] Information available until 30 September 2012.

[b] Indication was assigned based on codes recorded ever before (A). or codes recorded in the year prior (B) and categorized in the following groups:

1. Constipation (if the patient had a code for constipation in the past and no code for IBS).

2. IBS with constipation (if the patient had a code for constipation and a code for IBS in the past. or a code of IBS and >3 Rx of laxatives in year prior. that may indicate constipation as well).

3. IBS unspecific (a prior code for IBS with no constipation code. or no frequent use of laxatives).

4. Other indications (the remaining cases).

Table 1-3: Characteristics of Users of Prucalopride Aged 60+ Years, by Sex, During Study Period (January 2010 – September 2012)

	Male		Female		Total	
	N=7		N=80		N=87	
	n	%	n	%	n	%
Follow-up time (since first prescription in study period to last entry)[a]						
Up to 1 year	2	28.6%	47	58.8%	49	56.3%
1-2 years	5	71.4%	30	37.5%	35	40.2%
3+ years	0	0.0%	3	3.8%	3	3.4%
Duration of treatment						
<=13 days	0	0.0%	5	6.2%	5	5.7%
14-27 days	2	28.6%	7	8.8%	9	10.3%
28-89 days	3	42.9%	43	53.8%	46	52.9%
90-129 days	0	0.0%	7	8.8%	7	8.0%
>=130 days	2	28.6%	18	22.5%	20	23.0%
Indication (A. based on codes recorded ever before)[b]						
Only constipation	4	57.1%	39	48.8%	43	49.4%
IBS + constipation	0	0.0%	25	31.2%	25	28.7%
IBS unspecified	0	0.0%	7	8.8%	7	8.0%
Other	3	42.9%	9	11.2%	12	13.8%
Indication (B. based on codes recorded in year prior)[b]						
Constipation only in the year prior	3	42.9%	36	45.0%	39	44.8%
IBS with constipation in year prior	0	0.0%	6	7.5%	6	6.9%
IBS unspecified in the year prior	0		0		0	
Other	4	57.1%	38	47.5%	42	48.3%

Table 1-3: Characteristics of Users of Prucalopride Aged 60+ Years, by Sex, During Study Period (January 2010 – September 2012)

	Male		Female		Total	
	N=7		N=80		N=87	
	n	%	n	%	n	%
Number of constipation codes on or in 12 months before the first prescription date						
0	4	57.1%	41	51.2%	45	51.7%
1	1	14.3%	13	16.2%	14	16.1%
2	2	28.6%	15	18.8%	17	19.5%
3+	0	0.0%	11	13.8%	11	12.6%
Duration of treatment among those with >=1 constipation code on or in 12 months before the first prescription date	N=3		N=39		N=42	
<=13 days	0	0.0%	4	10.3%	4	9.5%
14-27 days	1	33.3%	4	10.3%	5	11.9%
28-89 days	1	33.3%	21	53.8%	22	52.4%
90-129 days	0	0.0%	4	10.3%	4	9.5%
>=130 days	1	33.3%	6	15.4%	7	16.7%

IBS = irritable bowel syndrome.

[a] Information available until 30 September 2012.

[b] Indication was assigned based on codes recorded ever before (A). or codes recorded in the year prior (B) and categorized in the following groups:

1. Constipation (if the patient had a code for constipation in the past and no code for IBS).

2. IBS with constipation (if the patient had a code for constipation and a code for IBS in the past. or a code of IBS and >3 Rx of laxatives in year prior. that may indicate constipation as well).

3. IBS unspecific (a prior code for IBS with no constipation code. or no frequent use of laxatives).

4. Other indications (the remaining cases).

Table 1-4: Characteristics of Users of PEG Aged 60+ Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=40,068		N=56,308		N=96,376	
	n	%	n	%	n	%
Follow-up time (since first prescription in study period to last entry)[a]						
Up to 1 year	12,732	31.80%	17,505	31.10%	30,237	31.40%
1-2 years	12,549	31.30%	17,295	30.70%	29,844	31.00%
3+ years	14,787	36.90%	21,508	38.20%	36,295	37.70%
Duration of treatment						
<=13 days	3,847	9.60%	5,074	9.00%	8,921	9.30%
14-27 days	7,312	18.20%	9,780	17.40%	17,092	17.70%
28-89 days	18,900	47.20%	26,835	47.70%	45,735	47.50%
90-129 days	2,508	6.30%	3,483	6.20%	5,991	6.20%
>=130 days	7,501	18.70%	11,136	19.80%	18,637	19.30%
Indication (A. based on codes recorded ever before)[b]						
only constipation	19,824	49.50%	24,845	44.10%	44,669	46.30%
IBS + constipation	1,836	4.60%	5,929	10.50%	7,765	8.10%
IBS unspecified	564	1.40%	1,504	2.70%	2,068	2.10%
other	17,844	44.50%	24,030	42.70%	41,874	43.40%
Indication (B. based on codes recorded in year prior)[b]						
Constipation only in the year prior	13,110	32.70%	15,707	27.90%	28,817	29.90%
IBS with constipation in year prior	124	0.30%	381	0.70%	505	0.50%
IBS unspecified in the year prior	62	0.20%	175	0.30%	237	0.20%
Other	26,772	66.80%	40,045	71.10%	66,817	69.30%

Table 1-4: Characteristics of Users of PEG Aged 60+ Years, by Sex, During Study Period (January 2010 – September 2012)

	Males		Females		Total	
	N=40,068		N=56,308		N=96,376	
	n	%	n	%	n	%
Number of constipation codes on or in 12 months before the first prescription date						
0	26,899	67.10%	40,419	71.80%	67,318	69.80%
1	10,848	27.10%	13,087	23.20%	23,935	24.80%
2	1,679	4.20%	1,949	3.50%	3,628	3.80%
3+	642	1.60%	853	1.50%	1,495	1.60%
Duration of treatment among those with >=1 constipation code on or in 12 months before the first prescription date	N=13,169		N=15,889		N=29,058	
<=13 days	1,439	10.90%	1,518	9.60%	2,957	10.20%
14-27 days	2,442	18.50%	2,867	18.00%	5,309	18.30%
28-89 days	6,110	46.40%	7,588	47.80%	13,698	47.10%
90-129 days	887	6.70%	1,036	6.50%	1,923	6.60%
>=130 days	2,291	17.40%	2,880	18.10%	5,171	17.80%

IBS = irritable bowel syndrome; PEG = polyethylene glycol 3350.

[a] Information available until 30 September 2012.

[b] Indication was assigned based on codes recorded ever before (A). or codes recorded in the year prior (B) and categorized in the following groups:

1. Constipation (if the patient had a code for constipation in the past and no code for IBS).

2. IBS with constipation (if the patient had a code for constipation and a code for IBS in the past. or a code of IBS and >3 Rx of laxatives in year prior. that may indicate constipation as well).

3. IBS unspecific (a prior code for IBS with no constipation code. or no frequent use of laxatives).

4. Other indications (the remaining cases).

ANNEX 2 DEFINITIONS AND CASE ASCERTAINMENT PROCESSES FOR ENDPOINTS OF INTEREST

Hospitalizations for Nonfatal AMI

The American Heart Association and the World Heart Federation define an AMI by the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, including ST-elevation myocardial infarction and non–ST-elevation myocardial infarction (Thygesen et al., 2012).

Acute myocardial infarction will be identified by hospital discharge diagnosis codes in patients discharged alive from the hospital. For CPRD and THIN patients without direct linkage to hospitalization discharge diagnoses (i.e., not linked to HES), algorithms based on available information recorded by the GP will be used to identify patients who have been diagnosed with an AMI and were hospitalized. Previously published, validated algorithms can be used. The PPV of the Read/OXMIS codes used historically by CPRD for AMI has been reported to be approximately 93% (95% CI, 90%-96%) (Hammad et al., 2008b).

Although chest pain units are used to facilitate rapid and safe discharge of patients with chest pain by providing up to 6 hours of clinical observation and biochemical cardiac testing and monitoring and exercise testing within 24 hours of attendance, it has been reported that there is some variability of protocol implementation across UK centers (Cross et al., 2007). However, it is expected that this is improving over time. Most important, patients who develop an AMI will be hospitalized and therefore captured in all data sources included in the study.

Hospitalizations for Nonfatal Stroke

An updated definition of stroke has been issued recently by the American Heart Association and American Stroke Association (Sacco et al., 2013):

> *"Central nervous system infarction is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. Central nervous system infarction occurs over a clinical spectrum: Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, while silent infarction by definition causes no known symptoms. Stroke also broadly includes intracerebral hemorrhage and subarachnoid hemorrhage."*

These acute events, either of ischemic or hemorrhagic vascular etiology, will be identified by hospital discharge diagnosis codes in patients alive at discharge when the suspected diagnosis at admission was an acute stroke.

For CPRD and THIN patients without direct linkage to hospitalization diagnoses, algorithms based on available information recorded by the GP will be used to identify patients who have been hospitalized and diagnosed with a stroke (see Table 3). Prior validated algorithms to identify ischemic strokes and cerebrovascular events can be used (Andersohn et al., 2006; Arana et al., 2006; Ray et al., 2009; Roumie et al., 2008a). For ischemic stroke, the PPV has been reported to be approximately 86% (95% CI, 79%-91%) in THIN (Ruigómez et al., 2010).

Cardiovascular Deaths

In the CPRD and THIN, participating GPs are required by the NHS to record in the database the date of death. The fact of death is well captured in the database, and date of death has been reported to be accurately recorded for most of the recorded deaths (Shah and Martinez, 2004). However, cause of death is recorded with a variable degree of completeness. Manual review of the historical chronological information surrounding the recorded date of death can provide useful information on the cause.

For ISD Scotland, and for CPRD and THIN practices linkable to HES and ONS, all deaths occurring during the study will be identified. ONS death certificate information includes the date and causes of death in ICD-10 codes.

ONS mortality data will be linked to the HES file to classify deaths as occurring inside versus outside the hospital. The underlying cause of death coded in the national death register file takes into account additional information provided by medical practitioners or coroners after the death has been registered.

Deaths with an underlying cause of death diagnosis code consistent with coronary heart disease death or sudden cardiac death (SCD) (see Table 3), without an alternative noncardiac cause of death and that occur in a noninstitutional setting and outside of the dates of a hospitalization, will be included in the exploratory endpoint as an out-of-hospital death.

In-Hospital Cardiovascular Deaths

In each data source, in-hospital deaths of patients who were not admitted for a non-CV cause can be identified through primary cardiovascular discharge diagnoses (see Table 3). Available supplemental information in identified free text and codes will be evaluated for the following underlying causes included in the operational definition of cardiovascular death (Hicks et al., 2012):

- Death due to AMI: death with a hospital cardiovascular discharge diagnosis occurring within 30 days after a diagnosis, either clinically or by autopsy findings, of AMI or recent myocardial infarction. These deaths will include those with any cardiovascular mechanism related to the event. Deaths resulting from a coronary revascularization procedure to treat an AMI or to treat a complication are included in this category. Therefore, included patients may die within the same admission for the AMI or during another follow-up admission within a time frame of 30 days after the AMI.
- Sudden cardiac death: the patient died unexpectedly from a cardiac cause but not following an AMI. The death can be witnessed or unwitnessed.
  - Witnessed unexpected death occurring (1) without new or worsening symptoms, or (2) rapidly after the onset of new or worsening cardiac symptoms (unless suggestive of AMI that will be classified as death due to AMI), or (3) with objective evidence of an arrhythmia, or (4) after unsuccessful resuscitation from cardiac arrest, or (5) after successful resuscitation from cardiac arrest and without a specific cardiac or noncardiac cause of death.

  - Unwitnessed unexpected death in an individual known to be alive and clinically stable within 24 hours before being found dead and without any evidence of a specific noncardiac cause of death.

- Death due to heart failure: death with a discharge diagnosis of clinical heart failure worsening regardless of its cardiovascular etiology. Evidence of functional or structural heart disease through specific cardiovascular codes must be present. Therefore, hospital admission should have been for heart failure or any other cardiovascular causes except AMI.
- Death due to stroke: death with a cardiovascular discharge diagnosis occurring within 30 days after a diagnosis, either clinically or by autopsy findings, of acute or recent stroke. These deaths frequently have a cardiovascular mechanism related to the event. Deaths resulting from a cerebrovascular procedure to treat a stroke or one of its complications are included in this category. Therefore, this category will include a patient who dies within the same admission for the acute stroke or during another follow-up admission within a time frame of 30 days after the acute event.
- Death due to cardiovascular procedures: death resulting from the immediate complication of a cardiac procedure (other than in the context of an AMI).
- Death due to cardiovascular hemorrhage: death caused by a nonstroke intracranial hemorrhage, nonprocedural or nontraumatic vascular bleeding (i.e., aortic aneurysm), or hemorrhage causing cardiac tamponade.
- Death due to other cardiovascular causes: death due to any other specific known cardiovascular causes not included in the above categories (e.g., pulmonary embolism, peripheral arterial disease, cardiac valvular disease).

Out-of-Hospital Coronary and Cerebrovascular Deaths

The classification and inclusion of events based only on hospitalizations will be most homogeneous across the included data sources in this study; however, a consequence will be the incomplete ascertainment of these events as approximately one-third of patients with an AMI die suddenly before arriving at the hospital (Anderson et al., 2009; Rothwell et al., 2005). Historically, deaths occurring outside of a hospital setting frequently have not been ascertainable in database studies and therefore have not been included in such studies' primary endpoints. We will identify out-of-hospital deaths in the CPRD, THIN, and ISD Scotland, where information on out-of-hospital deaths is available through recorded causes from death certificates or direct linkage to the national mortality registry. Therefore, an exploratory endpoint for sensitivity analysis will include out-of-hospital deaths in addition to MACE, but only for CPRD, THIN, and ISD Scotland; GePaRD will not be included in this pooled analysis.

Out-of-Hospital Coronary Heart Disease Death

Out-of-hospital deaths from coronary heart disease are defined as SCD or deaths due to myocardial infarction in persons dying outside of a hospital setting. These will be ascertained

through diagnoses recorded on autopsy reports and death certificates, as available, using a published validated computerized definition (Chung et al., 2010).

Events identified as out-of-hospital deaths must meet the following criteria:

- Have on the death certificate an underlying cause of death that is compatible with SCD or fatal myocardial infarction (Chung et al., 2010; Ray et al., 2009); the codes provided in Table 3 have been reported with a high PPV for SCD and AMI
- Have no terminal hospitalization
- Have a place of death that is not a hospital institution

Out-of-Hospital Death From Cerebrovascular Diseases
A similar approach will be used to identify out-of-hospital cerebrovascular deaths based on available information. Previously validated algorithms to identify strokes (including cerebrovascular death) will be used (see Table 3).

ANNEX 3 COUNTS OF PRUCALOPRIDE USERS BY DATA SOURCE AND ESTIMATED PRUCALOPRIDE INITIATORS AVAILABLE BY DATE OF DATA ACQUISITION

Table 3-1: Reported (Projected) Counts of Prucalopride Initiators, by Data Source and Year, 2010-2014

	Observed (Estimated or Projected) Annual Counts						
Data Source	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
ISD Scotland	57[a]	272	323	(424)	(555)	(727)	(952)
CPRD	67	254	329	108 (432)	(567)	(745)	(978)
THIN	54	195	272	5 (356)	(466)	(610)	(799)
GePaRD[b]	(259)	(825)	(1,167)	(1,376)	(1,651)	(1,981)	(2,377)

CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; ISD = Information Services Division; THIN = The Health Improvement Network.

[a] Assumed all female.

[b] The GePaRD was not able to provide user counts because of staffing limitations, and estimates were developed from published national data on reimbursed defined daily dose.

Source: Counts (not estimates) were based on e-mail communication from responding study investigators from data sources of interest. Estimates for all UK data sources were based on multiplying the user count from the previous year by the ratio 1.31. This ratio is derived from the (number of new users in 2013)/(number of new users in 2012) in the CPRD.

Table 3-2: Estimated Number of Prucalopride Initiators Available for Analysis by Varying Dates of Data Acquisition

	Cumulative Number of Prucalopride Initiators With Data Available	
Data Source	**Data Acquisition January 1, 2015[a]**	**Data Acquisition January 1, 2017[b]**
CPRD	1,345	2,768
CPRD+THIN	1,708	3,516
Total UK (CPRD+THIN+ Scotland)	2,784	5,875
Germany	2,251	5,278
Total UK and Germany	**5,035**	**11,152**

CPRD = Clinical Practice Research Datalink; THIN = The Health Improvement Network; UK = United Kingdom.

[a] CPRD total through Q3 2014, THIN total through Q3 2014, Scotland total through Q4 2013, Germany total through Q4 2012.

[b] CPRD total through Q3 2016, THIN total through Q3 2016, Scotland total through Q4 2015, Germany total through Q4 2014.

ANNEX 4 STUDY SIZE SCENARIOS

The amount of exposed follow-up time was defined as person-years of current use. The sample sizes were calculated so that

$$\text{Prob}(\exp(\ln(RR) + z \times SE(\ln(RR))) < H = 1-\beta$$

Where

- RR = risk ratio
- z = critical value of a Gaussian variable
- SE(ln(RR)) = sqrt(1/a – 1/N_1 + 1/b – 1/N_0) [formula 9.3 in Rothman (2012); asymptotic standard error of ln(RR)]
  - a = cases exposed
  - b = cases unexposed
  - N_1 = exposed people at risk
  - N_0 = unexposed people at risk
- H = hypothesis for RR
- β = type II error

After the required person-years was calculated (Table 4-1), the number of exposed subjects was calculated by multiplying the total person-years by 365 days per year and dividing by 130 days (the average follow-up time in days for prucalopride users), as shown in Table 4-2. Total events were calculated by multiplying the person-years by (ratio + 1) × rate, where ratio is the ratio of PEG person-years to prucalopride person-years, set to equal 5 for this study (Table 4-3).

Table 4-1 through Table 4-3 summarize study size calculations under various scenarios.

Table 4-1: Minimum Number of Exposed Person-Years to Have Either 80% or 90% Power to Reject Various Hypotheses Regarding the RR at the Two-Sided Alpha = 0.05 Level, Assuming the True RR is 1.0

		Hypothesis				
Rate[a]	**Power**	**RR ≥ 1.5**	**RR ≥ 2**	**RR ≥ 2.5**	**RR ≥ 3**	**RR ≥ 4**
0.0015	80%	38,142	13,050	7,469	5,200	3,270
0.0017		33,650	11,518	6,589	4,591	2,881
0.0020		28,589	9,791	5,599	3,900[b]	2,450
0.0030		19,041	6,521	3,729	2,600	1,631
0.0015	90%	51,060	17,470	10,001	6,959	4,370
0.0017		45,041	15,418	8,819	6,140	3,861
0.0020		38,281	13,100	7,501	5,221	3,280
0.0030		25,491	8,730	5,001	3,480	2,190

RR = risk ratio.

Note: The ratio of unexposed to exposed person-years is 5 to 1.

[a] Rate is per person-year in unexposed.

[b] See example below.

Table 4-2: Minimum Number of Exposed Subjects to Have Either 80% or 90% Power to Reject Various Hypotheses Regarding the RR at the Two-Sided Alpha = 0.05 Level, Assuming the True RR is 1.0

		Hypotheses				
Rate[a]	**Power**	**RR ≥ 1.5**	**RR ≥ 2**	**RR ≥ 2.5**	**RR ≥ 3**	**RR ≥ 4**
0.0015	80%	107,090	36,640	20,970	14,600	9,180
0.0017		94,480	32,340	18,500	12,890	8,090
0.0020		80,270	27,490	15,720	10,950	6,880
0.0030		53,460	18,310	10,470	7,300	4,580
0.0015	90%	143,360	49,050	28,080	19,540	12,270
0.0017		126,460	43,290	24,760	17,240	10,840
0.0020		107,480	36,780	21,060	14,660	9,210
0.0030		71,570	24,510	14,040	9,770	6,150

RR = risk ratio.

Note: The ratio of unexposed to exposed subjects is 5 to 1. Each person is assumed to contribute 130 person-days.

[a] Rate is per person-year in unexposed.

Table 4-3: Total Number of Expected Events (Exposed Plus Unexposed) Given the Minimum Number of Subjects From Table 4-2 at Either 80% or 90% Power to Reject Various Hypotheses Regarding the RR at the Two-Sided Alpha = 0.05 Level , Assuminng the True RR is 1.0

		Hypotheses				
Rate[a]	**Power**	**RR ≥ 1.5**	**RR ≥ 2**	**RR ≥ 2.5**	**RR ≥ 3**	**RR ≥ 4**
0.0015	80%	343	117	67	47	29
0.0017		343	117	67	47	29
0.0020		343	117	67	47	29
0.0030		343	117	67	47	29
0.0015	90%	460	157	90	63	39
0.0017		459	157	90	63	39
0.0020		459	157	90	63	39
0.0030		459	157	90	63	39

RR = risk ratio.

Note: The ratio of unexposed to exposed person-years is 5 to 1.

[a] Rate is per person-year in unexposed.

Alternately, we could use formula 9.5 in Rothman (2012) for rates in place of formula 9.3.

As an example, consider rate equals 0.0020, power equals 80%, upper bound of the 95% confidence interval equals 3, and ratio of PEG person-years to prucalopride person-years equals 5:1 (note b in Table 4-1). For 3,900 exposed patient-years, the standard error using formula 9.3 of Rothman (2012) is 0.39184, whereas using formula 9.5 of Rothman (2012), the standard error is 0.39223. This small difference makes no important difference to the power, hence the sample size.

ANNEX 5 RESUMES OF KEY STAFF

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Present position

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Education

1987-1988 Master of Science in Epidemiology, Harvard School of Public Health, Boston-USA. Fulbright-MSC fellowship.

1987 Certificate in statistical, epidemiological and operational methods applied in Medicine and Public Health with "grande distinction". Ecole de Santé Publique, Université Libre de Bruxelles-Belgium.

1986 Grado de Licenciado with honors, Facultad de Medicina, Universidad de Alicante-Spain.

1985-1986 Master of Public Health with "distinction" Ecole de Santé Publique, Université Libre de Bruxelles-Belgium.

1978-1984 M.D. degree, Facultad de Medicina, Universidad de Alicante-Spain.

1972-1978 Diplôme d´aptitude à accéder à l´Enseignement Supérieur, Certificat d´Enseignement Secondaire Inférieur et Supérieur, Institut Sainte Marie, Brussels-Belgium.

Professional experience

1992-1994 Senior Epidemiologist, Boston Collaborative Drug Surveillance Program, Boston University Medical Center-USA. Assistant Professor, Department of Epidemiology and Biostatistics, School of Public Health, Boston University-USA.

1988-1992 Head, Pharmacoepidemiology Unit, Medical Department, Ciba-Geigy, Basle-Switzerland.

1988	Summer Traineeship at the Boston Collaborative Drug Surveillance Program, Boston-USA.
1986-1987	Stagiairein the Department of Medical Research at the General Directorate XII of the European Communities, Brussels-Belgium.

Publications (as of May 2009)

180 García Rodríguez LA, Patrignani P, González-Pérez A.
Risk of myocardial infarction persisting after discontinuation of non-steroidal anti-inflammatory drugs in the general population.
J Thromb Haemost. 2009 May;7(5):892-4.

179 Moore A, Bjarnason I, Cryer B, García Rodríguez LA, Goldkind L, Lanas A, Simon L.
Evidence For Endoscopic Ulcers As Meaningful Surrogate Endpoint For Clinically Significant Upper Gastrointestinal Harm.
Clin Gastroenterol Hepatol. 2009 Apr 9. [Epub ahead of print]

178 Massó-González EL, Johansson S, Wallander MA, García Rodríguez LA.
Trends in the Prevalence and Incidence of Diabetes in the UK - 1996 to 2005.
J Epidemiol Community Health, Feb 2009; doi:10.1136/jech.2008.080382.

177 Martín-Merino ME, Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA.
Study of a cohort of patients newly diagnosed with depression in general practice: prevalence, incidence, comorbidity and treatment patterns.
Primary Care Companion J Clin Psychiatry 2009 (in press).

176 Ruigómez A, Wallander MA, Johansson S, García Rodríguez LA.
Irritable Bowel Syndrome and Gastroesophageal Reflux Disease in Primary Care: Is There a Link?
Dig Dis Sci. 2009 May;54(5):1079-86.

175 Ruigómez A, Massó-González EL, Johansson S, Wallander MA, and García-Rodríguez LA.
Chest pain without established ischaemic heart disease in primary care patients: associated comorbidities and mortality.
Br J Gen Pract. 2009 Mar;59(560):e78-86.

174 García Rodríguez LA, Tolosa LB, Ruigómez A, Johansson S, Wallander MA.
Rheumatoid arthritis in UK primary care: incidence and prior morbidity.
Scand J Rheumatol. 2008 Dec 31:1-5.

173 Huerta C, Johansson S, Wallander MA, García Rodríguez LA.
Risk of myocardial infarction and overall mortality in survivors of venous thromboembolism.
Thromb J. 2008;6:10.

172 García-Rodríguez LA, Ruigómez A, Martín-Merino E, Johansson S, Wallander MA.
Relationship Between Gastroesophageal Reflux Disease and COPD in UK Primary

Care.
Chest. 2008 Dec;134(6):1223-30. Epub 2008 Aug 8.

171 García-Rodríguez LA, Tacconelli S, Patrignani P.
Role of Dose Potency in the Prediction of Risk of Myocardial Infarction Associated With Nonsteroidal Anti-Inflammatory Drugs in the General Population.
JACC 2008;52(20):1628-1636.

170 Zhang H, García-Rodríguez LA, Hern_ndez-D_az S.
Antibiotic use and the risk of lung cancer.
Cancer Epidemiol Biomarkers Prev. 2008 ;17(6):1308-15.

169 de Abajo FJ, García-Rodríguez LA.
Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents.
Arch Gen Psychiatry. 2008;65(7):795-803.

168 García-Rodríguez LA, González-Pérez A, Stang MR, Wallander MA, Johansson S.
The safety of rosuvastatin in comparison with other statins in over 25000 statin users in the Saskatchewan Health Databases.
Pharmacoepidemiol Drug Saf. 2008;17:953-961.

167 García-Rodríguez LA, Massó-González EL, Wallander MA, Johansson S.
The safety of rosuvastatin in comparison with other statins in over 100000 statin users in UK primary care.
Pharmacoepidemiol Drug Saf. 2008;17:943-952.

166 Massó-González EL, García Rodríguez LA.
Proton pump inhibitors reduce the long-term risk of recurrent upper gastrointestinal bleeding: an observational study.
Aliment Pharmacol Ther. 2008 Sep 1;28(5):629-37. Epub 2008 Jun 26. PMID: 18616644.

164 Huerta C, Rivero E, García Rodríguez LA.
Incidence and risk factors for psoriasis in the general population.
Arch Dermatol. 2007;143(12):1559-65.

163 Toh S, García Rodríguez LA, Hernández-Díaz S.
Use of antidepressants and risk of lung cancer.
Cancer Causes Control. 2007;18(10):1055-64.

162 García Rodríguez LA, González-Pérez A.
Seguridad cardiovascular de los antinflamatorios no esteroideos. Luces y sombras.
Reumatol Clin. 2007;3(3):95-7.

161 García Rodríguez LA, González-Pérez A.
NSAIDs and the risk of acute myocardial infarction.
Nat Clin Pract Rheumatol. 2007;3(4):202-3.

160 Huerta C, Johansson S, Wallander MA, García Rodríguez LA.
Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom.
Arch Intern Med. 2007;167(9):935-43.

159 García Rodríguez LA, Egan K, FitzGerald GA.
Traditional nonsteroidal anti-inflammatory drugs and postmenopausal hormone therapy: a drug-drug interaction?
PLoS Med. 2007;4(5):e157.

158 Sjöberg T, García Rodríguez LA, Lindblad M.
Angiotensin-converting enzyme inhibitors and risk of esophageal and gastric cancer: a nested case-control study.
Clin Gastroenterol Hepatol. 2007;5(10):1160-1166.

157 García Rodríguez LA, Ruigómez A, Panés J.
Use of acid-suppressing drugs and the risk of bacterial gastroenteritis.
Clin Gastroenterol Hepatol. 2007;5(12):1418-23.

156 Ruigómez A, García Rodríguez LA, Johansson S, Wallander MA, Edvardsson N.
Risk of Cerebrovascular Accident After a First Diagnosis of Atrial Fibrillation.
Clinical Cardiology, 2007; 30 (12): 624 - 628.

155 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R.
Morbidity associated with sleep disorders in primary care: a longitudinal cohort study.
Primary Care Companion J Clin Psychiatry 2007;9;5:338-345.

154 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Dent J.
Endoscopic findings in a cohort of newly diagnosed gastroesophageal reflux disease patients registered in a UK primary care database.
Disease of Esophagus 2007;20(6):504-509.

153 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA.
Unspecified abdominal pain in primary care: the role of gastrointestinal morbidity.
Int J Clin Pract. 2007;61(10):1663-70.

152 Wallander MA, Johansson S, Ruigómez A, García Rodríguez LA, Jones R.
Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality.
Family Practice 2007;24(5):403-411.

151 Alonso A, García Rodríguez LA, Logroscino G, Hern_n MA.
Gout and risk of Parkinson disease: a prospective study.
Neurology. 2007;69:1696-700.

150 Hernández-Díaz S, García Rodríguez LA.
Nonsteroidal anti-inflammatory drugs and risk of lung cancer.
Int. J. Cancer 2007; 120:1565-1572.

149 García Rodríguez LA, Barreales Tolosa L.
Risk of Upper Gastrointestinal Complications Among Users of Traditional NSAIDs and COXIBs in the General Population.
Gastroenterology 2007; 132:498-506.

148 Ruigómez A, García Rodríguez LA, Panés J.
Risk of irritable bowel syndrome after an episode of bacterial gastroenteritis in general practice: influence of comorbidities.
Clinical Gastroenterology and Hepatology 2007; 5:465-469.

147 Lanas A, García-Rodríguez LA, Arroyo MT, Bujanda L, Gomollón F, Forné M, Aleman S, Nicolas D, Feu F, González-Pérez A, Borda A, Castro M, Poveda MJ and Arenas J, on behalf of the Investigators of the Asociación Española de Gastroenterología (AEG).
Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with NSAIDs, antiplatelet agents, and anticoagulants.
Am J Gastroenterol. 2007;102(3):507-15.

146 González-Pérez A, García Rodríguez LA.
Gallbladder disease in the general population: association with cardiovascular morbidity and therapy.
Pharmacoepidemiol Drug Saf. 2007;16(5):524-31.

145 García Rodríguez LA, Patrignani P.
The ever growing story of cyclo-oxygenase inhibition.
Lancet 2006;368(9549):1745-1747.

144 Johansson S, Ming EE, Wallander MA, García Rodríguez LA, Herings RM, Goettsch WG, González-Pérez A, McAfee AT, Walker AM.
Rosuvastatin safety: a comprehensive, international pharmacoepidemiology programme.
Pharmacoepidemiology Drug Safety 2006;15(7):454-61.

143 Lanas A, García-Rodríguez LA, Arroyo MT, Gomollon F, Feu F, González Pérez A, Zapata E, Bastida G, Rodrigo L, Santolaria S, Guell M, Martín de Argila C, Quintero E, Borda F, Piqué JM.
Risk of upper gastrointestinal ulcer bleeding associated with selective COX-2 inhibitors, traditional non-aspirin NSAIDs, aspirin, and combinations.
Gut 2006;55;1731-1738.

142 García Rodríguez LA, Lagergren J, Lindblad M.
Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case-control study in the United Kingdom.
Gut. 2006;55(11):1538-44.

141 Ruigómez A, García Rodríguez LA, Wallander M-A, Johansson S, Dent J.
Comparison of gastrooesophageal reflux disease and heartburn diagnoses in UK primary care.
Curr Med Res Opin. 2006;22 (6): 1661-68

140 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Eklund S.
Esophageal stricture: incidence, treatment patterns and recurrence rate.
Am J Gastroenterol 2006;101 (12) : 2685-2692.

139 Hernández-Díaz S, García Rodríguez LA.
Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications.
BMC Medicine 2006;4:22.

138 Huerta C, Varas-Lorenzo C, Castellsague J, García Rodríguez LA.
Nonsteroidal anti-inflammatory drugs and risk of first hospital admission for heart failure in the general population.
Heart 2006;92:1610-1615.

137 Varas-Lorenzo C, García Rodríguez LA, Maguire A, Castellsague J, Pérez-Gutthann S.
Use of oral corticosteroids and the risk of acute myocardial infarction.
Atherosclerosis. 2007;192(2):376-83.

136 Hernán MA, Logroscino G, García Rodríguez LA.
Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson disease.
Neurology 2006;66:1097-1099.

135 de Abajo FJ, Montero D, García Rodríguez LA, Madurga M.
Antidepressants and Risk of Upper Gastrointestinal Bleeding.
Basic & Clinical Pharmacology & Toxicology 2006;98(3):304-310.

134 Hernández-Díaz S, Varas-Lorenzo C, García Rodríguez LA.
Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction.
Basic & Clinical Pharmacology & Toxicology 2006;98:266-274.

133 García Rodríguez LA , Ruigómez A, Panés J.
Acute Gastroenteritis is Followed by an Increased Risk of Inflammatory Bowel Disease.
Gastroenterology 2006;130:1588-1594.

132 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Jones R.
Chest pain in general practice: incidence, comorbidity and mortality.
Family Practice. 2006;23:167-174

131 Lindblad M, García Rodríguez LA, Chandanos E, Lagergren J.
Hormone replacement therapy and risks of oesophageal and gastric adenocarcinomas.
Br J Cancer 2006 Jan 16;94(1):136-41.

130 Arana A, Varas C, González-Pérez A, Guti_rrez L, Bjerrum L, García Rodríguez LA.
Hormone Therapy And Cerebrovascular Events: A Population-Based Nested Case-Control Study.
Menopause. 2006;13(5):730-736.

129 González-Pérez A, García Rodríguez LA.
Upper gastrointestinal complications among users of paracetamol.
Basic and Clinical Pharmacology and Toxicology 2006;98:297-303.

128 González-Pérez A, Fern_ndez-Vidaurre C, Rueda A, Rivero E, García Rodríguez LA.
Cancer incidence in a general population of Asthma patients.
Pharmacoepidemiology and Drug Safety 2006;15:131-8.

127 Patrono C, García Rodríguez LA, Landolfi R, Baigent C.
Low-Dose Aspirin for the Prevention of Atherothrombosis.
N Engl J Med 2005;353:2373-83.

126 Hernán MA, Robins JM, Garcia Rodriguez LA.
Discussion on "Statistical Issues Arising in the Women's Health Initiative".
Biometrics. 2005;61(4):922-30.

125 García Rodríguez LA, González-Pérez A.
Long-term use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population.
BMC Medicine 2005;3:17.

124 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Thomas M, Price D.
Gastroesophageal Reflux Disease and Asthma: A Longitudinal Study in UK General Practice.
Chest. 2005;128(1):85-93.

123 Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA.
Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK.
BMC Cardiovascular Disorders 2005, 5:20.

122 García Rodríguez LA, González-Pérez A, Johansson S, Wallander MA.
Risk factors for Inflammatory Bowel Disease in the general population.
Alimentary Pharmacology & Therapeutics. 2005;22:309-315.

121 González-Pérez A, García Rodríguez LA.
Prostate cancer risk among men with diabetes mellitus.
Cancer Causes and Control. 2005;16:1055-1058.

120 Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA
Nonsteroidal Anti-Inflammatory Drugs and Risk of ARF in the General Population.
American Journal of Kidney Diseases. 2005;45:531-539.

119 García Rodríguez LA, González-Pérez A.
Use of antibiotics and risk of breast cancer.
American Journal of Epidemiology. 2005;161(7):616-619.

118 Lindblad M, García Rodríguez LA, Lagergren J.
Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study.
Cancer Causes and Control (In press).

117 Lindblad M, Lagergren J, García Rodríguez LA.
Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer.
Cancer Epidemiology, Biomarkers and Prevention. 2005;14(2):444-450

116 Huerta C, Lanes SF, García Rodríguez LA.
Respiratory medications and the risk of cardiac arrhythmias.
Epidemiology. 2005;16(3):360-6.

115 González-Pérez A, García Rodríguez LA.
Breast cancer risk among users of antidepressant medications.
Epidemiology. 2005;16:101-5.

114 Hernán MA, Logroscino G, García Rodríguez LA.
A prospective study of alcoholism and the risk of Parkinson's disease.
Journal of Neurology. 2004;251(Suppl 7):14-17.

113 de Abajo FJ, García Rodríguez LA.
Consumo de ácido acetilsalicílico en pacientes con diabetes mellitus (Aspirin use in patients with diabetes mellitus).
Medicina Clinica. 2004;123:236.

112 Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J.
Natural history of gastro-oesophageal reflux disease diagnosed in general practice.
Aliment Pharmacol Ther. 2004;20:751-760.

111 García Rodríguez LA, González-Pérez A.
Risk of breast cancer among users of aspirin and other antiinflammatory drugs.
British Journal of Cancer. 2004;91:525-529.

110 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;109:3000-3006.

109 Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, Fitzgerald D, Hirsh J, Husted S, Kvasnicka J, Montalescot G, García Rodríguez LA, Verheugt F, Vermylen J, Wallentin L.
Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology.
European Heart Journal. 2004;25:166-181.

108 De Abajo FJ, Montero D, Madurga M, García Rodríguez LA.

Acute and clinically relevant drug-induced liver injury: a population based case-control study.
British Journal of Clinical Pharmacology. 2004;58:71-80.

107 De Abajo FJ, Meseguer CM, Antiñol G García Rodríguez LA, Montero D, Castillo JR, Torelló J.
Labor induction with dinoprostone or oxitocine and postpartum disseminated intravascular coagulation: a hospital-based case-control study.
American Journal of Obstetrics and Gynecology. 2004;191:1637-1643.

106 García Rodríguez LA, González-Pérez A.
Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer.
Cancer Epidemiology, Biomarkers and Prevention 2004;13(4):649-53.

105 González-Pérez A, Ronquist G, García Rodríguez LA.
Breast cancer incidence and use of antihypertensive medication in women.
Pharmacoepidemiology and Drug Safety (In Press).

104 García Rodríguez LA, Hernández-Díaz S.
Risk of uncomplicated peptic ulcer among users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs.
American Journal of Epidemiology 2004;159:23-31.

103 Ronquist G, García Rodríguez LA, Ruigómez A, Johansson S, Wallander MA, Frithz G, Svrdsudd K.
Association between captopril, other antihypertensive drugs and risk of prostate cancer.
The Prostate 2004;58:50-56.

102 Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA.
Is there any association between myocardial infarction, gastro-oesophageal reflux disease and acid-suppressing drugs?
Aliment Pharmacol Ther 2003;18:973-978.

101 González-Pérez A, García Rodríguez LA, Lpez-Ridaura R.
Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis.
BMC Cancer 2003, 3:28.

100 Jick SS, Kaye JA, Vasilakis-Scaramoza C, García Rodríguez LA, Ruigómez A, Meier CR, Schlienger RG, Black C, Jick H.
Validity of the General Practice Research Database.
Pharmacotherapy 2003;23:686-689.

99 Hollowell J, Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA.
The incidence of bleeding complications associated with warfarin treatment in general practice in the United Kingdom.
Brit J of Gen Pract 2003;53:312-314.

98 Gonzlez A, García Rodríguez LA.
Estudios de cohortes y de casos y controles: que podemos esperar de ellos.
GH continuada 2003;2(1):44-48.

97 Bak S, Andersen M, Tsiropoulos I, García Rodríguez LA, Hallas J, Christensen K, Gaist D.
Risk of stroke associated with non-steroidal anti-inflammatory drugs: A nested case-control study.
Stroke 2003;34:379-386.

96 Ruigómez A, García Rodríguez LA, Johansson S, Wallander MA.
Is hormone replacement therapy associated with an increased risk of irritable bowel syndrome?
Maturitas 2003;44:133-140.

95 Huerta C, García Rodríguez LA, Wallander MA, Johansson S.
Users of oral steroids are at a reduced risk of developing irritable bowel syndrome.
Pharmacoepidemiology and Drug Safety 2003;12:1-6.

94 García Rodríguez LA, Hernández-Díaz S.
Non-Steroidal Anti-Inflammatory Drugs as a Trigger of Clinical Heart Failure.
Epidemiology 2003;14:240-246.

93 Salvador-Rosa A, Moreno-Pérez JC, Sonego D, García Rodríguez LA, de Abajo-Iglesias FJ.
EL PROYECTO BIFAP: Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria.
Atención Primaria 2002; 30(10): 655-661.

92 Castellsague J, García Rodríguez LA, Duque A, Pérez-Gutthann S.
Risk of serious skin disorders among users of oral antifungals. A population-based study.
BMC Dermatology 2002, 2:14.

91 Simon L, Smolen J, Abramson S, Appel G, Bombardier C, Brater DC, Breedveld F, Brune K, Burmester G, Crofford L, Dougados M, Dubois R, Fitzgerald G, Frishman W, García Rodríguez LA, Hochberg M, Kalden J, Laine L, Langman M, Prescott S, van de Putte L, Whelton A, White W, Williams G.

Controversies in COX-2 Selective Inhibition.
The Journal of Rheumatology 2002, Volume 29;7:1501-10.

90 Huerta C, Zhao SZ, García Rodríguez LA.
The risk of acute liver injury in a diabetic population.
Pharmacotherapy 2002;22(9):1091-6.

89 Lanes S, García Rodríguez LA, Huerta C.
Respiratory medications and risk of asthma death.
Thorax 2002;57:683-686.

88 Bak S, Tsiropoulos I, Kjaersgaard JO, Andersen M, Mellerup E, Hallas J, García Rodríguez LA, Christensen K, Gaist D.
Selective serotonin reuptake inhibitors and the risk of stroke: a population-based case-control study.
Stroke 2002 Jun;33(6):1465-73.

87 Gaist D, Jeppesen U, Andersen M, García Rodríguez LA, Hallas J, Sindrup SH.
Statins and risk of polyneuropathy: a case-control study.
Neurology 2002 May 14;58(9):1333-7.

86 Huerta C, García Rodríguez LA.
Risk of clinical blood dyscrasia in a cohort of antibiotic users.
Pharmacotherapy 2002 May; 22(5):630-6.

85 Ruigómez A, García Rodríguez LA, Johansson S, Wallander MA.
Risk of mortality in a cohort of newly diagnosed atrial fibrillation patients.
BMC Cardiovascular Disorders 2002;2:5.

84 Huerta C, García Rodríguez LA, Wallander MA, Johansson S.
Risk of irritable bowel syndrome among asthma patients.
Pharmacoepidemiology and Drug Safety 2002 Jan-Feb;11(1):31-5.

83 Kennerfalk A, Ruigómez A, Wallander MA, Wilhelmsen L, Johansson S.
Prescription drug therapy and health care utilization among elderly people in the United Kingdom (UK).
The Annals of Pharmacotherapy 2002;36:797-803.

82 Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA.
Incidence of chronic atrial fibrillation in general practice and its treatment pattern.
Journal of Clinical Epidemiology. 2002, 55:358-363.

81 Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA.
Treatment patterns among newly diagnosed heart failure patients in general practice.
European Journal of Clinical Pharmacology. (2002) 57: 813-817.

80 Hernández-Díaz S, García Rodríguez LA.
Incidence of serious upper gastrointestinal bleeding/perforation in the general

population: Review of epidemiologic studies.
Journal of Clinical Epidemiology. 2002;55:157-163.

79 García Rodríguez LA, Hernández-Díaz S.
Epidemiology of upper gastrointestinal side efects of non-steroid anti-inflammatory drugs. Chapter in Therapeutic roles of selective COX-2 inhibitors.
Edited by J.R. Vane and R.M. Botting. William Harvey Press 2001.

78 Patrono C, Patrignani P, García Rodríguez LA.
Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs.
The Journal of Clinical Investigation 2001;108:7-13

77 García Rodríguez LA.
The effect of NSAIDs on the risk of coronary heart disease: fusion of clinical pharmacology and pharmacoepidemiologic data.
Clinical and Experimental Rheumatology 2001 Nov-Dec; 19 (6 Suppl 25):S41-4.

76 García Rodríguez LA, Hernández-Díaz S, de Abajo FJ.
Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies.
British Journal of Clinical Pharmacology 2001 Nov;52(5):563-71.

75 Gaist D, García Rodríguez LA, Huerta C, Hallas J, Sindrup SH.
Are users of lipid lowering drugs at increased risk of peripheral neuropathy?
European Journal of Clinical Pharmacology. 2001;56:931-933

74 Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA.
Gender and drug treatment as determinants of mortality in a cohort of heart failure patients.
European Journal of Epidemiology. 2001;17:329-35.

73 García Rodríguez LA, Hernández-Díaz S.
The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen and combination of these agents.
Arthritis Research. 2001;3:98-101

72 Hernández-Díaz S, García Rodríguez LA.
Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs.
American Journal of Medicine. 2001;110:20-27

71 Hernández-Díaz S, García Rodríguez LA.
Steroids and risk of upper gastrointestinal complications.
American Journal of Epidemiology. 2001;153:1089-1093

70 Gaist D, García Rodríguez LA, Huerta C, Hallas J, Sindrup SH.
Lipid-lowering drugs and risk of myopathy: a population-based follow-up study.
Epidemiology. 2001;12:565-569

69 Johansson S, Wallander MA, Ruigómez A, García Rodríguez LA.
Incidence of newly diagnosed heart failure in UK general practice.
European Journal of Heart Failure. 2001;3:225-31.

68 García Rodríguez LA, Hernández-Díaz S.
Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs.
Epidemiology. 2001;12:570-576

67 Huerta C, García Rodríguez LA.
Incidence of ocular melanoma in the general population and in glaucoma patients.
Journal of Epidemiology and Community Health. 2001;55:338-339

66 Huerta C, García Rodríguez LA, Strom-Muller C, Arellano F.
The risk of obstructive airways disease in a glaucoma population.
Pharmacoepidemiology and Drug Safety. 2001;10:157-163

65 De Abajo FJ, García Rodríguez LA.
Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations.
BMC Clinical Pharmacology. 2001; 1:1.

64 García Rodríguez LA, Huerta-Alvarez C.
Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs.
Epidemiology 2001;12:88-93

63 De Abajo FJ, García Rodríguez LA, Montero D.
Antidepressant drugs:a potential new drug cause of upper gastrointestinal bleeding.
Digestive and Liver Disease. 2000; 32:455-457

62 García Rodríguez LA, Pérez Gutthann S, Jick S.
The UK General Practice Research Database.
In : Strom BL (editor). Pharmacoepidemiology, 3rd Ed. Chichester : John Wiley&Sons,Ltd., 2000. p:375-385.

61 Lipsky PE, Abramson SB, Breedveld FC, Brook P, Burmester R, Buttgereit F, Cannon GW, Catella-Lawson F, Crofford LJ, Doherty M, Dougados M, DuBois RN, Froelich J, García Rodríguez LA, Gibofsky A, Hernández-Díaz S, Hochberg MC, Krause A, Liang MH, Machold K, Peloso PM, Raisz LG, Schayes B, Scheiman JM, Simon LS, Smolen J.
Analysis of the effect of COX-2 specific inhibitors and recommendations for their use in clinical practice.
Journal of Rheumatology. 2000;6:1338-1340

60 Ruigómez A, García Rodríguez LA, Dev VJ, Arellano F, Raniwala J.
Are schizophrenia or antipsychotic drugs a risk factor for cataracts?
Epidemiology. 2000;11:620-623

59 Hernández-Díaz S, García Rodríguez LA.
Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. An overview of epidemiologic studies published in the 1990s.
Archives of Internal Medicine. 2000;160:2093-2099

58 García Rodríguez LA, Varas C, Patrono C.
Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women.
Epidemiology 2000;11:382-7

57 García Rodríguez LA, Huerta-Alvarez C.
Reduced incidence of colorectal adenoma among long-term users of nonsteroidal anti-inflammatory drugs: a pooled analysis of published studies and a new population based study.
Epidemiology. 2000;11:376-381

56 Lanes SF, García Rodríguez LA, Hwang GE.
Baseline risk of gastrointestinal disorders among new users of meloxicam, ibuprofen, diclofenac, naproxen and indomethacin.
Pharmacoepidemiology and Drug Safety. 2000;9:113-117

55 Eland IA, Huerta-Alvarez C, Stricker BHCh, García Rodríguez LA.
The risk of acute pancreatitis associated with acid-suppressing drugs.
British Journal of Clinical Pharmacology. 2000;49:473-478

54 Varas-Lorenzo C, García Rodríguez LA, Pérez-Gutthann S, Duque-Oliart A.
Hormone replacement therapy and incidence of acute myocardial infarction: A population-based nested case-control study.
Circulation. 2000;101:2572-257

53 García Rodríguez LA, Ruigómez A, Wallander MA, Johansson S, Nils-Olov Stlhammar.
Health resource utilization and drug treatment pattern in a cohort of patients with a first episode of gastroesophageal reflux disease.
Pharmacoepidemiology and Drug Safety. 1999;8:493-500

52 García Rodríguez LA, Ruigómez A, Wallander MA, Johansson S, Olbe L.
Detection of colorectal tumor and inflammatory bowel disease during follow-up of patients with initial diagnosis of irritable bowel syndrome.
Scandinavian Journal of Gastroenterology. 2000;3:306-311

51 Ruigómez A, García Rodríguez LA, Hasselgren G, Johansson Srk, Wallander MA.
Overall mortality among patients surviving an episode of peptic ulcer bleeding.
Journal of Epidemiology and Community Health. 2000;54:130-133

50 Castellsague J, García Rodríguez LA, Pérez Gutthann S, Agostinis L, Cattaruzzi C, Troncon MG.
Characteristics of users of inhaled long-acting 2-agonists in a Southern European population.
Respiratory Medicine. 1999;93:709-714

49 García Rodríguez LA, Duque A, Castellsague J, Prez Gutthann S, Stricker BHch.
A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs.
British Journal of Clinical Pharmacology. 1999;48:847-852

48 De Abajo FJ, García Rodríguez LA, Montero D.
Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study.
British Medical Journal. 1999;319:1106-1109

47 Ruigómez A, García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, Johansson S.
Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes.
American Journal of Epidemiology. 1999;150:476-481

46 Ruigómez A, Wallander MA, Johansson S, García Rodríguez LA.
One-year follow-up of newly diagnosed irritable bowel syndrome patients.
Alimentary Pharmacology & Therapeutics. 1999;13:1097-1102

45 Cattaruzzi C, Troncon MG, Agostinis L, García Rodríguez LA.
Positive predictive value of ICD-9th codes for upper gastrointestinal bleeding and perforation in the Sistema Informativo Sanitario Regionale database.
Journal of Clinical Epidemiology 1999;52:499-502.

44 Pérez Gutthann S, García Rodríguez LA, Duque Oliart A, Varas Lorenzo C.
Low-dose diclofenac, naproxen, and ibuprofen cohort study.
Pharmacotherapy. 1999;19(7):854-859

43 García Rodríguez LA, Ruigómez A.
Secondary prevention of upper gastrointestinal bleeding associated with maintenance acid-suppressing treatment in patients with peptic ulcer bleed.
Epidemiology. 1999;10:228-232

42 De Abajo FJ, García Rodríguez LA.
Risk of ventricular arrythmias associated with nonsedating antihistamine drugs.
British Journal of Clinical Pharmacology. 1999;47:307-313

41 García Rodríguez LA, Ruigómez A.
Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study.
British Medical Journal. 1999;318:565-566

40 Blackburn SC, Duque Oliart A, García Rodríguez LA, Prez Gutthann S.
Antiepileptics and blood dyscrasias: a cohort study.
Pharmacotherapy. 1998;18:1277-1283

39 Jick H, García Rodríguez LA, Pérez-Gutthann S.
Principles of epidemiologic research on adverse and beneficial drug effects.
Lancet. 1998;352:1767-1770.

38 Ruigómez A, García Rodríguez LA.
Presence of diabetes related complication at the time of NIDDM diagnosis: an important prognostic factor.
European Journal of Epidemiology. 1998;14:439-445.

37 García Rodríguez LA, Ruigómez A, Hasselgren G, Wallander MA, Johansson S.
Comparison of mortality from peptic ulcer bleed between patients with or without peptic ulcer antecedents.
Epidemiology. 1998;9:452-456.

36 García Rodríguez LA, Pérez Gutthann S.
Use of the UK General Practice Research Database for pharmacoepidemiology.
British Journal of Clinical Pharmacology. 1998;45:419-426.

35 García Rodríguez LA.
Variability in risk of gastrointestinal complications with different nonsteroidal anti-inflammatory drugs.
American Journal of Medicine. 1998;104(3A):30S-34S.

34 Varas-Lorenzo C, García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Pérez Gutthann S.
Hormone Replacement Therapy and the risk of hospitalization for Venous Thromboembolism: A population-based study in southern europe.
American Journal of Epidemiology. 1998;147:387-90.

33 Castellsague J, Pérez Gutthann S, García Rodríguez LA.
Recent epidemiological studies of the association between hormone replacement therapy and venous thromboembolism. A review.
Drug Safety 1998;18:117-23.

32 García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L.
Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs.
Archives of Internal Medicine. 1998;158:33-9.

31 García Rodríguez LA, Wallander MA, Johanson S, Bjrk S.
Renal disease and acid-suppressing drugs.
Pharmacoepidemiology and Drug Safety. 1997;6:247-251.

30 García Rodríguez LA.
Nonsteroidal antiinflammatory drugs, ulcers and risk: a collaborative meta-analysis.
Seminars in Arthritis and Rheumatism. 1997;26(suppl 1):16-20.

29 García Rodríguez LA, Ruigómez A.
Gastric acid, acid-suppressing drugs and bacterial gastroenteritis: how much of a risk?
Epidemiology. 1997;8:571-574.

28 García Rodríguez LA, Ruigómez A, Jick H.
A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom.
Pharmacotherapy 1997;17:721-8.

27 Pérez Gutthann S, García Rodríguez LA, Castellsague J, Duque Oliart A.
Hormone replacement therapy and risk of venous thromboembolism: population based case-control study.
British Medical Journal. 1997;314:796-800.

26 García Rodríguez LA, Wallander MA, Stricker BH.
The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs.
British Journal of Clinical Pharmacology. 1997;43:183-188.

25 Pérez Gutthann S, García Rodríguez LA, Raiford DS.
Individual non-steroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation.
Epidemiology. 1997;8:18-24.

24 Pérez Gutthann S, García Rodríguez LA, Raiford DS, Duque Oliart A, Ris Romeu J.
Non-steroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure.
Archives of Internal Medicine. 1996;156:2433-2439.

23 García Rodríguez LA, Mannino S, Wallander MA, Lindblom B.
A cohort study of the ocular safety of anti-ulcer drugs.
British Journal of Clinical Pharmacology. 1996; 42:213-216.

22 García Rodríguez LA, Stricker BH, Zimmerman HJ.
Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid.
Archives of Internal Medicine. 1996; 156:1327-1332.

21 Henry D, Lim L, García Rodríguez LA, Pérez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT.
Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of collaborative meta-analysis.
British Medical Journal. 1996;312: 1563-1566.

20 Raiford DS, Pérez Gutthann S, García Rodríguez LA.
Positive Predictive value of ICD-9 codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan hospital automated database.
Epidemiology 1996; 7:101-104.

19 García Rodríguez LA, Mannino S, Wallander MA.
Ocular safety of antiulcer drugs.
Lancet. 1995;345: 1059-1060.

18 García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Simon G.
Acute liver injury associated with droxicam use in the region of Friuli-Venezia Giulia.
British Journal of Clinical Pharmacology. 1995;40: 104-105.

17 García Rodríguez LA, Jick H.
Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal anti-inflammatory drugs.
Lancet. 1994;343: 769-772.

16 García Rodríguez LA, Jick H.
Risk of gynaecomastia associated with cimetidine, omeprazole and other anti-ulcer drugs.
British Medical Journal. 1994;308: 503-506.

15 García Rodríguez LA, Williams R, Derby LE, Dean AD, Jick H.
Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors.
Archives of Internal Medicine. 1994;154: 311-316.

14 International Medical Benefit/Risk Foundation Workshop.
Hormone replacement therapy and breast cancer risk.
Pharmacoepidemiology and Drug Safety. 1993;2: 103-105.

13 Pérez Gutthann S, García Rodríguez LA.
The increased risk of hospitalizations for acute liver injury in a population with exposure to multiple drugs.
Epidemiology. 1993;4: 496-501.

12 Jick H, Derby LE, García Rodríguez LA, Jick SS, Dean AD.
Nonsteroidal antiinflammatory drugs and certain rare serious adverse events: a cohort study.
Pharmacotherapy. 1993;13: 212- 217.

11 Pearse SB, García Rodríguez LA, Hartwell C, Russell G.
A pregnancy register of patients receiving carbamazepine in the UK.
Pharmacoepidemiology and Drug Safety. 1992;1: 321-325.

10 Mannino S, García Rodríguez LA, Jick SS.
NSAIDs, quinolones and convulsions: an epidemiologic approach.
Post-Marketing Surveillance. 1992; 6: 119-128.

9 García Rodríguez LA, Pérez Gutthann S, Walker AM, Lueck L.
The role of non-steroidal anti-inflammatory drugs in acute liver injury.
British Medical Journal. 1992; 305: 865-868.

8 Jick H, Derby LE, García Rodríguez LA, Jick SS.
Liver disease associated with diclofenac, naproxen and piroxicam.
Pharmacotherapy. 1992; 12: 207-212.

7 García Rodríguez LA, Walker AM, Pérez Gutthann S.
Non-steroidal anti-inflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study.
Epidemiology. 1992; 3: 337-342.

6 Bollini P, García Rodríguez LA, Pérez Gutthann S, Walker AM.
The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease.
Archives of Internal Medicine. 1992;152:1289-95.

5 Walker AM, García Rodríguez LA, Pérez Gutthann S.
La epidemiologa y la industria farmacetica.
Medicina Clnica. 1992; 98: 465-468.

4 García Rodríguez LA.
On duplicate efforts in pharmacoepidemiology.
The Epidemiology Monitor. 1991; 7: 6.

3 García Rodríguez LA, Pfaff GM, Schumacher MC, Walker AM, Hoffmeister H.
Replacement estrogen use and body mass index.
Epidemiology. 1990; 1: 219-223.

2 García Rodríguez LA, Cayolla Da Motta L.
Years of potential life lost: application of an indicator for assessing premature mortality in Spain and Portugal.
World Health Statistics Quarterly. 1989; 42: 50-56.

1 García Rodríguez LA, Nolasco A, Bolumar F, Alvarez-Dardet C.
Los aos potenciales de vida perdida: una forma de evaluar las muertes prematuras.
Medicina Clnica. 1986; 87: 55-57

Editorial reviewer

2006-	European Heart Journal
2005-	American Journal of Gastroenterology
2005-	Circulation
2005-	Gastroenterology
2004-	Canadian medical Association Journal
2004-	Journal of the National Cancer Institute
2003-	Pharmacoepidemiology and Drug Safety
2002-	Circulation
2001-	New England Journal of Medicine
1998-	The Lancet
1998-	Journal of Clinical Epidemiology.
1995-	American Journal of Epidemiology.
1993-	British Journal of Clinical Pharmacology
1992-	Epidemiology

Languages

Fluent: Spanish, French and English.

Good knowledge: Italian.

Basic knowledge: German.

Brief CV

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Degrees etc.

1972-77	BSc (Honours), First Class, Pharmacology, University of Aberdeen
1981	MBCHB (Dundee UIniversity)
1984	MRCP (UK)
1990	MD with Commendation. (DundeeUniversity)
1992	FRCP (Edin)
1998	FRCP (Lond)
1998	Doctor of Medicine Honoris Causa, University of Medicine & Pharmacy, Cluj Napoca, Romania
1999	Fellow of the European Society of Cardiology (FESC)
2001	Visiting Professor (Hypertension) Mayo Clinic, RochesterMN.
2002	European Society of Cardiology: Specialist in Hypertension
2003	Foundation Fellow (FISPE) International Society of Pharmacoepidemiology
2003	FRCPS(Glasg)
2005	Fellow of the British Pharmacological Society (FBPharmacolS)

Mini Bio

Tom MacDonald is Professor of Clinical Pharmacology and Pharmacoepidemiology in the Medical Research Institute at the University of Dundee, and honorary consultant physician at Ninewells Hospital and Medical School. His research interests are hypertension, cardiovascular disease and pharmacoepidemiology and drug safety. He is a past president of the International Society of Pharmacoepidemiology, a past member of the pharmacovigilance committee of the committee on safety of medicine and the current director of the Tayside Medicines Monitoring Unit (MEMO). He is a president-elect of the British Hypertension

Society and he is also the director of the Regional Cardiovascular Risk Clinic (a ESH accredited centre of excellence). He also directs the Hypertension Research Centre at Ninewells Hospital and Medical School. Professor MacDonald has been involved in clinical trials such as ASCOT & ASTRAL and he was UK coordinator of the VALUE trial and more recently he is on the trial executive committee for the British Hypertension Society, BHF program grant funded PATHWAY Studies. He is the chief investigator for the SCOT and FAST trials and on the executive for the HTA-funded ALL-HEART study.

Recent Publications (since 2005)

Cardiovascular

- L Wei, S Ebrahim, C Bartlett, P G Davey, F M Sullivan, T M MacDonald.Statin use in the secondary prevention of coronary heart disease in primary care: cohort study and comparison of inclusion and outcome with patients in randomised trials. BMJ 2005;330:821-6.
- Weinberger MH, White WB, Ruilope LM, MacDonald TM, Davidson RC, Roniker B, Patrick JL, Krause SL.Effects of eplerenone versus losartan in patients with low-renin hypertension.Am Heart J. 2005;150:426-33.
- Wei L, Murphy MJ, MacDonald TM. The impact on cardiovascular events of increasing high-density lipoprotein cholesterol with and without lipid-lowering drugs. Heart. 2005 Oct 10; [Epub ahead of print]
- Patterson D, Kloner R, Effron M, Emmick J, Bedding A, Warner M, Mitchell M, Braat S, Macdonald TM.The effect of tadalafil on the time to exercise-induced myocardial ischaemia in subjects with coronary artery disease.Br J Clin Pharmacol. 2005;60:459-68.
- Inkster M, Montgomery A, Donnan P, MacDonald T, Sullivan F, Fahey T. Organisational factors in relation to control of blood pressure: an observational study. Br J Gen Pract. 2005;55:931-7.
- Weinberger MH, White WB, Ruilope LM, MacDonald TM, Davidson RC, Roniker B, Patrick JL, Krause SL.Effects of eplerenone versus losartan in patients with low-renin hypertension.Am Heart J. 2005;150:426-33.
- Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA, Coca A, Ekman S, Girerd X, Jamerson K, Larochelle P, MacDonald TM, Schmieder R, Schork A, Stolt P, Viskoper R, Widimský J, Zanchetti A, for the VALUE Trial Investigators. Effects of Valsartan Compared to Amlodipine on Preventing Type 2 Diabetes in High Risk Hypertensive Patients: The VALUE trial. J Hypertension Journal of Hypertension 2006;24:1405-12.
- Inkster ME, Donnan PT, Macdonald TM, Sullivan FM, Fahey T. Adherence to antihypertensive medication and association with patient and practice factors. J Hum Hypertens. 2006 Jan 19; [Epub ahead of print]
- Aird FK, Greene SA, Ogston SA, MacDonald TM, Mukhopadhyay S. Vitamin A and lung function in CG. Journal of Cystic Fibrosis 2006;5:129-131

- Flynn RW, Macdonald TM, Jung RT, Morris AD, Leese GP. Mortality and Vascular Outcomes in Patients Treated for Thyroid Dysfunction. J Clin Endocrinol Metab. 2006 Mar 14; [Epub ahead of print]
- Patterson D, McInnes GT, Webster J, Mitchell M, MacDonald TM. Influence of a single dose of 20 mg tadalafil, a phosphodiesterase 5 inhibitor, on ambulatory blood pressure in subjects with hypertension. Brit J Clin Pharmacol 2006;62:280-7
- Patterson D, Brady AJB, MacDonald TM. Compliance to concordance in hypertension. In: Brady AJB, Petrie J (Eds). New perspectives in Hypertension. Merit Publishing International, Weybridge, 2006. Chapter17, 172-182.
- Parthasarathy HK, MacDonald TM. Primary hyperaldosteronism and other forms of mineralocorticoid hypertension. In : Lip G and Hall R. Comprehensive Hypertension. Chapter 67. Elsevier, New York (In Press)
- Parthasarathy HK, Macdonald TM. Mineralocorticoid receptor antagonists. Curr Hypertens Rep. 2007;9:45-52.
- Parthasarathy HK, Alhashmi K, McMahon A, Struthers AD, Connell JM, McInnes GT, Ford I, Macdonald TM. Does the aldosterone: renin ratio predict the efficacy of spironolactone over bendroflumethiazide in hypertension? A clinical trial protocol for RENALDO (RENin-ALDOsterone) study. BMC Cardiovasc Disord. 2007 May 9;7(1):14 [Epub ahead of print]
- MacDonald TM, Morant SV, Mozaffari E. Treatment patterns of hypertension and dyslipidaemia in hypertensive patients at higher and lower risk of cardiovascular disease in primary care in the UK. Journal of Human Hypertension 2007 Jul 5; [Epub ahead of print]
- MacDonald T M, Morant SV, Mozaffari E. Drug treatment discontinuation and achievement of target blood pressure and cholesterol in United Kingdom primary care. Current Medical Research and Opinion 2007 Oct 1; [Epub ahead of print]
- Wei L, Lang CC, Sullivan FM, Boyle P, Wang J, Pringle S, MacDonald TM. Impact on mortality following first acute myocardial infarction of distance between home and hospital: Cohort study. Heart 2007 Nov 5; [Epub ahead of print]
- Parthasarathy HK, Macdonald TM. Mineralocorticoid receptor antagonists. Current Hypertension Reports. 2007;9:45-52.
- MacDonald TM, Reginster J-Y, Littlejohn TW, Richard D, Lheritier K, Krammer G, Rebuli R. Effect on blood pressure of lumiracoxib versus ibuprofen in patients with osteoarthritis and controlled hypertension: a randomized trial. Journal of Hypertension 2008;26:1695-1702.
- Tzemos N, Lim PO, Wong S, Struthers AD, MacDonald TM. Adverse cardiovascular effects of salt loading in young normotensive individuals. Hypertension 2008;51:1525-30.
- Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour versus drug effects and ten-year follow up of outcome. British Journal of Clinical Pharmacology 2008;66:110-6.
- Kjeldsen SE, McInnes GT, Mancia G, Hua TA, Julius S, Weber MA, Coca A, Girerd X, Jamerson K, Larochelle P, MacDonald T, Schmieder RE, Anthony Schork M, Viskoper R, Widimsky J, Zanchetti A. Progressive effects of valsartan compared with

amlodipine in prevention of diabetes according to categories of diabetogenic risk in hypertensive patients: The VALUE trial. Blood Press. 2008;17:170-7

- Tzemos N, Lim PO, MacDonald TM. Exercise Blood Pressure and Endothelial Dysfunction in Hypertension. International Journal of Clinical Practice 2009; 63,202–206.
- Tzemos N, Lim PO, Macdonald TM. Valsartan Improves Endothelial Dysfunction in Hypertension: A Randomized, Double-Blind Study. Cardiovasc Ther. 2009;27:151-8. Jul 14. [Epub ahead of print]
- Mackenzie IS, Rutherford D, MacDonald TM. Nitric oxide and cardiovascular effects: new insights in the role of nitric oxide for the management of osteoarthritis. Arthritis Research & Therapy 2008;10 (Suppl 2):S3 (E-published ahead of print) .
- Flynn R W, Bonellie S R, Jung RT, MacDonald TM, Morris AD, Leese GPL. Serum Thyroid Stimulating Hormone Concentration and Morbidity from Cardiovascular Disease and Fractures in Patients on Long-term Thyroxine Therapy. Journal of Clinical Endocrinology & Metabolism 2009 (In Press)
- McMahon AD, Conway DI, MacDonald TM, McInnes GT. The Unintended Consequences of Clinical Trials Regulations. PLOS Medicine 2009 (In Press).
- Parthasarathy HK, Pieske B, Weisskopf M, Andrews CD, Brunel P, StruthersAD , MacDonald TM. A randomized, double-blind, placebo-controlled study to determine the effects of valsartan on exercise time in patients with symptomatic diastolic heart failure. European Journal of Heart Failure 2009;11:980-9.
- Mackenzie IS, Wei L, Rutherford D, Findlay EA, Saywood W, Campbell MK, MacDonald TM. Promoting public understanding of randomised clinical trials using the media: the 'Get Randomised' campaign. British Journal of Clinical Pharmacology 2009 2010;69:128-135.
- MacDonald TM, Richard D, Lheritier K and Krammer G. The effects of lumiracoxib 100 mg once daily versus ibuprofen 600 mg three times daily on the blood pressure profiles of hypertensive osteoarthritis patients taking different classes of antihypertensive agents. International Journal of Clinical Practice 2 Parthasarathy HK, Alhashmi K, McMahon AD, Struthers AD, McInnes GT, Ford I, Connell JM,
- MacDonald TM. Does the ratio of serum aldosterone to plasma renin activity predict the efficacy of diuretics in hypertension? Results of RENALDO. J Hypertens. 2010;28:170-7.2010;64:746-55. (e-published April 2010
- ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009;361:1953-62.
- Mackenzie IS, Wei L, Rutherford D, Findlay EA, Saywood W, Campbell MK, MacDonald TM. Promoting public understanding of randomised clinical trials using the media: the 'Get Randomised' campaign. British Journal of Clinical Pharmacology 2010;69:128-135.
- McMahon AD, Conway DI, Macdonald TM, McInnes GT. The unintended consequences of clinical trials regulations. .PLoS Med. 2009 Nov;3(11):e1000131. Epub 2009 Nov 17.
- Flynn R, MacDonald TM, Murray G, Ferguson C, Shah K, Doney A. The Tayside Stroke Cohort: Exploiting Advanced Regional Medical Informatics to Create a

Region-Wide Database for Studying the Pharmacoepidemiology of Stroke. Pharmacoepidemiology and Drug Safety 2010 (In Press)

- Mackenzie IS, Macdonald TM. Treatment of osteoarthritis in hypertensive patients. Expert Opin Pharmacother. 2010;11:393-403.
- Flynn RW, Macdonald TM, Murray GD, Doney A. Systematic review of observational research studying the long-term use of antithrombotic medicines following intracerebral haemorrhage. Cardiovascular Therapeutics 2010;28:177-84.
- Flynn RW, Macdonald TM, Murray GD, Doney A. Systematic review of observational research studying the long-term use of antithrombotic medicines following intracerebral haemorrhage. Cardiovascular Therapeutics 2010;28:Mar 10. [Epub ahead of print]
- Flynn RW, Macdonald TM, Murray GD, Doney AS. Antiplatelet Medicine Prescribing and Subsequent Events Following Intra-cerebral Haemorrhage. Stroke 2010;41:2606-11.
- Brown MJ, McInnes GT, Cherif P, C, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. Lancet 2011;377:312-20. Epub 2011 Jan 12
- Mackenzie IS, Coughtrie MWH, MacDonald TM, Wei L. Antiplatelet drug interactions. Journal of Internal Medicine 2010 Nov 14. doi: 10.1111/j.1365-2796.2010.02299.x. [Epub ahead of print]
- Parthasarathy1 H K, Ménard J, WhiteWB, Young WF, Jr., Williams GH, Williams B, Ruilope LM, McInnes GT, Connell JM, MacDonald TM. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. Journal of Hypertension 2011 J Hypertens. 2011;29:980-990.
- Sheng X, Murphy MJ, MacDonald TM, Wei L. Effectiveness of statins on total cholesterol and cardiovascular disease and all-cause mortality in osteoarthritis and rheumatoid arthritis. Journal of Rheumatology 2012;39:32-40
- Sheng X, Murphy MJ, Macdonald TM, Schembri S, Simpson W, Winter J, Winter JH, Wei L Effect of Statins on Total Cholesterol Concentrations, Cardiovascular Morbidity, and All-Cause Mortality in Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. Clin Ther. 2012;34:374-84.
- Brown MJ, Cruickshank JK, Macdonald TM. Navigating the shoals in hypertension: discovery and guidance. BMJ. 2012 Jan 13;344:d8218. doi: 10.1136/bmj.d8218.
- Flynn RW, Macdonald TM, Murray GD, Macwalter RS, Doney AS. Persistence, Adherence and Outcomes with Antiplatelet Regimens following Cerebral Infarction in the Tayside Stroke Cohort. Cerebrovasc Dis. 2012;33:190-197.
- Nadir MA, Rekhraj S, Wei L, Lim TK, Davidson J, MacDonald TM, Lang CC, Dow E and Struthers AD. Improving The Primary Prevention Of Cardiovascular Events By Using Biomarkers To Identify Individuals With Silent Heart Disease. Journal of the AmericanCollege of Cardiology 2012;60:960-8.

Pharmacoepidemiology/Drug Safety

- Flynn RW, Morris AD, Jung RT, Macdonald TM, Leese GP. Does an automated thyroid register improve the clinical management of hypothyroid patients? An observational study. Clinical Endocrinology 2005;63:116-8
- MacFadyen† RJ, MacDonald TM Cardiovascular safety of COX-2 inhibition: time to inform systems of postmarketing surveillance? Therapy 2005; 2:3, 1–4.
- Wei L, MacDonald TM. The Tayside Medicines Monitoring Unit (MEMO). In: Strom B.L. (Editor) Pharmacoepidemiology (Fourth edition), John Wiley, Chichester 2005
- MacDonald T M, Wei Li. Is there an interaction between the cardiovascular protective effects of low-dose aspirin and ibuprofen? Basic&Clinical Pharmacology & Toxicology 2006;98:275-80
- MacDonald TM. Acetaminophen: Risk-management urgently required. Pharmacoepidemiology and Drug Safety 2006;15:406-9.
- MacDonald TM. A European's Perspective of COX2 Drug Safety. Journal of Cardiovascular Pharmacology 2006;47 Suppl 1:S92-7.
- Wei L, Macdonald TM, Watson AD, Murphy MJ. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study.Pharmacoepidemiol Drug Saf. 2007;16:385-92.
- Parkinson J, Wei L, MacDonald TM. View from the real world. In: Davies M, Kermani F. (Eds). Patient Compliance: Sweetening the pill. Gower, Aldershot 2006 Chapter 2, 7-21.
- Wei L, Chen R, Macdonald TM. Channelling of SSRIs and SNRIs use in the Tayside population, Scotland. Pharmacoepidemiol Drug Saf. 2007 May 24; [Epub ahead of print]
- Wei L, Lang CC, Sullivan FM, Boyle P, Wang J, Pringle S, MacDonald TM. Impact on mortality following first acute myocardial infarction of distance between home and hospital: Cohort study. Heart 2007 Nov 5; [Epub ahead of print]
- Leese GP, Flynn RV, Jung RT, Macdonald TM, Murphy MJ, Morris AD. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS).Clin Endocrinol (Oxf). 2008;68:311-6.
- Wei L; Spiers E, Reynolds N, Walsh S, Fahey T; MacDonald TM. Association between coeliac disease and cardiovascular disease. Alimentary Pharmacology & Therapeutics 2008;15;27:514-9.
- Murphy MJ, Wei L, Watson AD, MacDonald TM. 'Real-life' reduction in cholesterol with statins, 1993 to 2002. British Journal of Clinical Pharmacology 2008;65:587-92.
- MacDonald TM, Morant SV. Prevalence and treatment of isolated and concurrent hypertension and hypercholesterolaemia in the United Kingdom. British Journal of Clinical Pharmacology 2008;65:775-86.
- Chan FK, Abraham NS, Scheiman JM, Laine L; First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Collaborators: Abraham NS, Baigent C, Bresalier RS, Chan FK, Cryer B, Farkouh ME, Fendrick AM, Juni P, Laine L, Lanas A, MacDonald T,

Malfertheiner P, Patrono C, Peterson WL, Peura DA, Scheiman JM, Sung J, Wallace J.Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Am J Gastroenterol. 2008 Nov;103:2908-18. [Epub 2008 Oct 1]

- Burmester G, Lanas A, Biasucci L, Hermann M, Lohmander S, Olivieri I, Scarpignato C, Smolen J, Hawkey C, Bajkowski A, Berenbaum F, Breedveld F, Dieleman P, Dougados M, MacDonald T, Mola EM, Mets A, Van Den Noortgate N, Stoevelaar H. Concise report: The appropriate use of non-steroidal anti-inflammatory drugs in rheumatic disease: opinions of a multidisciplinary European expert panel. Ann Rheum Dis 2010;Published Online First: 10 September 2010 doi:10.1136/ard.2010.128660
- Schembri S, Morant S, Winter John, MacDonald TM. Influenza but not pneumococcal vaccination protects against all cause mortality in patients with chronic obstructive pulmonary disease. Thorax 2009 (Published online 24th March 2009
- Schembri S, Anderson W, Morant S, Winter J,Thompson P, Pettitt D, MacDonald TM, Winter J. Predicting hospitalisation and death from Chronic Obstructive Pulmonary Disease. Respiratory Medicine 2009;103:1461-7. Epub 2009 Jun 9.
- Sheng X, Wei L, Murphy MJ, MacDonald TM. Statins and total (not LDL) cholesterol concentration and outcome of myocardial infarction: results from a meta-analysis and an observational study. European Journal of Clinical Pharmacology 2009;65:1071-80. [Epub ahead of print]
- Simon LS, Strand CV, Boers M, Brooks PM, Tugwell PS, Bombardier C, Fries JF, Henry D, Goldkind L, Guyatt G, Laupacis A, Lynd L, Macdonald T, Mamdani M, Moore A, Saag KS, Silman AJ, Stevens R, Tyndall A.How to ascertain drug safety in the context of benefit. Controversies and concerns. J Rheumatol. 2009;36:2114-21.
- Flynn R, MacDonald TM, Murray G, Ferguson C, Shah K, Doney A. The Tayside Stroke Cohort: Exploiting Advanced Regional Medical Informatics to Create a Region-Wide Database for Studying the Pharmacoepidemiology of Stroke. Pharmacoepidemiology and Drug Safety 2010;19:737-44
- Flynn RW,Macdonald TM, Schembri N, Murray GD, Doney AS. Automated Data Capture from Free-text Radiology Reports to Enhance Accuracy of Hospital Inpatient Stroke Codes. Pharmacoepidemiology and Drug Safety 2010;19:843-7
- Mackenzie IS, Coughtrie MWH, MacDonald TM, Wei L. Antiplatelet drug interactions. Journal of Internal Medicine 2010;268:516-29.
- Wei L, StruthersAD, FaheyT, Watson AD and MacDonald TM. A population-based longitudinal analysis of spironolactone use and renal toxicity. BMJ 2010; 340:c1768. doi: 10.1136/bmj.c1768
- Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. British Journal of Clinical Pharmacology 2011;71:600-7.
- Mackenzie IS, Mantay BJ, McDonnell PG, Wei L, MacDonald TM. Managing security and privacy concerns over data storage in healthcare research. Pharmacoepidemiology & Drug Safety. 2011;20:885-93.

- Mackenzie IS, Macdonald TM, Shakir S, Dryburgh M, Mantay BJ, McDonnell P, Layton D. Influenza H1N1 (swine flu) vaccination: a safety surveillance feasibility study using self-reporting of serious adverse events and pregnancy outcomes.. Br J Clin Pharmacol. 2011 Nov 15. doi: 10.1111/j.1365-2125.2011.04142.x. [Epub ahead of print]
- Wei L, Macdonald TM, Mackenzie IS. Co-prescription of co-trimoxazole and spironolactone in elderly patients. (Editorial) BMJ 2011;343:d5656
- Mackenzie IS, Wei L, Paterson KR, Macdonald TM. Cluster randomised trials of prescription medicines or prescribing policy- public and general practitioner opinions in Scotland. Br J Clin Pharmacol. 2012;74:354-61.
- Rutherford D, Wei L, Mackenzie IS, MacDonald TM. The Philosophy of Doing Observational Medicines Safety Research. Journal of Clinical Research and Bioethics. 2012;3:1 http://dx.doi.org/10.4172/2155-9627.1000131
- Wei l, Macdonald TM, Mackenzie IS. Pioglitazone and bladder cancer: A propensity score matched cohort study. Br J Clin Pharmacol. 2012 May 11. doi: 10.1111/j.1365-2125.2012.04325.x. [Epub ahead of print
- Wei1 L, Professor MacDonald T, Shimi S. The association between appendicectomy in females and subsequent pregnancy rate: A cohort study. Fertility and Sterility 2012;98:401-5.
- Macdonald T., I. Mackenzie and Wei L. Novel Ways to Get Good Trial Data: The UK Experience. Discussion Paper, Institute of Medicine, Washington, DC. 2012. http://iom.edu/Global/Perspectives/2012/GoodTrialDataUK.aspx (accessed May 18, 2012).
- Preiss D, Tikkanen MJ, Welsh P Ian Ford I, Lovato LC, Elam MB, LaRosa JC, DeMicco DA, Colhoun HM, Goldenberg I, Murphy MJ, MacDonald TM, Pedersen TR, Keech AC, Ridker PM, Kjekshus J, Sattar N, McMurray JJV. Lipid Modifying Therapies and the Risk of Pancreatitis: a Meta-Analysis. JAMA 2012; 308:804-11
- Mackenzie IS, Wei L, MacDonald TM. Cardiovascular safety of lumiracoxib: a meta-analysis of randomised controlled trials in patients with osteoarthritis. European Journal of Clinical Pharmacology 2013;69(2):133-41. doi: 10.1007/s00228-012-1335-1. Epub 2012 Jun 26.
- Mackenzie IS, MacDonald TM, Thompson A, Steve Morant, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. British Medical Journal 2012 Jul 13;345:e4447.
- Sheng X, Murphy MJ, MacDonald TM, Wei L. The comparative effectiveness of statin therapy in selected chronic diseases compared with the remaining population. BMC Public Health. 2012 Aug 30;12:712. [Epub ahead of print]
- Wei L, MacDonald TM, Shimi SM. Appendicectomy is Associated With Increased Pregnancy Rate: A Cohort Study. Ann Surg. 2012;256:1039-44.
- Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and Acute Pancreatitis. Arch Intern Med. 2012 Nov 26:1-3. doi: 10.1001/2013.jamainternmed.477. [Epub ahead of print] JAMA Intern Med. 2013 Jan 28;173(2):162-4
- Macdonald TM, Mackenzie IS, Wei L, Hawkey CJ, Ford I; SCOT study group collaborators. Methodology of a large prospective, randomised, open, blinded endpoint streamlined safety study of celecoxib versus traditional non-steroidal anti-inflammatory drugs in patients with osteoarthritis or rheumatoid arthritis: protocol of the standard care versus celecoxib outcome trial (SCOT). BMJ Open. 2013 Jan 29;3(1). pii: e002295. doi: 10.1136/bmjopen-2012-002295. Print 2013.
- Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW and Murphy MJ. Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. Kidney Int. 2013 Mar 13. doi: 10.1038/ki.2013.76. [Epub ahead of print]
- Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the United Kingdom 1990-2010: A descriptive study in the General Practice Research Database. Journal of Neurology, Neurosurgery & Psychiatry 2013 (In Press)

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Senior Director, Epidemiology

Education

MPH, Epidemiology, University of North Carolina, School of Public Health, Chapel Hill, NC

PhD, Biology, Case Western Reserve University, Cleveland, OH

MS, Biology, Case Western Reserve University, Cleveland, OH

BS, Zoology, University of Wisconsin, Madison WI

Summary of Professional Experience

Patricia Tennis, PhD, MPH, is Senior Director of Epidemiology at RTI Health Solutions and was previously Senior Director of Safety Epidemiology at a large international pharmaceutical company, where she designed and implemented safety studies and risk management activities to evaluate medications within the therapeutic areas of neurology, psychiatry, respiratory, and metabolic diseases. Dr. Tennis was the lead epidemiologist on international pregnancy exposure registries. At RTI Health Solutions and elsewhere, she has overseen the conduct of numerous epidemiology studies and participated in discussions of drug safety issues with regulatory agencies in the US, Canada, and Europe. She is a fellow of the International Society of Pharmacoepidemiology and has numerous publications. Dr. Tennis's graduate education involved a minor in population genetics, and while within the pharmaceutical industry, she provided epidemiologic consultation for genetic studies. She brings to RTI Health Solutions her decades of experience and expertise to clients facing issues of drug safety and risk management.

Employment Chronology

2005 to present	Senior Director of Epidemiology	RTI Health Solutions RTI International
2002 to 2005	Global Head of Epidemiology	RTI Health Solutions RTI International
2001 to 2002	Senior Director of Safety Epidemiology	GlaxoSmithKline
1998 to 2000	Director, Neurology and Psychiatry Epidemiology	Glaxo Wellcome
1997 to 1998	Director, CNS, Metabolic, GI, Anesthesia Epidemiology	Glaxo Wellcome
1995 to 1997	Associate Director, CNS, Metabolic, GI, Anesthesia Epidemiology	Glaxo Wellcome
1992 to 1995	Group Leader, Chronic Disease Epidemiology	Burroughs Wellcome
1990 to 1992	Epidemiologist III	Burroughs Wellcome
1989 to 1990	Epidemiologist II/Statistician	Burroughs Wellcome

1988 to 1989	Visiting Scientist	Gesellschaft fuer Strahlen und Umwelt Forschung (Institute for Radiation and Environmental Research) Munich, Germany
1986 to 1987	Postdoctoral Fellow in Pharmacoepidemiology/ Visiting Instructor	University of North Carolina Chapel Hill, NC
1984 to 1986	Postdoctoral Trainee in Cardiovascular Epidemiology	University of North Carolina Chapel Hill, NC

Other Professional Activities

Fellow, International Society of Pharmacoepidemiology

Leadership Course, Center for Creative Leadership, 2000

Essentials of Supervision, Burroughs Wellcome Co., Research Triangle Park, NC, 1994

Leadership/Teamwork Training, Burroughs Wellcome Co., Research Triangle Park, NC

Project Management, Burroughs Wellcome Co., Research Triangle Park, NC, 1992

Scientific Writing, Burroughs Wellcome Co., Research Triangle Park, NC, 1991

Multivariate Analysis (semester course), Ohio State University, Columbus OH, 1983

Publications and Manuscripts

Riera-Guardia N, Saltus CW, Bui CL, Harris DH, Kaye JA, Tennis P, et al. Changes in the landscape of health care database research from 2000 to 2011. RTI Press publication No. RR-0019-1308. Research Triangle Park, NC: RTI Press; 2013.Available at: http://www.rti.org/publications/rtipress.cfm?pubid=21345. Accessed August 26, 2013.

Mines D, Tennis P, Curkendall S, Li, Peterson C, Andrews EB, et al. Topiramate use in pregnancy and risk of oral clefts. Pharmacoepidemiol Drug Saf. 2012;21(Suppl 3):320. doi: 10.1111/j.1399-5448.2012.03324.x.

Tennis P, Toback SL, Andrews EB, McQuay LJ, Ambrose CS. A US postmarketing evaluation of the frequency and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years: 2009-2010 season. Vaccine 2012;30(42):6099-102.

Karve S, Candrilli SD, Kappelman M, Tolleson-Rinehart S, Tennis P, Andrews EB. Healthcare utilization and comorbidity burden among children and young adults in the United States with systemic lupus erythematosus and inflammatory bowel disease. J Pediatr. 2012;161(4):662-670.e2.

Tennis P, Rothman KJ, Bohn RL, Tan H, Zavras A, Laskarides C, et al. Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. Pharmacoepidemiol Drug Saf. 2012;21(8):810-7.

Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. Br J Dermatol. 2011;165(3):465-73.

Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine. 2011;29(31):4947-52.

Toback SL, Beigi R, Sifakis F, Tennis P, Calingaert B. Maternal outcomes among pregnant women receiving live attenuated influenza vaccine. Influenza Other Respi Viruses. 2011 Jun 14. doi: 10.1111/j.1750-2659.2011.00266.x. [Epub ahead of print].

Cunnington M, Weil J, Messenheimer J, Ferber S, Yerby M, Tennis P. Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology. 2011;76(21):1817-23.

Tennis P, Andrews E, Lanza L, Johannes C. Use of secondary population-based databases to evaluate the safety of medications. 2008. RTI Press publication No. MR-0007-0809. Research Triangle Park, NC: RTI International. Available at: http://www.rti.org/rtipress. Accessed October 13, 2008.

Devine S, West SL, Andrews E, Tennis P, Eaton S, Thorp J, Olshan A. Validation of neural tube defects in the full featured—general practice research database. Pharmacoepidemiol Drug Saf. 2008;17(5):434-44.

Tennis P, Andrews E, Hickman P, Miller D, Hollis K, Cook S. The relationship between dosing of alosetron and discontinuation patterns reported by patients participating in a follow-up programme. Aliment Pharmacol Ther. 2007;25(3):317-22.

Andrews EB, Tennis P. Promise and pitfalls of administrative data in evaluating pregnancy outcomes. Pharmacoepidemiol Drug Saf. 2007;16(11):1181-3.

Rubino A, McQuay LJ, Gough SC, Kvasz M, Tennis P. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with type 2 diabetes: a population-based analysis in the UK. Diabet Med. 2007;24:1412-8.

Rubino A, Roskell N, Tennis P, Mines D, Weich S, Andrews E. Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. BMJ. 2007;334(7587):242. doi:10.1136/bmj.39041.445104.BE.

Miller, DP, Bennett L, Hollis KA, Tennis P, Cook SF, Andrews E. A patient follow-up survey programme for alosetron: assessing compliance to and effectiveness of the risk management programme. Aliment Pharmacol Ther. 2006;24(5):869-78.

Andrews EB, Eaton SC, Hollis KA, Hopkins JS, Ameen V, Hamm LR, Cook SF, Tennis P, Mangel AW. Prevalence and demographics of irritable bowel syndrome: results from a large web-based survey. Aliment PharmacoTherap. 2005;22:935-42.

Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology. 2005;64(7):1134-8.

Tennis P, Sherrill B, Fernandez C, Dolan C. Cancer risk in asthmatic populations. Ann Allergy Asthma Immunol. 2005;95(4):354-60.

Cunnington M, Tennis P. Lamotrigine and the risk of malformations in pregnancy. Neurology. 2005;64(6):955-60.

Morrell MJ, Isojarvi J, Taylor AE, Dam M, Ayala R, Tennis P, et al. Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. Epilepsy Res. 2003;54:189-99.

Tennis, P, Eldridge RR, and the International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. Epilepsia. 2002;43(10):161-7.

Reiff-Eldridge R, Heffner CR, Ephross SA, Tennis PS, White AD, Andrews EA. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: A pharmaceutical company commitment. Am J Obstet Gynecol. 2000;182(1 Pt 1):159-63.

Tennis P, Eldridge R, Lamotrigine Pregnancy Registry Scientific Advisory Committee. Six-year interim results of the lamotrigine pregnancy registry. Epilepsia. 40(Suppl 2):196.

Tennis P, Stern R. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology. 1997;49:542-6.

Tennis P, Eldridge R, and the Lamotrigine Pregnancy Registry Committee. Interim results from the lamotrigine pregnancy registry. Epilepsia. 1997;38(suppl 3):266.

Bryant-Comstock L, Hogan P, Shumaker S, Tennis P. Relationship of seizure severity to employment status and education. Epilepsia. 1997;38(suppl 8):H.08.

Hogan P, Bryant-Comstock L, Shumaker S, Tennis P. The effects of Lamotrigine add-on therapy on health care resource utilization. Epilepsia. 1997;38(suppl 8):6.091.

Derby LE, Tennis P, Jick H. Sudden unexplained death among subjects with refractory epilepsy. Epilepsia 1996;37(10):931-5.

Leestma JE, Annegers JF, Brodie M, Brown S, Schraeder P, Tennis P, et al. Sudden unexplained death in epilepsy: observations from a large clinical development program. Epilepsia. 1997;38(1)47-55.

Tennis P, Wozniak C, Cosmatos I, Frick M. A large prospective study of lamotrigine safety. Epilepsia. 1996;37(suppl 5):161.

Tennis P, Eldridge R, Lamotrigine Pregnancy Registry Advisory Committee. Monitoring birth outcomes in the lamotrigine pregnancy registry. Epilepsia. 1996;37(suppl 4):39.

Smith TR, Shumaker S, Rapp S, McFarlane M, Tennis P. Adjunctive lamictal in epilepsy: response to treatment (ALERT) - baseline sample characteristics. Epilepsia. 1996;37(suppl 5):165.

Eldridge R, Tennis P, Lamotrigine Pregnancy Registry Advisory Committee. Monitoring birth outcomes in the lamotrigine pregnancy registry. Epilepsia. 1995;36(S4):90.

Tennis P, Cole TB, McNutt M, Annegers JF, Leestma JE, Rajput A. Cohort study of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. Epilepsia. 1995;36(1):29-36.

Tennis P, Andrews E, Bombardier C, Wang Y, Strand L, West R, et al. Record linkage to conduct an epidemiologic study on the association of rheumatoid arthritis and lymphoma in the province of Saskatchewan, Canada. J Clin Epidemiol. 1993;46:685-95.

Tennis P, Bombardier C, Malcolm E, Downey W. Validity of rheumatoid arthritis diagnoses listed in the Saskatchewan hospital separations database. J Clin Epidemiol. 1993;46:675-83.

Jick SS, Cole TB Mesher RA, Tennis P, Jick H. Idiopathic epilepsy and sudden unexplained death. Pharmacoepidemiol Drug Saf. 1992;1:59-64.

Tennis P. Drug utilization by the 30-64 yr old people in two cities in the Federal Republic of Germany in 1984. Eur J of Clin Pharmacol. 1990;38:447-52.

Tennis P, Hense HW. Changing patterns of antihypertensive drug treatment between 1984 and 1987. Results from a population cohort study in southern Republic of Germany. Eur J Clin Pharmacol. 1990;39:1-7.

Tennis P, Andrews E, Tilson H. The relationship between rheumatoid arthritis and risk of cancer, controlling for the effects of drugs, in hospitalized patients of Saskatchewan Canada. In: Edlavitch SA, editor. Pharmacoepidemiology. Chelsea, MI: Lewis Publ.; 1989. p. 261-71.

Tennis PS, Wing S, Tyroler HA. Racial differences in geographic variation of ischemic heart disease and its decline in women of the southeastern US, 1968-78. National Heart Blood and Lung Institute Workshop on Coronary Heart Disease in Women; Jan 1986.

Tennis P. Genetic divergence of body size produced by food size in laboratory populations of Acheta domesticus (Orthoptera:Gryllidae). Can J Zool. 1985;63:1385-402.

Tennis P. Survivorship, spatial pattern and habitat structure of field crickets (Nemobiinae and Gryllinae) in two old fields. Environ Entomol. 1983;12:110-6.

Tennis PS, Koonce JF, Teraguchi M. Studies on food size as a selection pressure on body size. I. The effects of food size on the average fitness of two size strains of Acheta domesticus (L). Evolution. 1979;33:95-103.

Tennis PS, Koonce JF, Teraguchi M. The effects of population density and food surface area on body weight of Acheta domesticus (L) (Orthoptera:Gryllidae). Can J Zool. 1977;55:2004-10.

Kitchell JF, Koonce JF, Tennis PS. Phosphorus flux through fishes. Verh Internat Verein Limnol. 1975;19:2478-84.

Posters and Presentations

Midkiff KD, Calingaert B, Tennis P, Harris D, Andrews EB. Using an automated computer-based algorithm to increase the efficiency of selecting the best match from National Death Index linkage results. Pharmacoepidemiol Drug Saf. 2012;21(Supp 3):S396.

Mines D, Tennis P, Curkendall S, Li D-K, Peterson C, Andrews EB, et al. Topiramate use in pregnancy and risk of oral clefts. Pharmacoepidemiol Drug Saf. 2012;21(Supp 3):S320.

Riera-Guardia N, Saltus C, Bui C, Harris D, Kaye J, Tennis P, et al. Back in Barcelona, the landscape of database research over the last decade. Pharmacoepidemiol Drug Saf. 2012;21(Supp 3):S306-7.

Tennis P, Davis K, Sturmer T, Brown J, Lanes S. Symposium on addressing challenges in using multiple data sources to evaluate medication risk factors for asthma mortality in persistent asthma. Pharmacoepidemiol Drug Saf. 2011;20(Supp 1):S268.

Tennis P. Health care databases: different methods for evaluating infant outcomes including GPRD, claims data. Comparing outcome ascertainment across a variety of study methods and validation studies. Symposium presented at the 26th Annual International Conference of Pharmacoepidemiology and Therapeutic Risk Management; 2010. Brighton, UK.

Tennis P, Andrews EB, Tobak S, Ambrose C, McQuay L, Rousculp M. Claims algorithms to quantify use of live attenuated influenza vaccine among non-recommended children. Pharmacoepidemiol Drug Saf. 2010;19(Supp 1):S239.

Tennis P, Rothman KJ, Bohn R, Tan H, Anthony M, Zavras A, Calingaert B. Multiple myeloma and IV Bisphosphonate are risk factors for osteonecrosis of the jaw. Pharmacoepidemiol Drug Saf. 2010;19(Supp 1):S313.

Tennis P, Zavras A, Lakarides C, Tan H. Predictive value of ICD and CPT codes for identifying osteonecrosis of the jaw (ONJ). Pharmacoepidemiol Drug Saf. 2009;18(Supp 1):S153.

Tennis P, Cosmatos I, Wozniak C, Whitman M. Evaluation of dose escalation as a risk factor for aderse events in a prospective postmarketing surveillance study. Pharmacoepidemiol Drug Saf. 1997;6(Supp 2):S69.

Tennis P, Stern R. A record linkage study on risk of hospitalization for serious cutaneous conditions after initiation of phenytoin, carbamazepine, and sodium valproate in Saskatchewan, Canada. Pharmacoepidemiol Drug Saf. 1994;3(Supp 1):S29.

Courses Taught

Pharmacoepidemology lectures on various topics, Epidemiology Department, School of Public Health, University of North Carolina, Chapel Hill, NC

Drug Utilization (single lecture), Berlin/European Extension course of McGill University

Pharmacoepidemiology (Short course with Dr. Harry Guess), The German-American Summer School, Bochum, Germany

Pharmacoepidemiology, Department of Epidemiology, University of North Carolina, Chapel Hill, NC

Languages

German: speaking and reading

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EDUCATION

11/2007 **Master in Public Health**,HarvardSchool of Public Health, Boston, MA, USA,

Concentration: Quantitative Methods

Focus: Epidemiology, Decision Sciences

07/2007 **Doctorate in Medical Sciences**, Humboldt University Berlin, Germany

Advisors: Prof. Wernecke (Berlin, Germany) and Prof. Siebert (Hall i.T., Austria)

Thesis: Evaluation of single and combined imaging technologies for the detection of pancreatic cancer and assessment of resectability

11/1999 **Diplom in Statistics**, Ludwig-Maximilians-University, Munich, Germany

Thesis: Development of a prognostic score for polytrauma patients

Minor subjects: Biology, Theoretical Medicine, Computer Science

PROFESSIONAL EXPERIENCE

since 04/2012 **Head of Drug Safety Unit**

Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH (till 12/2012 BIPS - Institute for Epidemiology and Prevention Research), Department of Clinical Epidemiology

02/2009 – 03/2010 **Research Associate**

BIPS - BIPS - Institute for Epidemiology and Prevention Research, Department of Biometry and Data Management, Unit Statistical Methods in Pharmacoepidemiolgy:

Validation of the German Pharmacoepidemiological Research Database (GePaRD), planning and conduct of pharmacoepidemiological studies, comparison of (pharmaco)epimediological study designs in large databases

03/2004 – 04/2004 **Visiting Fellow**, Institute of Technology Assessment (ITA),

Massachusetts General Hospital, Harvard Medical School, Boston, USA

03/2001 – 02/2008 **Research Associate**

Department of Medical Statistics, Medical School Charité, Humboldt University Berlin, Germany

Statistical consulting, teaching, and applied research

01/2000 – 12/2000 **Research Associate**

Department of Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-University, Munich, Germany

Assisted Prof. Hasford on the MedNet Leukaemia Project

TEACHING EXPERIENCE

SS 2013 **Instructor**"Pharmacoepidemiology"

Master Program Epidemiology, University Mainz, Germany

SS 2012 **Instructor**"Statistical Methods"

Master Program Public Health, University Bremen, Germany

WS 2007/08 **Instructor** "Geostatistics"

Master Program Geodäsie und Kartographie, University of Applied Sciences, Berlin, Germany

08/2007 **Teaching Assistant** "RDS 288 – Methods for Decision Making in Medicine"

Harvard School of Public Health, Boston, USA

Instructor: M. G. Myriam Hunink, MD, PhD

2001 – 2008	**Instructor:**undergraduate and graduate level statistics and biostatistics courses Medical School Charité, Humboldt University, Berlin, Germany
2002 – 2008	**Instructor:**intermediate and advanced courses on Biostatistics and Clinical Trials for Investigators Coordinating Center for Clinical Trials, Medical School Charité, Humboldt University, Berlin
2000 – 2006	**Instructor:**development and teaching of a new course of biostatistics for pharmacists Chamber of Pharmacists Baden-Württemberg, Stuttgart, Germany
WS 2000	**Teaching Assistant** "Clinical Epidemiology" School of Public Health and Epidemiology, Ludwig-Maximilians-University, Munich, Germany Instructor: Prof. Hofman

PROFESSIONAL MEMBERSHIPS

- International Biometric Society IBS, German Region
- International Society for Pharmacoepidemiology (ISPE)
- German Society for Epidemiolgy (Deutsche Gesellschaft für Epidemiologie, DGEpi)
- till 11/2010 Vice-Chair of the working group "Statistical methods in clinical research" of the German Society of Medical Information Science, Biometrics and Epidemiology (Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie, gmds)
- since 5/2012 Chair of the working group "Pharmacoepidemiology" of the German Society of Medical Information Science, Biometrics and Epidemiology (gmds) and the German Society for Epidemiolgy (DGEpi)
- Reviewer for conferences of the German Society of Medical Information Science, Biometrics and Epidemiology (gmds), the German Society for Epidemiolgy (DGEpi) and the International Society for Pharmacoepidemiology (ISPE
- Reviewer for scientific journals, e.g. Pharmacoepidemiology and Drug Safety