PASS information

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the Netherlands
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Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
Joint PASS	No
Research question and objectives	To assess patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care in routine clinical practice in the Netherlands. To provide a description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration). To determine time-trends in the characteristics of first-time use of rivaroxaban. To study the occurrence of hospitalization for three bleeding events (primary safety outcomes): intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding among users of rivaroxaban (for the treatment of deep vein thrombosis [DVT] or pulmonary embolism [PE] and prevention of recurrent DVT and PE, stroke prevention in atrial fibrillation and prevention of atherothrombotic events following an acute coronary syndrome) in comparison with individuals receiving

	current standard of care. Secondary objectives: to study the occurrence of other bleeding events leading to hospitalization, non-infective liver disease (secondary safety outcomes) and to study outcomes related to effectiveness (DVT/PE, ischaemic stroke and myocardial infarction) and all-cause mortality.
Country(-ies) of study	The Netherlands
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Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
MAH contact person	Gunnar Brobert

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2 List of abbreviations

ACS	Acute Coronary Syndromes
ALT	Alanine aminotransferase
ASA	Acetylsalicylic acid
AST	Asparagine aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CrCl	Creatinine Clearance
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicine Agency
ENCePP	European Network of Centres in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General Practitioner
INR	International Normalized Ratio
IRB	Institute Review Board
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PAS	Post-authorization study
PASS	Post-authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PCI	Percutaneous intervention
PCP	Primary Care Practitioner
PE	Pulmonary Embolism
PRAC	Pharmacovigilance Risk Assessment Committee
REC	Research Ethics Committee
RMP	Risk Management Plan
SPAF	Stroke Prevention in Atrial Fibrillation
VTE	Venous thromboembolism

3 Responsible parties

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4 Abstract

A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the Netherlands

Version 5.2, 20 Jan 2015

Dr Ron MC Herings

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Rationale and background

Rivaroxaban is an oral, direct Factor Xa inhibitor with multiple indications, including: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE (DVT/PE treatment); stroke prevention in atrial fibrillation (SPAF); and prevention of atherothrombotic events (when combined with antiplatelet therapy) following an acute coronary syndrome (ACS). The use of anticoagulants is associated with the risk of bleeding, and monitoring of the safety profile and patterns of rivaroxaban use in routine care is required. This study in the Netherlands forms part of a post-authorization safety study programme in several European countries.

Research question and objectives

To provide a detailed description of patients who are prescribed oral rivaroxaban for the first time in comparison with those who are prescribed standard of care for the first time, and describe the characteristics of rivaroxaban use (including indication, dose and duration of treatment). To determine time-trends in the characteristics of first-time use of rivaroxaban. Primary safety outcomes are the occurrence of hospitalization for intracranial haemorrhage, gastrointestinal bleeding or urogenital bleeding, among users of rivaroxaban in comparison with individuals receiving current standard of care.

Study design

This study has a cohort design.

Population

Study drug users will be selected form the outpatient pharmacy database in the PHARMO Database Network. All patients aged 2 years and above who have been registered in the database for at least 1 year before the index date will be included. For part of this population, data from General Practice is available which is crucial for the assignment of the indication of use.

Variables

Detailed descriptive variables will be captured for the population, including co-medications. Primary safety outcomes are the occurrence of hospitalization for intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding. Other outcomes of interest include hospitalization for bleeding events not defined in the primary outcome (other bleeding), non-infective liver disease, outcomes related to effectiveness (DVT/PE, ischaemic stroke, myocardial infarction), and all-cause mortality.

Data sources

Data will be obtained from a linked cohort created using the PHARMO Database Network. The PHARMO Database Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands.

Study size

The size of the population receiving rivaroxaban will be dependent on market uptake. Based on an incidence of haemorrhagic stroke in vitamin K antagonist-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 vitamin K antagonist-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with vitamin K antagonist-treated patients, with a power of 80%.

Data analysis

The patient populations will be described according to the descriptive variables, overall and stratified by indication where possible (VTE prevention, DVT/PE treatment, SPAF, ACS, other), naïve or non-naïve status, and switching status. Age- and sex-adjusted odds ratios and 95% confidence intervals (CI) for the descriptive variables, will be computed using logistic regression models both overall and stratified by indication and by naïve or non-naïve status, and switching status.

Crude incidence rates for the safety and effectiveness outcomes will be estimated in the cohorts for DVT/PE treatment, SPAF and ACS. Incidence will be computed using the person–time contribution of the study cohorts, stratified into current, recent, past and non-use.

Age- and sex-adjusted rate ratios with 95% CIs will be estimated for each of the three primary adverse outcomes comparing rivaroxaban with standard of care using Poisson regression analysis based on person–time contribution.

Milestones

Data collection will start from 10 December, 2011 (day after rivaroxaban received marketing authorization for DVT treatment in the Netherlands) and finish on 31 December, 2018.

5 Amendments and updates

Table 1: Amendments

Number	Date	Section of study protocol	Amendment	Reason
6	Jan 2015	9.3.2.1 9.7.2 9.7.2.1	Addition to section on bleeding definition Addition to section on renal failure definition Addition of section to handle missing data	Response to PRAC review
5	Nov 2014	8.2 9.3.1 9.7.1 9.7.2.1 Annex 3	Additional variables for patient characterisation and analyses thereof; strengthened analyses of renal impairment. Table 12, ICD codes related to renal impairment added	Response to PRAC review
4	May 2014	General	Extension of study timelines. Comparator updated for acute coronary syndromes. Added secondary safety outcome: “other bleeding” Transfer to EMA protocol template. Label wording updated. Current protocol is V5.0.	PRAC request
3	Mar 2012		Inclusion of additional indication, treatment of pulmonary embolism. V4.0 of protocol.	Label expansion
2	Dec 2011		Inclusion of additional indication, acute coronary syndrome. V3.0 of protocol submitted with EU RMP V	Label expansion

			7.1	
1	Apr 2011		Inclusion of additional indication, stroke prevention in atrial fibrillation. V2.0 of protocol submitted with EU RMP V 6.1.	Label expansion

6 Milestones

Table 2: Milestones

Milestone	Planned date
Start of data collection (Marketing Authorization granted for DVT treatment)	Q1 2012
Interim report 1 2 years drug utilization data and crude incidences for primary safety outcomes	Q4 2015
Interim report 2 4 years drug utilization data and crude incidences for primary safety outcomes	Q4 2017
End of data collection	Q4 2018
Final data availability	Q4 2019
Progress reports	Annual in November 2014–19
Final report of study results with full outcomes analysis	Q4 2020
Registration in the EU PAS register	Study to be registered after PRAC approval

7 Rationale and background

Rivaroxaban, a direct Factor Xa inhibitor, is licensed for multiple indications:

- The treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients (DVT/PE treatment) (15 mg rivaroxaban twice daily [bid] for 3 weeks, then 15 mg or 20 mg once daily [od]).
- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (stroke prevention in atrial fibrillation [SPAF]) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (20 mg rivaroxaban od).
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (recommended dose: 10 mg rivaroxaban od for 35 days following hip replacement surgery and 14 days following knee replacement surgery).
- Co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (recommended dose 2.5 mg bid).

As is the case with other anticoagulants, clinical studies of rivaroxaban have identified haemorrhage as an important safety outcome (Lassen et al. 2008; Turpie et al. 2009). A post-authorization safety study programme is planned for several European countries. The aim of this document is to summarize the design of a population-based study to characterise new users of rivaroxaban, assess patterns of drug utilization, including adherence to label recommendations, and to assess the risk of bleeding associated with rivaroxaban treatment in comparison with treatment with standard of care, in routine clinical practice in the Netherlands, for DVT/PE treatment, SPAF and ACS. For DVT/PE treatment and SPAF, standard of care is treatment with a vitamin K antagonist (acenocoumarol or phenprocoumon), and for the secondary prevention of ACS, standard of care is antiplatelet drug(s) such as low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor. The standard of care treatments for ACS will require at least dual antiplatelet and be analysed as combination treatment, irrespective of the individual drug combinations used.

8 Research questions and objectives

This post-authorization study was designed to assess patient characteristics and patterns of drug utilization and to quantify outcomes related to safety and effectiveness in new users of rivaroxaban compared with new users of standard of care.

8.1 Primary objective

8.1.1 Patient characteristics and drug utilization

- To provide a description of patients who are dispensed oral rivaroxaban for the first time in comparison with those who are dispensed standard of care for the first time, and describe the characteristics of rivaroxaban use (including dose and duration).

- To determine time-trends in the characteristics of first-time use of rivaroxaban.

8.1.2 Safety and effectiveness outcomes

- To study the occurrence of hospitalization for three bleeding events (primary safety outcomes): intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding among users of rivaroxaban (for VTE treatment, SPAF and ACS) in comparison with individuals receiving standard of care.

8.2 Secondary objective(s)

- To study the occurrence of hospitalization for bleeding events not specified as primary safety outcomes ("other bleeding") in comparison with individuals receiving current standard of care (secondary safety outcome).
- To study the occurrence of non-infective liver disease (secondary safety outcome).
- To study outcomes related to effectiveness (DVT/PE, ischaemic stroke, myocardial infarction).
- To study all-cause mortality.
- To conduct sub-group analysis of safety and effectiveness outcomes in populations of special interest:
  - patients with decreased renal function
  - elderly patients
  - patients with cardiovascular comorbidities e.g. hypertension or diabetes.

9 Research methods

9.1 Study design

This study has a cohort design.

Cohorts of first-time users of either rivaroxaban or standard of care will be identified using the date of first dispensing (index date) of the respective drug (index drug).

A patient will be considered eligible to enter the study cohort as a first-time user of rivaroxaban or a first-time user of "standard of care" when he or she has a first dispensing of the drug recorded during the enrolment period. In the Netherlands, for VTE prevention, DVT/PE treatment and SPAF, standard of care is treatment with a vitamin K antagonist (acenocoumarol or phenprocoumon), and for the secondary prevention of ACS, standard of care is antiplatelet drug(s) such as low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor.

Patients who qualify as members of both cohorts on the same day, will be excluded. First-time users who have any record of being prescribed the other study drug prior to the enrolment period can only join their index drug cohort; these will be categorized as non-naïve, see below (i.e. patients with a previous dispensing of rivaroxaban can only join the standard of care cohort and those with a past dispensing for standard of care can only join the rivaroxaban cohort).

Patients who are first-time users of both rivaroxaban and comparison study drugs during the enrolment period will be assigned to a cohort based on first dispensing, with the date of this dispensing being the index date.

Many patients with ACS have a history of ischaemic heart disease for which platelet inhibition is standard treatment, and thus exclusion of patients with prior use of platelet inhibitors risks excluding a majority of typical ACS patients. Therefore, in patients treated for ACS, those who have been using a vitamin K antagonist or another oral anticoagulant before the index date will be excluded but those who have been using one or more platelet inhibitors will remain eligible to enter the study.

Standard of care for ACS patients is combination therapy, and as such cohort assignment will be based on first use of rivaroxaban (in combination with aspirin or clopidogrel, or multi-antiplatelet therapy), or use of aspirin and clopidogrel and/or other antiplatelet medications.

Study subjects for DVT/PE treatment and SPAF will be categorized as naïve or non-naïve patients according to their previous use of any comparator drugs (Figure 1). Naïve patients will be those without a previous dispensing of the comparator drug recorded before the index date. Non-naïve patients will be those with one or more dispensing of the comparator drug recorded before the index date. Non-naïve patients will be further subdivided into recent switchers (patients exposed to the other study drug in the 6 months prior to the index date) and distant switchers (patients exposed to the other study drug more than 6 months prior to the index date).

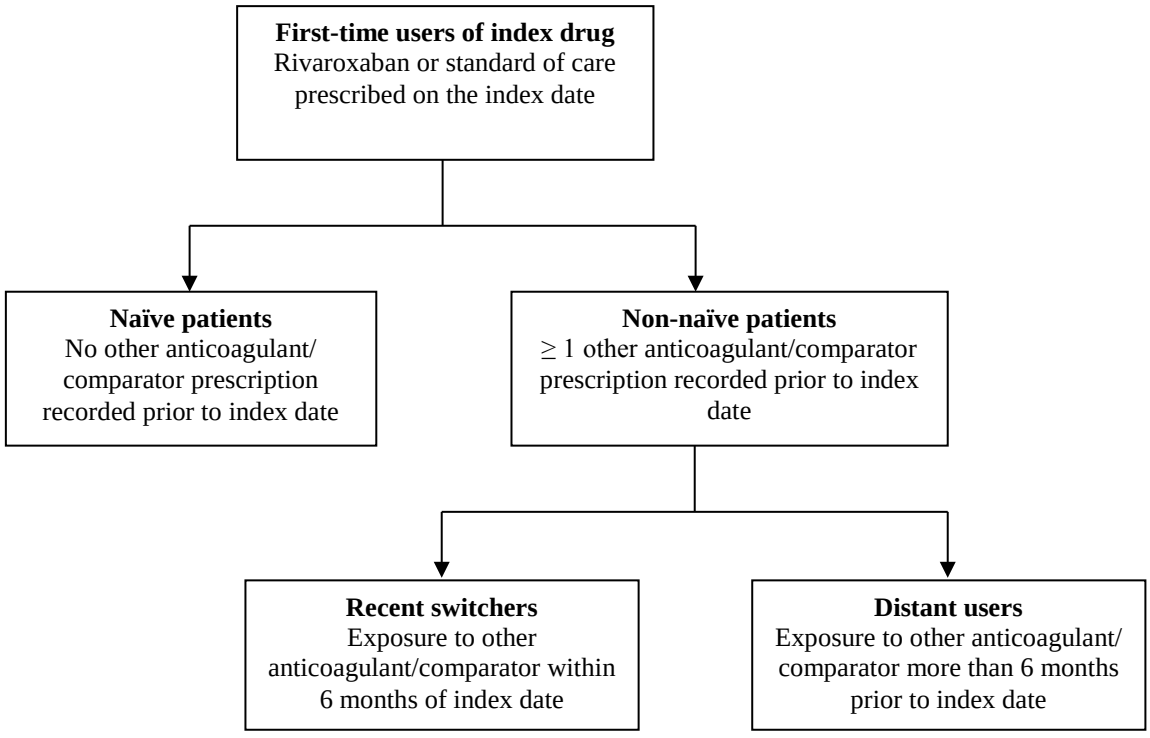

Figure 1. Subdivision of study cohorts for DVT/PE treatment and SPAF.

Data collected for comparison of cohorts is described in Section 9.3

Strengths of the study pertaining to the research question include:

- It uses observational data from routine clinical practice with no selection and no possibility to influence prescribing behaviour.
- PHARMO is a well-validated resource for pharmacoepidemiology research (see Section 9.2).

9.2 Setting

Study drug users will be selected from the outpatient pharmacy database. This database records all outpatient dispensings from primary and secondary care in a well-defined geographic area. All study drug users living in this area will be captured in the database. All patients aged 2 years and above who have been registered in the database for at least 1 year before the index date will be included. A sub-population will be defined of patients for whom GP recorded information is also available.

The enrolment period will start on December 10, 2011 (the day after rivaroxaban received first marketing authorization in the Netherlands for the 'treatment of DVT and long-term secondary prevention of recurrent DVT and PE'). End of enrolment will be 31 December 2017 and end of follow-up will be 31 December 2018. Interim reports will be provided for data collected 2 and 4 years after the date that rivaroxaban receives reimbursement approval for DVT treatment (see Section 6 for detailed milestones). The characteristics of the two study cohorts in the first year and subsequent years of the enrolment period will be compared.

The drug utilization analysis (Section 8.1.1) will be performed in the sub-population captured by both the outpatient pharmacy database and the GP database, in order to enrich the data for the assignment of indication of use.

The Adverse Outcomes analysis (Sections 8.1.2 and 8.2) will be performed in the full rivaroxaban cohort (outpatient pharmacy database with outcomes available from Medical Register), using the dosing as a proxy for the indication when this information is not available, and in the subcohort of comparator drug users captured by both the outpatient pharmacy database and the GP database.

9.3 Variables

9.3.1 Patient characteristics and drug utilization

Descriptive variables of drug utilization will be presented only for the subpopulation captured by both the outpatient pharmacy database and the GP database, as only in this subpopulation sufficient information for the assignment of the indication of use is available. The following characteristics, including risk factors/potential confounders for the outcomes under study, will be presented for comparison between the two cohorts:

- age and sex distribution at index date 
- dose of index drug at index date (not available for vitamin K antagonists as dosing is determined in anticoagulation clinics) 

- dispensed amount (can be used to estimate duration of treatment)
- where available based on hospital discharge diagnosis or from available GP notes, diagnosis associated with the prescribing of the index drug (where not available, dose and duration of index drug will be used as a proxy for the associated diagnosis among rivaroxaban users). Hospital discharge diagnoses and procedures will be identified within 4 weeks before until 7 days after the index date and GP diagnosed will be identified during the index month or in the month before the index date.
- proportion of patients defined as naïve, non-naïve, recent switchers and distant switchers
- number of pregnant women at index date (if communicated by midwife or gynaecologist)
- number of pregnancies after index date (if communicated by midwife or gynaecologist)
- type of other anticoagulant use before the index date among the non-naïve group
- use of specific prescribed medications both in the year before the index date and following the index date, confirming the ACS indication: antiplatelet drugs (low-dose acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticlopidine and ticagrelor);
- use of other medications both in the year before the index date and following the index date: anticoagulants (including dabigatran etexilate and apixaban), antiarrhythmic drugs, antihypertensive drugs, statins, anti-diabetic agents, non-steroidal anti-inflammatory drugs, oral corticosteroids, acid-suppressive drugs, disease-modifying anti-rheumatic drugs, antidepressants, antipsychotic drugs, oral contraceptives, hormone-replacement therapy, strong inhibitors of either cytochrome P450 3A4 or P-glycoprotein (e.g. the systemic azole antimycotics ketoconazole, itraconazole, voriconazole and posaconazole and the HIV-protease inhibitor ritonavir), strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine or phenobarbital) and fluconazole.
- renal status (estimated glomerular filtration rate [eGFR] or creatinine clearance [CrCl] to be obtained where available, and time of measurement relative to index date). Renal status to be defined as: normal renal function (CrCl > 80 mL/min); mild (CrCl < 80–50 mL/min), moderate (CrCl < 50–30 mL/min) or severe (CrCl < 30 mL/min) renal impairment and end-stage renal disease (CrCl < 15 mL/min) or requirement for dialysis).
- smoking status and body mass index (BMI) recorded in the year before the index date and following the index date.
- hospital admissions for bleeding (see ICD-9 codes in Annex 3) in the year before the index date.
- healthcare utilization (e.g. hospital admissions) in the year prior to the index date.

9.3.2 Safety and effectiveness outcomes

For each outcome, potential cases will be identified using ICD-9-CM diagnostic codes (Annex 3) from hospital discharge diagnosis records.

For the purpose of this study, clinically relevant bleedings will be defined as bleedings leading to hospital admission. This restriction is needed to minimize differential misclassification caused by the variability in patients' behavior in seeking care for less severe bleedings. Similarly, the physicians'

attitude towards recording these events may differ between new drugs and standard of care. The consequence of restricting to bleedings identified through hospitalization or referrals is that bleedings leading to death before contact with a health care professional or hospital admission will be ignored. It is assumed that the number of bleeding events missed due to this restriction is small. Nevertheless, the magnitude and impact of this restriction will be assessed in another study of this PASS program (Swedish Record-linkage study).

9.3.2.1 Occurrence of intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding: case definitions

Intracranial haemorrhage (*Annex 3, Table 4)*

Cases of intracranial haemorrhage will be identified in patients admitted to the hospital that meet the criteria for one of the three following categories:

- incident cases of intracerebral haemorrhage recorded following or in association with computed tomography, magnetic resonance imaging (MRI) or x-ray angiography, or an appropriate therapeutic procedure.
- incident cases of subarachnoid haemorrhage recorded following computed tomography, MRI, X-ray angiography or lumbar puncture, or an appropriate therapeutic procedure.
- incident cases of epidural, dural, subdural and arachnoid haemorrhage recorded following computed tomography, MRI, x-ray angiography or lumbar puncture, or an appropriate therapeutic procedure.

As therapeutic procedures are not captured in the database, potential cases will be identified by hospital discharge diagnoses (ICD-9-CM). PHARMO will apply for chart review on therapeutic procedures to define the case (see Section 9.4).

Gastrointestinal bleeding (Annex 3, Table 5)

A patient will have to meet the following criteria to be considered a case of gastrointestinal bleeding:

- the specific site of bleeding originating in the upper or lower gastrointestinal tract or, more specifically, in the oesophagus, stomach, duodenum, jejunum, ileum, colon or rectum.
- for upper gastrointestinal bleeding, the lesion type being erosion, gastritis, duodenitis or peptic (gastric or duodenal) ulcer.
- the lesion type being NOT related to cancer.

Cases will be identified by hospital discharge diagnoses (ICD-9-CM).

Urogenital bleeding (Annex 3, Table 6)

A patient will have to be admitted to the hospital for urogenital bleeding, i.e. the specific site of bleeding originating in the urogenital tract.

Cases will be identified by hospital discharge diagnoses (ICD-9-CM).

9.3.2.2 Secondary safety outcome: case definition

Other bleeding leading to hospitalization (Annex 3, Table 7)

A patient will have to meet the following criteria to be considered a case of "other bleeding":

- admitted to hospital with a bleeding event occurring before hospitalization (i.e. excluding in-hospital bleeding events).

Cases will be identified by hospital discharge diagnoses (ICD-9-CM).

Non-infective liver disease (Annex 3, Table 8)

A patient will have to meet both of the following criteria to be considered a case of non-infective liver disease:

- The patient having been admitted to hospital with acute liver injury.
- Free of cancer, other liver disease (including infectious hepatitis, chronic liver disease etc.), gallbladder or pancreatic disease and alcoholism.

Potential cases will be identified by hospital discharge diagnoses (ICD-9-CM) and chart review will be applied for (see Section 9.4) to define the case. If chart review is approved and laboratory values are available in the chart, the following additional criterion will be applied: an increase of more than three times the upper limit of the normal range in alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or a combined increase in ALT, AST or alkaline phosphatase (AP) and total bilirubin, provided one of them is twice the upper limit of the respective normal range.

9.3.2.3 Secondary outcomes related to effectiveness

DVT and PE (Annex 3, Table 9)

A patient will have to meet the following criteria to be considered a case of DVT or PE:

- the patient having been admitted to hospital with a diagnosis of DVT or PE

or

- having a DVT or PE diagnosis documented in the general practitioner database.

Ischaemic stroke (Annex 3, Table 10)

A patient will have to meet the following criteria to be considered a case of ischaemic stroke: the patient having been admitted to hospital with a diagnosis of ischaemic stroke.

MI (Annex 3, Table 11)

A patient will have to meet the following criteria to be considered a case of MI: the patient having been admitted to hospital with a diagnosis of MI.

9.3.2.4 Deaths (all-cause mortality)

Date of death is available in the PHARMO database network, as registered in the different databases (GP, pharmacy, hospital deaths) and confirmed through linkage with the Dutch central bureau of genealogy.

9.4 Data sources

Data for the study will be obtained from a linked cohort created using the PHARMO Database Network. The PHARMO Database Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands. These different data sources are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record-linkage method can be found elsewhere (van Herk-Sukel et al. 2010; Herings RMC 2012)

The longitudinal nature of the PHARMO Database Network system enables follow-up of more than 4 million residents (25% of total population) of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between data sources differs. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is 1year. All electronic patient records in the PHARMO Database Network include information on age, sex, socio-economic status and mortality. Other information available is dependent on the data source

To address the objectives of the present study, the following data sources will be used: outpatient pharmacy database, Dutch National Medical Register, general practitioner (GP) data and inpatient pharmacy database. The outpatient pharmacy database has a source population of about 4 million residents and is fully linked to the national Dutch National Medical Register. The GP and inpatient pharmacy databases each represent different, partially overlapping subsets of the outpatient pharmacy/Medical Register source population.

The drug utilization analysis will be performed in the subpopulation captured by both the outpatient pharmacy database and the GP database, in order to enrich the data for the assignment of indication of use. The Adverse Outcomes analysis will be performed in the full rivaroxaban cohort (outpatient pharmacy database with outcomes available from Medical Register), using the dosing regimen as a proxy for the indication when this information is not available, and in the subcohort of comparator drug users captured by both the outpatient pharmacy database and the GP database.

The PHARMO Network has been used in previous studies of anticoagulant use and bleeding risk (Penning-van Beest et al. 2005; Penning-van Beest et al. 2007; Penning-van Beest et al. 2008; van der Linden et al. 2009).

Hospital discharge diagnoses in the Dutch National Medical Register are recorded using ICD-9-CM codes. Currently, Dutch hospitals are transitioning from ICD-9 to ICD-10 coding but the majority of hospitals still uses ICD-9. PHARMO will update the code lists to include ICD-10 codes as soon as most admissions are in ICD-10.

PHARMO can apply for chart review to extract additional information about a case in the hospital where he/she was admitted. However, approval is needed from the database provider (Dutch National Medical Register) as well as the individual hospitals.

9.5 Study Size

All patients registered in the PHARMO outpatient pharmacy database and meeting the inclusion criteria will be included. The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest (DVT/PE treatment, ACS and SPAF).

According to a preliminary sample size calculation, based on an incidence of haemorrhagic stroke in vitamin K antagonist-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 vitamin K antagonist-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with vitamin K antagonist-treated patients with a power of 80%.

9.6 Data management

The PHARMO Database Network combines data from different sources (pharmacy, hospital, laboratory etc.). These different sources are probabilistically linked through validated algorithms that ensure the privacy of the patients is maintained. Before databases are linked, those patients for whom linkage-critical information (date of birth, gender, GP) is missing are removed.

For each study, specific checks on the linked data are performed, depending on which data sources are used. Patients are regarded eligible to be included in a study if they are registered and can be followed in all required databases. For the PHARMO pharmacy databases specifically, prescriptions that have not been dispensed (because patients did not collect them) are removed from the dataset. Furthermore, the prescribed dosage regimen and dispensed quantity are checked and extremely high dosages and quantities for the specific type of drug are regarded as missing values.

Study data are manipulated and analysed using the utility SAS Enterprise Guide, an environment for SAS enabling the storage of syntaxes or codes belonging to a single study in one project file, subdivided into project flows for different aspects of a study. All programming is developed in accordance with standard operating procedures and reviewed by an experienced analyst at PHARMO. Furthermore, all results and reports are audited by the Quality Control department, using a standardized check list.

9.7 Data analysis

The following analyses will be performed.

9.7.1 Patient characteristics and drug utilization

The overall patient populations will be described according to the descriptive variables mentioned in Section 9.3.1. and stratified by naïve or non-naïve status, and switching status.

The patient populations, stratified by indication (VTE prevention, DVT/PE treatment, SPAF, ACS, other), will be described according to the descriptive variables. Where information from hospital admissions or GP notes are not available, the diagnosis associated with the prescribing of rivaroxaban will be assigned to one of the indications based on the dose and duration of treatment (see Section 7).

The baseline risk of being dispensed one of the co-medications or being hospitalized for bleeding prior to the index date will be assessed by computing the odds ratio of being dispensed that drug or being hospitalized for that indication among first-time users of rivaroxaban compared with first-time users of standard of care. Age- and sex- adjusted odds ratios and 95% confidence intervals will be computed using logistic regression models both overall and stratified by indication. Cohorts will be stratified based on naïve or non-naïve status, and switching status within the non-naïve group.

9.7.2 Safety and effectiveness outcomes

The two cohorts (of first-time users of rivaroxaban and first-time users of standard of care) will be followed up from the index date until 12 months after the end of the enrolment period for potential outcomes (safety and effectiveness). For each outcome, the first hospitalization for that outcome during the follow-up period will be identified. A separate follow-up will be performed for each of the outcomes.

For all outcomes (for DVT/PE treatment, SPAF and ACS), crude incidence rates will be estimated in both cohorts, using an as-treated approach. In this, person– time will be categorized into current, recent, past and non use. Current use will refer to person–time up to 7 days after the end of supply of the index drug, recent use will refer to person–time up to 90 days after the end of current use, past use will include all person–time contribution after the end of recent use up to 1 year after the end of current use, non-use will include all remaining time person–time contribution after past-use until end of follow-up.

Age- and sex-adjusted rate ratios with 95% CIs will be estimated for each of the three adverse outcomes comparing rivaroxaban with standard of care using Poisson regression analysis. Where numbers and data permit, adjustment will be made for relevant co-medication (described in the drug utilization section), indication and previous hospitalization for bleeding.

As a general strategy, no data imputation strategies will be applied to supplement missing data. The requirement for inclusion is complete data for critical variables such as exposure to rivaroxaban or standard of care and hospitalizations for bleedings or any other outcome event; otherwise this individual is not eligible to be a member of the study population. However, missing values may occur for potential confounder or effect modifying variables. In this case, individuals with missing values will be kept in the analysis and a separate category will be created for missing values of that variable. In sub-analyses to evaluate confounding or effect modification by variables with a large proportion of missing values, the evaluation will be considered to be conducted on the subset with complete data for the variable of interest.

9.7.2.1 Sub-cohorts

The PHARMO Database Network consists of databases which differ in geographical catchment area. Data from GP records and inpatient dispensings are available for different sub-cohorts of the source population, which is based on the outpatient pharmacy dispensing database.

General practitioner data will be used as an additional source for identification of the indication of study drug use in the drug utilization analysis and to identify renal status in the safety analysis.

To determine the renal status of patients primary care information and hospital discharge diagnoses will be used. For the subset of patients with GP data, eGFR values (when available) allow classification of the GFR. In the total subset, ICD-9 hospital discharge diagnoses related to renal impairment will be used (Table 12):

In addition, use or non-use of medication used by patients with advanced renal disease is available. Patients will then be characterised as:

End-stage renal disease

- a code for dialysis (V45.1 or V56) given within one year before index date.

Advanced renal disease

- a diagnosis of chronic renal failure (585) given 3 years or more before index date or
- any diagnosis of renal disease (see list) before index in combination with use of phoshate binding drugs, sodium bicarbonate or erytropoetic drugs within one year before index date.
- not being categorized as end stage renal disease (see above)

Mild renal disease

- any diagnosis of renal disease (see ICD-9 list) before index
- not being categorized as end stage or advanced renal disease (see above)

No renal disease

- none of the above

Grouped by renal status, data will be analysed to determine:

- initial indication for rivaroxaban
- rivaroxaban dose received
- crude incidences (calculated as described above) of primary safety outcomes and outcomes related to effectiveness by renal function and by dose

Inpatient dispensing data will be used to follow patients from the date that rivaroxaban or standard of care is started in hospital. The occurrence of an intracranial haemorrhage, gastrointestinal bleeding or urogenital bleeding during hospitalization will be determined on the basis of discharge diagnoses and, if feasible, medical chart review.

It is likely that a potential misclassification of renal failure will be more pronounced in mild renal failure whereas severe forms of renal failure most likely will be readily identified.

9.7.2.2 Sensitivity analyses

Sensitivity analyses will be performed around the start and stop of treatment to account for differences in the mode of action of rivaroxaban, vitamin K antagonists and other comparators. This will be taken into account in the analyses of outcomes. Analysis of data gathered in the drug utilization/patient characteristics part of the study will allow for the recognition of any unexpected biases, which can subsequently be accounted for in the outcomes analyses.

9.8 Quality control

For each outcome, potential cases will be identified using ICD-9-CM diagnostic codes (Annex 3) from discharge diagnosis records in the hospital database. If additional information is needed to determine the case, then PHARMO will apply for medical chart review in the hospital where the case was admitted. However, approval is needed from the database provider (Dutch National Medical Register) as well as the individual hospitals.

9.9 Limitations of the research methods

Limitations of this study include:

- The possibility for unmeasured confounders for bleeding affecting the data e.g. inadequate or missing recording of ethnicity, alcohol intake or over-the-counter use of some medications.
- Underreporting of events occurring in-hospital i.e. bleeding events occurring during admission for another diagnosis are not recorded as a primary diagnosis and recoding of secondary diagnoses are not mandatory.
- Prescriptions started in-hospital or events in the immediate post-discharge period may be missed from outpatient (pharmacy and general practitioner) records.
- Inadequate data concerning medication compliance.
- Potential for misclassification of exposure to vitamin K antagonist due to complex dosing with multiple strengths of tablet.
- For the effectiveness outcome of DVT/PE, it is possible that discharge diagnoses may lack sensitivity, and data may need to be interpreted with caution (Severinsen et al. 2010).

9.10 Other aspects

None applicable.

10 Protection of human subjects

The study will be conducted in accordance with Good Epidemiology Practices (ISPE 2007). Ethical approval will not be relevant because all data sources used are anonymous and are linked through probabilistic linkage using demographic variables of the patients. All other identifying information will be deleted after linkage of the various databases. This approach is approved by the Dutch Data Protection Authority ('College Bescherming Persoonsgegevens'). Confidentiality of patient records

will be maintained at all times. All analyses of electronic records will be performed using appropriately de-identified data without access to personal identifying information. All study reports will contain aggregate data only and will not identify individual patients or physicians. Medical record abstraction, if available, will only be performed after receiving a waiver of authorization from the relevant data holder's privacy board and approval from an Institute Review Board (IRB). At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting of adverse events.

11 Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

12 Plans for disseminating and communicating study results

- The study is registered on clinicaltrials.gov (NCT01947985) and will be registered on the ENCePP/EU PAS Register website once PRAC approval is achieved.
- Reports will be shared with the authorities as outlined in Section 6.
- Routine updates will be provided annually in the PBRER.
- The principal investigator intends to presented and/or publish data from this study in internationally recognised forums following Good Publication Practice.

13 List of references

European Medicines Agency (2012) "Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products."

Herings RMC, P. L. (2012). Pharmacy -based Medical Record Linkage Systems, John Wiley & Sons Ltd.

ISPE. (2007). "Guidelines for good pharmacoepidemiology practices (second revision)." Retrieved 10 Oct, 2010, from http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

Lassen, M. R., W. Ageno, et al. (2008). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty." N Engl J Med **358**(26): 2776-2786.

Penning-van Beest, F., J. Erkens, et al. (2005). "Main comedications associated with major bleeding during anticoagulant therapy with coumarins." Eur J Clin Pharmacol **61**(5-6): 439-444.

Penning-van Beest, F. J., J. Koerselman, et al. (2007). "Quantity and quality of potential drug interactions with coumarin anticoagulants in the Netherlands." Pharm World Sci **29**(6): 671-675.

Penning-van Beest, F. J., J. Koerselman, et al. (2008). "Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants." J Thromb Haemost **6**(2): 284-290.

Severinsen, M. T., S. R. Kristensen, et al. (2010). "Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution." J Clin Epidemiol **63**(2): 223-228.

Turpie, A. G., M. R. Lassen, et al. (2009). "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial." Lancet **373**(9676): 1673-1680.

van der Linden, M. W., S. Gaugris, et al. (2009). "COX-2 inhibitors: complex association with lower risk of hospitalization for gastrointestinal events compared to traditional NSAIDs plus proton pump inhibitors." Pharmacoepidemiol Drug Saf **18**(10): 880-890.

van Herk-Sukel, M. P., L. V. van de Poll-Franse, et al. (2010). "New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System." Eur J Cancer **46**(2): 395-404.

Annex 1. List of stand-alone documents

Table 3: List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title:
A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the Netherlands.

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8
1.1.2 End of data collection[2]	☒	☐	☐	8
1.1.3 Study progress report(s)	☒	☐	☐	8
1.1.4 Interim progress report(s)	☒	☐	☐	8
1.1.5 Registration in the EU PAS register	☒	☐	☐	8
1.1.6 Final report of study results.	☒	☐	☐	8

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	9
2.1.2 The objective(s) of the study?	☒	☐	☐	9, 10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9,10
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	17,18

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	12
4.2.2 Age and sex?	☒	☐	☐	12
4.2.3 Country of origin?	☒	☐	☐	12
4.2.4 Disease/indication?	☒	☐	☐	12,13
4.2.5 Co-morbidity?	☒	☐	☐	12,13
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	17
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	13–15
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	18

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	12,13
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	16
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16
8.1.3 Covariates?	☒	☐	☐	16
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	12,13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	12,13
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	12,13
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	16
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory	☒	☐	☐	16

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	16

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17
10.3 Are descriptive analyses included?	☒	☐	☐	17
10.4 Are stratified analyses included?	☒	☐	☐	17
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	17,18
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	17,18

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	19
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	16,17
11.3 Are methods of quality assurance described?	☒	☐	☐	18
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	18,19
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	19 19
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	16
12.3 Does the protocol address other limitations?	☒	☐	☐	18,19

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	19
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	19
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19

Comments:

Annex 3. Additional information: ICD-9-CM codes.

Table 4. ICD-9-CM codes for intracranial haemorrhage.

ICD-9-CM code	Description
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial haemorrhage

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table 5. ICD-9-CM codes for gastrointestinal bleeding.

ICD-9-CM code	Description
456.0	Esophageal varices with bleeding
456.20	Esophageal varices in diseases classified elsewhere, with bleeding
530.7	Gastroesophageal laceration-hemorrhage syndrome (Mallory-Weiss syndrome)
531.0	Acute gastric ulcer with haemorrhage
531.2	Acute gastric ulcer with haemorrhage and perforation
531.4	Chronic or unspecified gastric ulcer with haemorrhage
531.6	Chronic or unspecified gastric ulcer with haemorrhage and perforation
532.0	Acute duodenal ulcer with haemorrhage
532.2	Acute duodenal ulcer with haemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with haemorrhage
532.6	Chronic or unspecified duodenal ulcer with haemorrhage and perforation
533.0	Acute peptic ulcer with haemorrhage
533.2	Acute peptic ulcer with haemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer with haemorrhage
533.6	Chronic or unspecified peptic ulcer with haemorrhage and perforation
534.0	Acute gastrojejunal ulcer with haemorrhage
534.2	Acute gastrojejunal ulcer with hemorrhage and perforation
534.4	Chronic or unspecified gastrojejunal ulcer with haemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with haemorrhage and perforation
569.3	Haemorrhage of rectum and anus
578.0	Haematemesis
578.1	Blood in stool (melaena)
578.9	Haemorrhage of gastrointestinal tract, unspecified

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table 6. ICD-9-CM codes for urogenital bleeding.

ICD-9-CM code	Description
596.7	Haemorrhage into bladder wall
599.7	Haematuria
602.1	Congestion or haemorrhage of prostate
621.4	Haematometra
623.6	Vaginal hematoma (hematocolpos)
626.2	Excessive or frequent menstruation
626.3	Puberty bleeding
626.5	Ovulation bleeding
626.6	Metrorrhagia
626.7	Postcoital bleeding
626.8	Other specified abnormal uterine and vaginal bleeding
626.9	Abnormal uterine and vaginal bleeding, unspecified
627.0	Premenopausal menorrhagia
627.1	Bleeding, postmenopausal
878.4	Open wound of vulva

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Table 7. ICD-9-CM codes for other bleeding leading to hospitalization can be provided on request.

Table 8. ICD-9-CM codes for non-infective liver disease.

ICD-9-CM code	Description
570	Acute and subacute necrosis of liver
571.40	Chronic hepatitis, unspecified
571.41	Chronic persistent hepatitis
571.49	Chronic hepatitis, other
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
572.0	Abscess of liver
572.1	Portal pyemia
572.2	Hepatic coma
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
573.0	Chronic passive congestion of liver
573.3	Hepatitis, unspecified
573.4	Hepatic infarction
573.8	Other specified disorders of liver
573.9	Unspecified disorder of liver

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Table 9. ICD-9-CM codes for deep vein thrombosis (DVT) and pulmonary embolism (PE)

ICD-9-CM code	Description
415.1	Pulmonary embolism and infarction
451.0	Phlebitis and thrombophlebitis of superficial leg veins
451.11	Deep vein thrombosis, femoral
451.19	Deep vein thrombosis, leg veins, spec
451.2	Thrombophlebitis, leg veins, unspec
451.81	Thrombophlebitis, iliac
451.89	Thrombophlebitis, spec
451.9	Thrombophlebitis, unspec
452.	Portal vein thrombosis
453.0	Budd-Chiari syndrome
453.1	Thrombophlebitis migrans
453.2	Thrombophlebitis of vena cava
453.3	Thrombophlebitis of renal vein
453.8	Venous embolism and thrombosis of deep vessels of lower extremity
671.30	Deep phlebothrombosis, antepartum, episode of care unspecified
671.31	Deep phlebothrombosis, antepartum, delivered, with or without mention of antepartum condition
671.32	Deep phlebothrombosis, antepartum, delivered, with mention of postpartum complication
671.33	Deep phlebothrombosis, antepartum, antepartum condition or complication
671.34	Deep phlebothrombosis, antepartum, postpartum condition or complication
671.40	Deep phlebothrombosis, postpartum, episode of care unspecified
671.41	Deep phlebothrombosis, postpartum, delivered, with or without mention of antepartum condition
671.42	Deep phlebothrombosis, postpartum, delivered, with mention of postpartum complication
671.43	Deep phlebothrombosis, postpartum, antepartum condition or complication
673.20	Obstetrical blood-clot embolism, unspecified as to episode of care or not applicable
673.21	Obstetrical blood-clot embolism, delivered, with or without mention of antepartum condition
673.22	Obstetrical blood-clot embolism, delivered, with mention of postpartum complication
673.23	Obstetrical blood-clot embolism, antepartum condition or complication
673.24	Obstetrical blood-clot embolism, postpartum condition or complication

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Table 10. ICD-9-CM codes for ischaemic stroke

ICD-9-CM code	Description
433.0	Occlusion and stenosis of basilar artery
433.1	Occlusion and stenosis of carotid artery
433.2	Occlusion and stenosis of vertebral artery
433.3	Occlusion and stenosis of precerebral arteries mult/bilat
433.8	Occlusion and stenosis of precerebral arteries, spec
433.9	Occlusion and stenosis of precerebral arteries, unspec
434.0	Cerebral thrombosis
434.1	Cerebral embolism
434.9	Occlusion of cerebral artery, unspec
435.0	Basilar artery syndrome
435.1	Vertebral artery syndrome
435.2	Subclavian steal syndrome
435.8	Transient ischemic attack, spec.
435.9	Transient ischemic attack, unspec.
436	Acute but ill-defined cerebrovascular disease

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Table 11. ICD-9-CM codes for myocardial infarction (MI)

ICD-9-CM code	Description
410.0	MI, acute, anterolateral
410.1	MI, acute, anterior, NOS
410.2	MI, acute, inferolateral
410.3	MI, acute, inferoposterior
410.4	MI, acute, other inferior wall, NOS
410.5	MI, acute, other lateral wall
410.6	MI, acute, true posterior
410.7	MI, acute, subendocardial
410.8	MI, acute, spec.
410.9	MI, acute, unspec.

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Table 12 ICD-9-CM codes related to renal impairment

ICD-9-CM code	Description
250.4	Diabetes with renal manifestations
249.4	Secondary diabetes mellitus with renal manifestations
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
581	Nephrotic syndrome
583.81	Nephritis and nephropathy, NOS, in diseases classified elsewhere
585	Chronic kidney disease (no subcodes available)
586	Renal failure, unspecified
593.6	Postural proteinuria
791.0	Proteinuria
V42.0	Kidney transplant
V45.1	Renal dialysis status
V56	Encounter for dialysis and dialysis catheter care

ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification.

Annex 4. Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the Netherlands
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16646
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	Dr
Address	Bayer Pharma AG, D-13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: Jan. 22nd, 2015, Michael Kayser

Signature Page – Principal Investigator

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the Netherlands
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16646
Study type	☒ PASS ☐ non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Marketing authorization holder(s)	Bayer Healthcare AG
Function	Principal Investigator
Name	Ron MC Herings
Title	Dr
Address	PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 21-01-2015,