PASS information

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the United Kingdom
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Date of last version of protocol	20 Jan 2015
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Active substance	B01AF01 Antithrombotic agents, direct Factor Xa Inhibitors, Rivaroxaban
Medicinal product	Xarelto®
Product reference	BAY 59-7939
Procedure number	EMEA/H/C/00944
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 United Kingdom. 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 or referral to a specialist from primary care for three bleeding events (primary safety outcomes): (a) intracranial haemorrhage, (b) gastrointestinal bleeding and (c) 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 deaths.
Country(-ies) of study	United Kingdom
Author	Dr Luis A García Rodríguez Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain In collaboration with the Xarelto Epidemiology PASS Programme Group.

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
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The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

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2 List of abbreviations

ACS	Acute Coronary Syndromes
ALT	Alanine aminotransferase
ASA	Acetylsalycylic acid
AST	Asparagine aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CEIFE	Centro Español de Investigación Farmacoepidemiológica (Spanish Centre for Pharmacoepidemiological Research)
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
HES	Hospital Episode Statistics
INR	International Normalized Ratio
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
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
THIN	The Health Information Network
UK	United Kingdom
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 United Kingdom

Version 5.2, 20 Jan 2015

Principal investigator: Dr Luis A García Rodríguez

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In collaboration with the Xarelto Epidemiology PASS Programme Group.

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; 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 United Kingdom 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 or referral to a specialist 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

All patients aged 2 years and above who have been enrolled in The Health Improvement Network (THIN) database for at least 1 year and had their first prescription recorded in the database at least 1 year ago will be included.

Variables

Detailed descriptive variables will be captured for the population, including co-medications and comorbidities. Primary safety outcomes are the occurrence of hospitalization for intracranial haemorrhage, gastrointestinal bleeding and urogenital bleeding. Other outcomes of interest include of 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 deaths.

Data sources

THIN. The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution.

Study size

The size of the population receiving rivaroxaban will be dependent on market uptake across the indications of interest. Based on an incidence of haemorrhagic stroke in warfarin-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 warfarin-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with warfarin-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 (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 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 both 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 09 December, 2011 (when rivaroxaban received marketing authorization for DVT treatment in the UK) 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 9.7.2.5 9.7.2.6	Addition to section on bleeding definition Addition to section on renal failure definition Addition a section on how to handle missing data	Response to PRAC review
5	Nov 2014	8.2 9.3.1 9.7.1 9.7.2.5	Additional variables for patient characterisation and analyses thereof; strengthened analyses of renal impairment	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 7.1	Label expansion
1	Apr 2011		Inclusion of additional indication, stroke prevention	Label expansion

			in atrial fibrillation. V2.0 of protocol submitted with EU RMP V 6.1.	

6 Milestones

Table 2: Milestones

Milestone	Planned date
Start of data collection (Marketing Authorization granted for DVT treatment)	Q4 2011
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, Ageno et al. 2008; Turpie, Lassen et al. 2009). A post-authorization safety study programme is planned for several European countries. This document summarizes the design of a population-based study to characterize 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 compared with the standard of care in routine clinical practice in the UK, for ACS, DVT/PE treatment and SPAF. For DVT/PE treatment and SPAF, standard of care is treatment with the most widely used vitamin K antagonist, warfarin, 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.

8 Research questions and objectives

This post-authorization study was designed 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.

8.1 Primary objective

8.1.1 Patient characteristics and drug utilization

- 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.

8.1.2 Safety and effectiveness outcomes

- To study the occurrence of hospitalization or referral to a specialist from primary care for three bleeding events (primary safety outcomes): (a) intracranial haemorrhage, (b) gastrointestinal bleeding and (c) urogenital bleeding among users of rivaroxaban (for DVT/PE treatment, SPAF and ACS) in comparison with individuals receiving current standard of care.

8.2 Secondary objectives

- 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 including nested case–control analyses.

Cohorts of first-time users of either rivaroxaban or comparators will be identified using the date of first prescription (index date) of the respective drug (index drug) (Figure 1).

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 prescription of the drug recorded during the enrolment period. In the UK, for VTE prevention, DVT/PE treatment and SPAF, standard of care is treatment with the most widely used vitamin K antagonist, warfarin, 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 have any record of being prescribed their index drug prior to the enrolment period or who qualify as members of both cohorts on the same day, will be excluded. If a patient qualifies as first-time user of both rivaroxaban and "standard of care" comparison drug during the enrolment period, she/he will be assigned to the cohort of drug first prescribed during the enrolment period, with the date of this prescription 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, 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, where the comparator is warfarin, will be categorized as naïve or non-naïve patients according to their previous use of any anticoagulant/comparator drugs (Figure 1). Naïve patients will be those without a previous prescription recorded before the index date. Non-naïve patients will be those with one or more relevant prescriptions recorded before the index date. Ascertainment of naïve/non-naive status will also be confirmed by Read Code in addition to Drug Codes, e.g. Read Codes for warfarin monitoring, INR values >2, as this may be recorded in the absence of a Drug Code for warfarin.

Non-naïve patients will be further subdivided into recent switchers (patients exposed to the other anticoagulant/comparator in the 6 months prior to the index date) and distant switchers (patients exposed to the other anticoagulant/comparator more than 6 months prior to the index date).

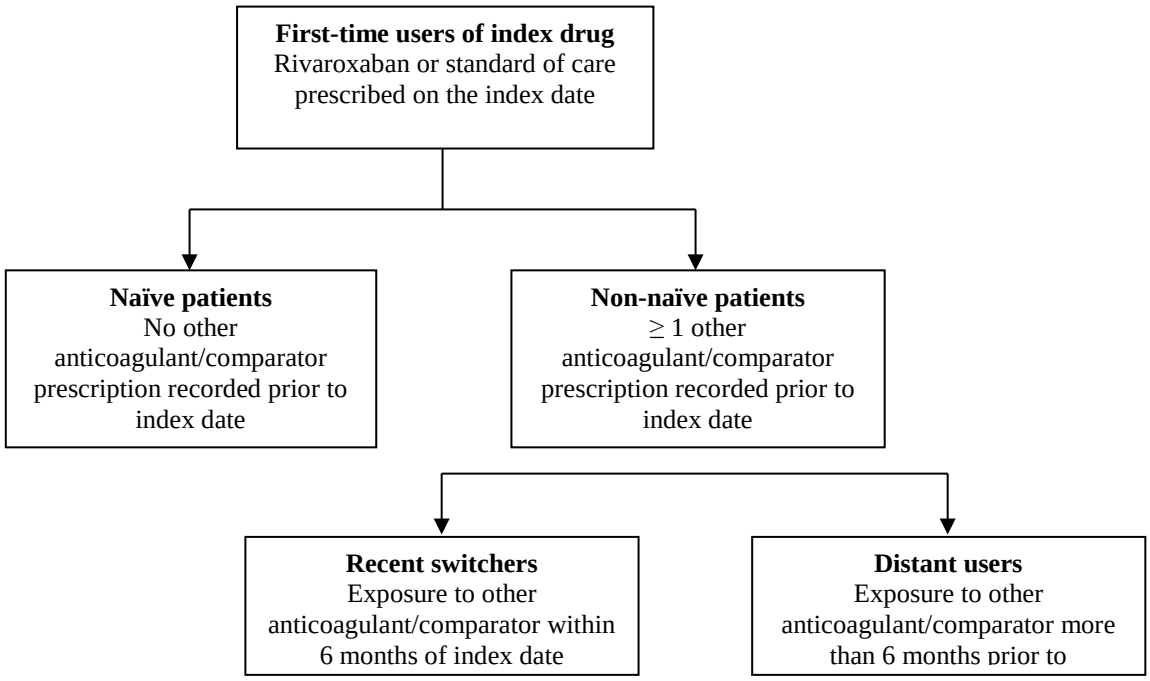

Figure 1 Subdivision of study cohorts for DVT/PE treatment and SPAF.

Data collected for comparison of cohorts is described in Section 9.3. The characteristics of the two study cohorts in the first year and subsequent years of the enrolment period will be compared.

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.
- Manual review of free text comments, questionnaires sent to primary care practitioners (PCPs) and cross-validation with hospital episode statistics (HES) in a subgroup of practices are possible, allowing for robust validation of outcomes.
- THIN is a well-validated resource for pharmacoepidemiology research (see Section 9.2).

9.2 Setting

All patients aged 2 years and above who have been enrolled with a primary care physician for at least 1 year and had their first prescription recorded in the database at least 1 year ago will be included.

The population included in THIN is representative of the UK as a whole in terms of age, sex and geographic distribution (Bourke, Dattani et al. 2004; Blak, Thompson et al. 2011). THIN has been extensively validated for use in pharmacoepidemiology (Lewis, Schinnar et al. 2007), and has been used successfully in studies of bleeding risk (Tata, Fortun et al. 2005; Smeeth, Cook et al. 2006; García Rodríguez and Barreales Tolosa 2007; de Abajo and Garcia-Rodriguez 2008; Massó González and Garciá Rodríguez 2008; Raine, Wong et al. 2009; Cea Soriano and García Rodríguez 2010; Gaist, Wallander et al. 2013; Garcia-Rodriguez, Gaist et al. 2013).

The enrolment period will start on the day after rivaroxaban receives first marketing authorization 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 NICE approval for DVT treatment (see Section 6 for detailed milestones).

To study outcomes of interest (Section 8) for patients receiving rivaroxaban and comparators for DVT/PE treatment, SPAF or ACS, the same source population will be used as in the drug utilization study.

9.3 Variables

9.3.1 Patient characteristics and drug utilization

The following variables, including risk factors/potential confounders for the outcomes under study, will be collected for comparison between the two cohorts:

- age and sex distribution at index date; 
- dose of index drug at index date and duration of treatment (including pack size); 
- diagnosis associated with the prescribing of the index drug; 
- proportion of patients defined as naïve, non-naïve, recent switchers and distant switchers; 

- type and duration of other anticoagulant use before the index date among the non-naïve group;
- number of pregnant women at index date;
- number of pregnancies after the index date;
- 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 prescribed 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 steroids, 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 disease based on diagnoses, most recently recorded before the index date and in following the index date, with estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) to be obtained where available;
- comorbidity based on diagnoses most recently recorded before the index date and in following the index date, such as haemorrhagic disease, liver disease, pancreatic disease, cancer (including the presence of malignant neoplasm), cardiovascular disease, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia and obesity), peripheral arterial disease, respiratory disease (asthma and chronic obstructive pulmonary disease), rheumatoid arthritis, osteoarthritis, gastrointestinal disease (recent gastrointestinal ulceration [including peptic ulcer disease], gastritis and duodenitis, dyspepsia and gastroesophageal reflux disease), oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities, thyroid disease, surgical procedures (including PCI, CABG, and recent brain, ophthalmic or spinal surgery, where recorded), presence of a prosthetic heart valve (if recorded), alcohol-related disorders, ventricular arrhythmia, anaemia, and history of intracranial haemorrhage, urogenital bleeding and gastrointestinal bleeding; if possible, a CHADS score will be calculated based on the presence of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke or transient ischaemic attack; also, where possible, a HAS-BLED score for major bleeding risk (hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age > 65, medication usage predisposing to bleeding, alcohol usage history, labile INR [if available]) will be calculated;
- smoking status, body mass index (BMI) and Townsend score: most recently recorded before the index date and following the index date;
- healthcare utilization in the year prior to the index date (e.g. PCP visits, outpatient visits and hospital admissions).

9.3.2 Safety and effectiveness outcomes

For each outcome, potential cases will be identified using diagnostic Read codes (Annex 3) and, where appropriate, computerized patient profiles (including any free text comments) will be reviewed with all identifying information removed. Diagnostic confirmation using patients' original medical records will be performed where possible. When required, information contained in HES among the subset of practices linked to THIN, will be used.

For the purpose of this study, clinically relevant bleedings will be defined as bleedings leading to hospital admission or referrals to a specialist. 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 might be missed. 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 referred to a specialist or admitted to 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.

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.
- the patient having been referred to a specialist or admitted to hospital.

Urogenital bleeding (Annex 3, Table 6)

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

- the specific site of bleeding originating in the urogenital tract.
- the patient having been referred to a specialist or admitted to hospital.

9.3.2.2 Secondary safety outcomes: 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).

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

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

- 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 and total bilirubin, provided one of them is twice the upper limit of the respective normal range.
- the patient having been referred to a specialist or admitted to hospital.
- free of cancer, other liver disease (including infectious hepatitis, chronic liver disease etc.), gallbladder or pancreatic disease and alcoholism.

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.

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

For ascertainment of mortality automatic computer searches will be performed, based on:

- Read Codes
- Death certification incorporated in THIN
- Registration status of the patient recorded in THIN.

Of note, among all individuals with an entry of death, several strategies will be used to ascertain the cause of death. THIN database has specific entries (additional health data) for recording cause of death. In the UK, the death certificate consists of Part I and II. Part I is used to show the immediate cause of death or any underlying cause, and is completed taking into account the causal sequence: 1a states the condition that led directly to death; 1b the intermediate cause of death; and 1c the underlying cause of death. Part II is used when one or more conditions contribute to death but are not part of the main causal sequence leading to death. Although we look for the death certificate (Part I and II) it should be noted, this information is only recorded in a few instances (20%).

Among remaining patients with no direct cause of death recorded, all information is reviewed from the year prior to the date of death, as well as up to 30 days after (this time window is implemented as the PCP sometimes records information after the patient's death) to assign cause of death. Causes of death can be classified according to a specific question e.g. into cardiovascular disease death and non-cardiovascular disease death.

9.4 Data sources

The data source for this study will be The Health Improvement Network (THIN) database in the UK. THIN includes information on over 3 million patients (approximately 5% of the UK population) that is systematically recorded by participating PCPs as part of their routine patient care and is anonymized and sent to THIN for use in research projects. The computerized information includes demographics, details of PCP visits, referrals to specialists and hospital admissions (including diagnostic and treatment information), results of laboratory tests and a free-text section. Prescriptions issued by the PCP are recorded electronically and the indication can be ascertained by reviewing the patient's clinical history. The Read classification is used to code specific diagnoses as reasons for each consultation (O'Neil, Payne et al. 1995; Stuart-Buttle, Read et al. 1996), and a drug dictionary based on data from the MULTILEX classification is used to record prescriptions (First Data Bank 2014).

Recently, a number of practices included in THIN database have been linked to the HES database. HES is a data warehouse containing details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in England.

9.5 Study Size

All patients enrolled in THIN 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 warfarin-treated patients of 5 per 1000 person-years, 12,000 rivaroxaban-treated patient-years and 48,000 warfarin-treated patient-years would be required to exclude a 50% increased risk of haemorrhagic stroke in rivaroxaban-treated patients compared with warfarin-treated patients with a power of 80%.

9.6 Data management

For each study project, all material including: study protocol, copy of Scientific Review Committee approval, algorithms and data collections, datasets, STATA programs, results from validation exercises and questionnaires, final STATA programs, and final report and publications are kept in one folder cross-shared by the CEIFE team. Monthly back-ups are performed and kept in a secure location, and all material is kept for a minimum of 10 years.

As a standard process, one researcher prepares the list of codes, test the computer algorithms to be used and runs statistical analysis after agreement on all phases of analyses with the rest of the team. After performing the crude analysis, several multivariable regression models are performed before choosing the final model. As one measure of quality control, another researcher independently performs several checks in reviewing commands and analyses performed in order to minimise data errors.

9.7 Data analysis

The following analyses will be performed.

9.7.1 Patient characteristics and drug utilization

The patient populations will be described according to the descriptive variables mentioned in Section 9.3.1. overall and stratified by indication (VTE prevention, DVT/PE treatment, SPAF, ACS, other), naïve or non-naïve status, and switching status.

The baseline risk of being dispensed one of the co-medications or presenting with one of the comorbidities prior to the index date will be assessed by computing the odds ratio of being prescribed that drug or presenting with that comorbidity 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 for the descriptive variables (Section 9.3.1), will be computed using logistic regression models both overall and stratified by indication and by naïve or non-naïve status, and switching status.

Manual review of patient profiles will be used to ascertain as accurately as possible exposure time in a random sample of warfarin users. In addition, INR measurements will be used as a proxy for warfarin exposure, which is more valid measure of true exposure to warfarin.

9.7.2 Safety and effectiveness outcomes

The two cohorts (of first-time users of rivaroxaban and first-time users of comparators) 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 referral or hospitalization for that

outcome during the follow-up period will be identified. A separate follow-up will be performed for each of the outcomes.

Crude incidence rates will be estimated in both 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. 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.

9.7.2.1 Primary safety outcomes

Crude incidence rates will be estimated for each of the three primary adverse outcomes in both cohorts. 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 (current, recent and past use as defined in Section 9.7.2).

Where numbers and data permit, adjustment will be made for baseline medication and comorbidity variables described in the drug utilization section, including indication and history of adverse outcomes (referral or hospitalization for haemorrhagic stroke, gastrointestinal bleeding or urogenital bleeding recorded at any time before the index date).

If numbers of final cases permit, estimation of the relative risk among rivaroxaban users will be adjusted for known risk factors of the specific outcome using logistic regression models in nested case-control analyses.

9.7.2.2 Secondary safety outcome: other bleeding

Crude incidence rate will be estimated for “other bleeding” in both cohorts. Age- and sex-adjusted rate ratios with 95% CIs will be estimated comparing rivaroxaban with standard of care using Poisson regression analysis. Where numbers and data permit, adjustment will be made for baseline medication and comorbidity variables described in the drug utilization section.

9.7.2.3 Secondary safety outcome: non-infective liver disease

Crude incidence rate will be estimated for non-infective liver disease in both cohorts. Age- and sex-adjusted rate ratios with 95% CIs will be estimated for non-infective liver disease comparing rivaroxaban with standard of care using Poisson regression analysis. Where numbers and data permit, adjustment will be made for baseline medication and comorbidity variables described in the drug utilization section.

9.7.2.4 Outcomes related to effectiveness

Crude incidence rates will be estimated for each effectiveness outcome in both cohorts. Age- and sex-adjusted rate ratios with 95% CIs will be estimated for each effectiveness outcome comparing rivaroxaban with standard of care using Poisson regression analysis. Where numbers and data permit, adjustment will be made for baseline medication and comorbidity variables described in the drug utilization section.

9.7.2.5 Sub-analysis by renal status

Results from laboratory tests perfomed in primary care are automatically recorded in THIN.

- As in previous studies we will use serum creatinine values to compute estimated glomerular filtration rate (eGFR). We will calculate the eGFR using the Modification on Diet in Renal Disease (MDMR) formula: eGFR = 186(Serum Creatine−1.154 × age−0.203) × 0.742 [if female].
- In THIN, creatinine values are recorded using International System of Units (SI) as µmol/L, and we will divide serum creatinine value by a factor of 88.4 to convert it to conventional unit as mg/dL. Additional clinical information on dialysis and kidney transplantation will also be ascertained.

The subset of patients with recorded renal status will be analysed to determine:

- the proportion of patients with normal renal function (CrCl > 80 mL/min); mild (CrCl < 80–50 mL/min), moderate (CrCl < 50–30 mL/min) or severe (CrCl < 30–15 mL/min) renal impairment; and the proportion with end-stage renal disease (CrCl < 15 mL/min) or a requirement for dialysis;
- 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.

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.

9.7.2.6 Strategy for handling missing data

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 in a small proportion 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 (if any), the evaluation will be considered to be conducted on the subset with complete data for the variable of interest.

9.7.2.7 Sensitivity analyses

Sensitivity analyses will be performed around the start and stop of treatment to account for any differences in the mode of action of rivaroxaban (rapid onset/offset of action, short half-life), warfarin (slow onset/offset of action, long half-life) 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 diagnostic Read codes (Annex 3) and, where appropriate, computerized patient profiles (including any free text comments) will be reviewed with all identifying information removed. Diagnostic confirmation using the patients' original medical records will be performed where possible by means of sending a questionnaire to the PCP. When required, we will use the information contained in HES among the subset of THIN practices linked to THIN.

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.
- Potential for misclassification of exposure to warfarin due to complex dosing with multiple strengths of tablet.
- Prescriptions started in-hospital or events in the immediate post-discharge period may be missed from general practitioner notes.
- Incomplete data concerning medication compliance: drug use is based on prescriptions written by the treating physician, but no information is available to confirm if the drug was actually taken by the patient.

9.10 Other aspects

None applicable.

10 Protection of human subjects

This study protocol will be approved by a Research Ethics Committee (REC), and the study will be conducted in accordance with Good Pharmacoepidemiology Practices (ISPE 2007).

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 (NCT01947998) 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 present and/or publish data from this study in internationally recognized forums following Good Publication Practice.

13 List of references

Blak, B. T., M. Thompson, et al. (2011). "Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates." Inform Prim Care **19**(4): 251-255.

Bourke, A., H. Dattani, et al. (2004). "Feasibility study and methodology to create a quality-evaluated database of primary care data." Inform Prim Care **12**(3): 171–177.

Cea Soriano, L. and L. A. García Rodríguez (2010). "Risk of upper gastrointestinal bleeding in a cohort of new users of low-dose ASA for secondary prevention of cardiovascular outcomes." Front Pharmacol: doi: 10.3389/fphar.2010.00126.

de Abajo, F. J. and L. A. Garcia-Rodriguez (2008). "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 **65**(7): 795-803.

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

First Data Bank. (2014). "MULTILEX for primary care." Retrieved 07 May, 2014, from http://www.fdbhealth.co.uk/solutions/multilex/.

Gaist, D., M. A. Wallander, et al. (2013). "Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network." Pharmacoepidemiol Drug Saf **22**(2): 176-182.

Garcia-Rodriguez, L. A., D. Gaist, et al. (2013). "Antithrombotic drugs and risk of hemorrhagic stroke in the general population." Neurology **81**(6): 566-574.

García Rodríguez, L. A. and L. Barreales Tolosa (2007). "Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population." Gastroenterology **132**(2): 498–506.

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.

Lewis, J. D., R. Schinnar, et al. (2007). "Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research." Pharmacoepidemiol Drug Saf **16**(4): 393–401.

Massó González, E. L. and L. A. Garciá Rodríguez (2008). "Proton pump inhibitors reduce the long-term risk of recurrent upper gastrointestinal bleeding: an observational study." Aliment Pharmacol Ther **28**(5): 629-637.

O'Neil, M., C. Payne, et al. (1995). "Read Codes Version 3: a user led terminology." Methods Inf Med **34**(1-2): 187–192.

Raine, R., W. Wong, et al. (2009). "Sociodemographic variations in the contribution of secondary drug prevention to stroke survival at middle and older ages: cohort study." BMJ **338**: b1279.

Smeeth, L., C. Cook, et al. (2006). "Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting." Lancet **367**(9516): 1075-1079.

Stuart-Buttle, C. D., J. D. Read, et al. (1996). "A language of health in action: Read Codes, classifications and groupings." Proc AMIA Annu Fall Symp: 75–79.

Tata, L. J., P. J. Fortun, et al. (2005). "Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding?" Aliment Pharmacol Ther **22**(3): 175-181.

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.

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 United Kingdom.

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)	☒	☐	☐	17
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)	☒	☐	☐	12
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)	☒	☐	☐	16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	13–15
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	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)	☒	☐	☐	16
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?	☒	☐	☐	20
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?	☒	☐	☐	19
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	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)	☐ ☐	☐ ☐	☒ ☒	
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?	☒	☐	☐	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)?	☒	☐	☐	19,20
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	19,20

Comments:

Annex 3. Additional information: Read codes

Table 4. Read codes for intracranial haemorrhage.

Read code	Description
7004100	Evacuation of haematoma from temporal lobe of brain
7004200	Evacuation of haematoma from cerebellum
7004300	Evacuation of intracerebral haematoma NEC
7008200	Aspiration of haematoma of brain tissue
7017000	Evacuation of subdural haematoma
7032000	Evacuation of extradural haematoma
G622.00	Subdural haematoma - nontraumatic
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
S62A.00	Traumatic extradural haematoma
S630.12	Intracranial haematoma following injury
G612.00	Basal nucleus haemorrhage
G615.00	Bulbar haemorrhage
G613.00	Cerebellar haemorrhage
S62..00	Cerebral haemorrhage following injury
S62z.00	Cerebral haemorrhage following injury NOS
S624.00	Closed traumatic extradural haemorrhage
S620.00	Closed traumatic subarachnoid haemorrhage
S622.00	Closed traumatic subdural haemorrhage
G610.00	Cortical haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G616.00	External capsule haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
14AF.00	H/O sub-arachnoid haemorrhage
662o.00	Haemorrhagic stroke monitoring
G611.00	Internal capsule haemorrhage
G61..00	Intracerebral haemorrhage
G617.00	Intracerebral haemorrhage
G618.00	Intracerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere
G61z.00	Intracerebral haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G61X000	Left sided intracerebral haemorrhage
S625.00	Open traumatic extradural haemorrhage
G62..00	Other and unspecified intracranial haemorrhage
S630.00	Other cerebral h'ge after injury no open intracranial wound
S63..00	Other cerebral haemorrhage following injury
S63z.00	Other cerebral haemorrhage following injury NOS
G614.00	Pontine haemorrhage
G61X100	Right sided intracerebral haemorrhage
G600.00	Ruptured berry aneurysm
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G680.00	Sequelae of subarachnoid haemorrhage

Read code	Description
G61..12	Stroke due to intracerebral haemorrhage
G60X.00	Subarachnoid haemorrh from intracranial artery
G60..00	Subarachnoid haemorrhage
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60z.00	Subarachnoid haemorrhage NOS
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622500	Subdural h'ge inj no open intracran wnd+>24hr LOC -restored
S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S622400	Subdural h'ge inj no open intracranial wnd+>24 LOC +recovery
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622200	Subdural h'ge inj no open intracranial wound+<1hr loss consc
S622100	Subdural h'ge inj no open intracranial wound+no loss consc
S62..13	Subdural haemorrhage following injury
G621.00	Subdural haemorrhage - nontraumatic
G623.00	Subdural haemorrhage NOS
S62..14	Traumatic cerebral haemorrhage
S627.00	Traumatic subarachnoid haemorrhage
S628.00	Traumatic subdural haemorrhage
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
S624600	Extradural h'ge inj no open intracra wnd+LOC unspec duration
S624300	Extradural h'ge inj no open intracran wnd+1-24hr loss consc
S624400	Extradural h'ge inj no open intracran wnd+>24hr LOC+recovery
S624500	Extradural h'ge inj no open intracran wnd+>24hr LOC-restored
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S624200	Extradural h'ge inj no open intracranial wnd+<1hr loss consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S625300	Extradural h'ge inj + open intracran wnd+1-24hr loss consc
S625400	Extradural h'ge inj + open intracran wnd+>24hr LOC+recovery
S625500	Extradural h'ge inj + open intracran wnd+>24hr LOC -restored
S625z00	Extradural h'ge inj + open intracran wnd+concussion unspec
S625600	Extradural h'ge inj + open intracran wnd+LOC unspec duration
S625200	Extradural h'ge inj + open intracranial wnd+<1hr loss consc
S625000	Extradural h'ge inj + open intracranial wnd + unspec consc
S625100	Extradural h'ge inj + open intracranial wound+no loss consc
S62..11	Extradural haemorrhage following injury
Q200600	Extradural haemorrhage in fetus or newborn
129C.00	Family history of subarachnoid haemorrhage

Read code	Description
S621.00	Open traumatic subarachnoid haemorrhage
S623.00	Open traumatic subdural haemorrhage
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S631100	Oth cerebral h'ge inj + open intracranial wnd+no loss consc
S631.00	Other cerebral h'ge after injury + open intracranial wound
S621400	Subarach h'ge inj + open intracran wnd +>24hr LOC + recovery
S621500	Subarach h'ge inj + open intracran wnd+>24hr LOC -restored
S621600	Subarach h'ge inj + open intracran wnd+LOC unspec duration
S620200	Subarachnoid h'ge inj no open intracran wnd+<1hr loss consc
S620400	Subarachnoid h'ge inj no open intracran wnd+>24 LOC+recovery
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620300	Subarachnoid h'ge inj no open intracran wound + 1-24hr LOC
S620000	Subarachnoid h'ge inj no open intracran wound + unspec consc
S621300	Subarachnoid h'ge inj + open intracran wnd+1-24hr loss consc
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S621200	Subarachnoid h'ge inj + open intracran wound+<1hr loss consc
S621000	Subarachnoid h'ge inj + open intracran wound + unspec consc
S621100	Subarachnoid h'ge inj + open intracranial wound + no LOC
S62..12	Subarachnoid haemorrhage following injury
S623500	Subdural h'ge inj + open intracran wnd+>24hr LOC -restored
S623600	Subdural h'ge inj + open intracran wnd+LOC unspec duration
S623400	Subdural h'ge inj + open intracran wound+>24hr LOC +recovery
S623300	Subdural h'ge inj + open intracranial wnd+1-24hr loss consc
S623z00	Subdural h'ge inj + open intracranial wnd+concussion unspec
S623200	Subdural h'ge inj + open intracranial wound+<1hr loss consc
S623100	Subdural h'ge inj + open intracranial wound+no loss consc
S623000	Subdural h'ge inj + open intracranial wound + unspec consc
S62A000	Traumatic extradural haemat without open intracranial wound
S62A100	Traumatic extradural haematoma with open intracranial wound
Q200000	Cerebral haemorrhage unspecified

CVA, cerebrovascular accident; H/O, history of; LOC, loss of consciousness; NEC, not elsewhere classified; NOS, not otherwise specified.

Table 5. Read codes for gastrointestinal bleeding.

Read code	Description
14C9.00	H/O: melaena
19E4.12	C/O – melaena
4737.11	Melaena – O/E of faeces
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB – Gastrointestinal Bleeding
J68z000	Gastric Haemorrhage Nos
J68z100	Intestinal Haemorrhage Nos
J68z200	Upper Gastrointestinal Haemorrhage
J68zz00	Gastrointestinal Tract Haemorrhage Nos
14C8.00	H/O: haematemesis
1994	Vomiting blood - fresh
1994.11	Blood in vomit - symptom
1995	Vomiting blood - coffee ground
4A23.00	Vomit: frank blood present
4A23.11	Blood in vomit O/E
4A24.00	Vomit: coffee ground
4A24.11	Coffee ground vomit
4A5..00	Vomit occult blood
4A5..11	Occult blood in vomit
4A51.00	Vomit occult blood positive
4A52.00	Vomit occult blood negative
4A5Z.00	Vomit occult blood nos
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110400	Acute gastric ulcer with obstruction
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111400	Chronic gastric ulcer with obstruction
J11y100	Unspecified gastric ulcer with haemorrhage
J11y400	Unspecified gastric ulcer with obstruction
J120100	Acute duodenal ulcer with haemorrhage
J120400	Acute duodenal ulcer with obstruction
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121400	Chronic duodenal ulcer with obstruction
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y400	Unspecified duodenal ulcer with obstruction
J130100	Acute peptic ulcer with haemorrhage
J130400	Acute peptic ulcer with obstruction
J131100	Chronic peptic ulcer with haemorrhage
J131400	Chronic peptic ulcer with obstruction
J13y100	Unspecified peptic ulcer with haemorrhage
J13y400	Unspecified peptic ulcer with obstruction

Read code	Description
J140100	Acute gastrojejunal ulcer with haemorrhage
J140400	Acute gastrojejunal ulcer with obstruction
J141100	Chronic gastrojejunal ulcer with haemorrhage
J141400	Chronic gastrojejunal ulcer with obstruction
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y400	Unspecified gastrojejunal ulcer with obstruction
J150000	Acute haemorrhagic gastritis
J68..00	Gastrointestinal haemorrhage
J680.00	Haematemesis
J680.11	Vomiting of blood
7022100	Proximal gastric vagotomy
7022111	Highly selective vagotomy
7022400	Vagotomy & pyloroplasty
7612111	Balfour excision of gastric ulcer
7612500	Resection of gastric ulcer by cautery
7619100	Gastrotomy and ligation of bleeding point of stomach
761J.00	Operations on gastric ulcer
761J.11	Stomach ulcer operations
761J100	Closure of gastric ulcer nec
761J111	Suture of ulcer of stomach nec
761Jy00	Other specified operation on gastric ulcer
761Jz00	Operation on gastric ulcer nos
7627	Operations on duodenal ulcer
7627100	Suture of duodenal ulcer not elsewhere classified
7627y00	Other specified operation on duodenal ulcer
7627z00	Operation on duodenal ulcer nos
G850.00	Oesophageal varices with bleeding
G852000	Oesophageal varices with bleeding in diseases EC
G852100	Oesophageal varices without bleeding in diseases EC
J10y000	Haemorrhage of oesophagus
J107.00	Mallory-Weiss syndrome
J108.00	Mallory - Weiss tear
J573.00	Haemorrhage of rectum and anus
J573000	Rectal haemorrhage
J573011	Rectal bleeding
J573012	PRB - Rectal bleeding
J573100	Anal haemorrhage
J573.11	Bleeding PR
J573z00	Haemorrhage of rectum and anus NOS
J510900	Bleeding diverticulosis
J573.00	Haemorrhage of rectum and anus
J573000	Rectal haemorrhage

C/O, complaint of; EC, elsewhere classified; GIB; gastrointestinal bleeding; H/O, history of; LOC, loss of consciousness; O/E, on examination; NEC, not elsewhere classified; NOS, not otherwise specified; PR, per rectum; PRB, per rectal bleeding.

Table 6. Read codes for urogenital bleeding.

Read code	Description
14D5.00	H/O: haematuria
1A45.00	Blood in urine - haematuria
1A45.12	Haematuria - symptom
K032100	Recurrent benign haematuria syndrome
K0A2.00	Recurrent and persistent haematuria
K0A2000	Recurrent+persistnt haematuria minor glomerular abnormality
K0A2100	Recur+persist haematuria
K0A2200	Recur+persist haematuria difus membranous glomerulonephritis
K0A2300	Recur+persist haemuria df mesangial prolif glomerulnephritis
K0A2400	Recur+persist haemuria df endocaplry prolifrtv glomeruloneph
K0A2500	Recur+persist hmuria df mesangiocapilary glomerulonephritis
K0A2600	Recurrent and persistent haematuria
K0A2700	Recur+persist haematuria difus crescentic glomerulonephritis
K197.00	Haematuria
K197.11	Traumatic haematuria
K197.12	Essential haematuria
K197000	Painless haematuria
K197100	Painful haematuria
K197200	Microscopic haematuria
K197300	Frank haematuria
K197400	Clot haematuria
K53y600	Haematosalpinx
K544.00	Haematometra
K595.11	Intermenstrual bleeding - regular
K596.00	Metrorrhagia
K596.11	Intermenstrual bleeding - irregular
K597.00	Postcoital bleeding
K59A.00	Premenopausal postcoital bleeding
K59B.00	Postmenopausal postcoital bleeding
K59y.11	Metropathia haemorrhagica
K59y000	Retained menstruation
K59yx00	Dysfunctional uterine haemorrhage NOS
K59yx11	Dysfunctional uterine bleeding
K59yy00	Functional uterine haemorrhage NOS
K5C2.00	Haematocolpos
K5E..00	Other abnormal uterine and vaginal bleeding
K5Ez.00	Abnormal uterine and vaginal bleeding
Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding
158..12	Vaginal bleeding
1584.00	Heavy episode of vaginal bleeding
7F22700	Pack to control postnatal vaginal bleeding
7F22711	Pack to control postnatal vaginal bleeding
K56y111	Bleeding - vaginal NOS
K56y112	BPV - Vaginal bleeding
K595.00	Ovulation bleeding
K59y.00	Other menstruation disorders
K59yz00	Other menstruation disorder NOS

Read code	Description
K5E2.00	Abnormal vaginal bleeding

BPV, bleeding per vagina; H/O, history of; NOS, not otherwise specified.

Table 7. Read codes for “other bleeding” leading to hospitalization will be provided on request.

Table 8. Read codes for non-infective liver disease/acute liver injury.

Read code	Description
44d2.00	Liver Function Tests Abnormal
44E2.00	Serum Bilirubin Raised
44g2.00	Liver Enzymes Abnormal
J60..00	Acute And Subacute Liver Necrosis
J600.00	Acute Necrosis Of Liver
J600000	Acute Hepatic Failure
J600011	Acute Liver Failure
J600100	Acute Hepatitis - Noninfective
J600200	Acute Yellow Atrophy
J600z00	Acute Necrosis Of Liver Nos
J601.00	Subacute Necrosis Of Liver
J601000	Subacute Hepatic Failure
J601100	Subacute Hepatitis - Noninfective
J601200	Subacute Yellow Atrophy
J601z00	Subacute Necrosis Of Liver Nos
J60z.00	Acute And Subacute Liver Necrosis Nos
J622.00	Hepatic Coma
J622.11	Encephalopathy - Hepatic
J625.00	[X] Hepatic Failure
J625.11	[X] Liver Failure
J62y.11	Hepatic Failure Nos
J62y.12	Liver Failure Nos
J62y.13	Hepatic Failure
J633.00	Hepatitis Unspecified
J633000	Toxic Hepatitis
J633z00	Hepatitis Unspecified Nos
J635.00	Toxic Liver Disease
J635000	Toxic Liver Disease With Cholestasis
J635100	Toxic Liver Disease With Hepatic Necrosis
J635200	Toxic Liver Disease With Acute Hepatitis
J635X00	Toxic Liver Disease, Unspecified
J636.00	Central Haemorrhagic Necrosis Of Liver
J63y.00	Other Specified Liver Disorder
J63y100	Nonspecific Reactive Hepatitis
J63yz00	Other Specified Liver Disorder Nos
J66y600	Obstructive Jaundice Nos
R024.00	[D]Jaundice (Not Of Newborn)
R024000	[D]Cholaemia Nos
R024100	[D]Icterus Nos
R024111	[D]Jaundice
R024z00	[D]Jaundice (Not Of Newborn) Nos
R148.00	[D]Abnormal Liver Function Test
R148000	[D]Abnormal Liver Scan
R148.11	[D]Lft's Abnormal
R148z00	[D]Abnormal Liver Function Test Nos
7804200	Open Wedge Biopsy Of Lesion Of Liver
7807000	Diagnostic Laparoscopic Examination And Biopsy Liver LESION

780A000	Percutaneous Transvascular Biopsy Of Lesion Of Liver
780A100	Percutaneous Biopsy Of Lesion Of Liver Nec
780A111	Menghini Needle Biopsy Of Liver
780A112	Needle Biopsy Of Liver Nec
780A113	Sheeba Needle Biopsy Of Liver
780B000	Biopsy Of Liver Nec
780B011	Biopsy Of Lesion Of Liver Nec
44G3100	Alt/Sgpt Level Abnormal
44H5100	Ast/Sgot Level Abnormal
44H5200	Ast/Sgot Level Raised
14C5.00	H/O: Liver Disease
14C6.00	H/O: Jaundice
25G3.00	O/E -Liver Moderately Enlarged
25G4.00	O/E - Liver Grossly Enlarged
44G2.00	Liver Enzymes Abnormal
D307000	Deficiency Of Coagulation Factor Due To Liver Disease
J624.00	Hepatorenal Syndrome
Jyu7000	[X]Toxic Liver Disease With Other Disorders Of Liver
Jyu7600	[X]Toxic Liver Disease
SP14200	Hepatic Failure As A Complication Of Care
SP14300	Hepatorenal Syndrome As A Complication Of Care
ZC2CH11	Dietary Advice For Liver Disease
J63z.00	Liver disease NOS
J635700	Acute hepatic failure due to drugs

Table 9. Read codes for DVT and PE

Read	Description
G801.00	Deep vein phlebitis and thrombophlebitis of the leg
G801.11	Deep vein thrombosis
G801.12	Deep vein thrombosis, leg
G801.13	DVT - Deep vein thrombosis
G801000	Phlebitis of the femoral vein
G801100	Phlebitis of the popliteal vein
G801200	Phlebitis of the anterior tibial vein
G801300	Phlebitis of the dorsalis pedis vein
G801400	Phlebitis of the posterior tibial vein
G801500	Deep vein phlebitis of the leg unspecified
G801600	Thrombophlebitis of the femoral vein
G801700	Thrombophlebitis of the popliteal vein
G801800	Thrombophlebitis of the anterior tibial vein
G801900	Thrombophlebitis of the dorsalis pedis vein
G801A00	Thrombophlebitis of the posterior tibial vein
G801B00	Deep vein thrombophlebitis of the leg unspecified
G801C00	Deep vein thrombosis of leg related to air travel
G801D00	Deep vein thrombosis of lower limb
G801E00	Deep vein thrombosis of leg related to intravenous drug use
G801F00	Deep vein thrombosis of peroneal vein
G801z00	Deep vein phlebitis and thrombophlebitis of the leg NOS
G802.00	Phlebitis and thrombophlebitis of the
G802000	Thrombosis of vein of leg
G80y.00	Other phlebitis and thrombophlebitis
G80y.11	Phlebitis and/or thrombophlebitis of iliac vein
G80y000	Phlebitis of the common iliac vein
G80y100	Phlebitis of the internal iliac vein
G80y200	Phlebitis of the external iliac vein
G80y300	Phlebitis of the iliac vein unspecified
G80y400	Thrombophlebitis of the common iliac
G80y500	Thrombophlebitis of the internal iliac vein
G80y600	Thrombophlebitis of the external iliac vein
G80y700	Thrombophlebitis of the iliac vein unspecified
G80y800	Phlebitis and thrombophlebitis of the iliac vein NOS
G80y900	Thrombophlebitis of the breast -Mondor's disease
G80y911	Mondor's disease
G80yz00	Other phlebitis and thrombophlebitis
G80z.00	Phlebitis and thrombophlebitis NOS
G80z000	Phlebitis NOS
G80z100	Thrombophlebitis NOS
G80zz00	Phlebitis and thrombophlebitis NOS
G80..00	Phlebitis and thrombophlebitis
G800.11	Saphenous vein phlebitis
G800.12	Saphenous vein thrombophlebitis
G800000	Phlebitis of the long saphenous vein
G800100	Phlebitis of the short saphenous vein
G800300	Thrombophlebitis of the long saphenous vein
G800400	Thrombophlebitis of the short saphenous vein
G401.00	Pulmonary embolism
G401.12	Pulmonary embolus
14A8.12	H/O: thrombosis
2I17.00	O/E - phlebitis

G402.00	Pulmonary infarct
G82..00	Other venous embolism and thrombosis
L096400	Pulmonary embolism following abortive pregnancy
L414.12	Phlegmasia alba dolens - obstetric
L43..00	Obstetric pulmonary embolism
L430.00	Obstetric air pulmonary embolism
L430000	Obstetric air pulmonary embolism unspecified
L430100	Obstetric air pulmonary embolism - delivered
L430300	Obstetric air pulmonary embolism with a/n complication
L430400	Obstetric air pulmonary embolism with p/n complication
L430z00	Obstetric air pulmonary embolism NOS
L431.00	Amniotic fluid pulmonary embolism
L431000	Amniotic fluid pulmonary embolism unspecified
L431100	Amniotic fluid pulmonary embolism - delivered
L431300	Amniotic fluid pulmonary embolism with a/n complication
L431400	Amniotic fluid pulmonary embolism with p/n complication
L431z00	Amniotic fluid pulmonary embolism NOS
L432.00	Obstetric blood-clot pulmonary embolism
L432000	Obstetric blood-clot pulmonary embolism unspecified
L432100	Obstetric blood-clot pulmonary embolism - delivered
L432300	Obstetric blood-clot pulmonary embolism + a/n complication
L432400	Obstetric blood-clot pulmonary embolism + p/n complication
L432z00	Obstetric blood-clot pulmonary embolism NOS
L433.00	Obstetric pyaemic and septic pulmonary embolism
L433000	Obstetric pyaemic and septic pulmonary embolism unspecified
L433100	Obstetric pyaemic and septic pulmonary embolism - delivered
L433z00	Obstetric pyaemic and septic pulmonary embolism NOS
L43y.00	Other obstetric pulmonary embolism
L43y000	Other obstetric pulmonary embolism unspecified
L43y100	Other obstetric pulmonary embolism - delivered
L43y200	Other obstetric pulmonary embolism - delivered + p/n comp
L43y300	Other obstetric pulmonary embolism with antenatal comp
L43y400	Other obstetric pulmonary embolism with postnatal comp
L43yz00	Other obstetric pulmonary embolism NOS
L43z.00	Obstetric pulmonary embolism NOS
L43z000	Obstetric pulmonary embolism NOS, unspecified
L43z100	Obstetric pulmonary embolism NOS - delivered
L43z200	Obstetric pulmonary embolism NOS - delivered with p/n comp
L43z300	Obstetric pulmonary embolism NOS with antenatal complication
L43z400	Obstetric pulmonary embolism NOS with postnatal complication
L43zz00	Obstetric pulmonary embolism NOS
ZV12900	[V] Personal history of pulmonary embolism

Table 10. Read codes for ischaemic stroke

Read Codes	Description
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction – cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome

G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
G673.00	Cerebral aneurysm, nonruptured
G673000	Dissection of cerebral arteries, nonruptured
G673100	Carotico-cavernous sinus fistula
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral arte
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G6...00	Cerebrovascular disease
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
G68..00	Late effects of cerebrovascular disease
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA

Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
14AK.00	H/O: Stroke in last year
662M.00	Stroke monitoring
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
L440.12	Stroke in the puerperium
ZV12511	[V]Personal history of stroke
7A24400	Open embolectomy of cerebral artery
7A24500	Open embolectomy of circle of Willis
7A24600	Open embolisation of cerebral artery
7A24700	Open embolisation of circle of Willis
7A25000	Percutaneous transluminal embolisation of cerebral artery
7A25100	Percutaneous transluminal embolisation of circle of Willis
7A25200	Embolisation of cerebral artery NEC
7A25300	Embolisation of circle of Willis NEC
8HBJ.00	Stroke / transient ischaemic attack referral
8HTQ.00	Referral to stroke clinic
ZLEP.00	Discharge from stroke serv
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati

Table 11. Read codes for myocardial infarction (MI)

Read	Description
G30..00	Acute myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall

G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
14A3.00	H/O: myocardial infarct
14A4.00	H/O: myocardial infarct >60
3232.00	ECG: old myocardial infarction
3235.00	ECG: subendocardial infarct
323Z.00	ECG: myocardial infarct NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G307100	Acute non-ST segment elevation myocardial infarction
G312.00	Coronary thrombosis not resulting in myocardial infarction
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G364.00	Rupture chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G384.00	Postoperative subendocardial myocardial infarction
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site

Annex 4. Signature pages

Signature Page – Principal Investigator

Title	A pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in the United Kingdom
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16647
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	Dr Luis A García Rodríguez
Title	MD
Address	Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain

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

Date, Signature: 20 January 2015

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 United Kingdom
Protocol version identifier	5.2
Date of last version of protocol	20 Jan 2015
IMPACT study number	16647
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