Drug Safety Research Unit (DSRU)

An observational post-authorization Modified Prescription-Event Monitoring safety study to monitor the safety and utilization of rivaroxaban (XARELTO®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England

Protocol

PASS information

Title	An observational post-authorization Modified Prescription-Event Monitoring safety study to monitor the safety and utilization of rivaroxaban (XARELTO®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England
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Marketing authorisation holder(s)	Bayer Pharma AG, D-13353 Berlin, Germany
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Research question and objectives	To study the utilisation and long-term safety of rivaroxaban in new-user patients (rivaroxaban naïve who may or may not be antithrombotic therapy naïve) initiated in primary care and patients initiated in secondary care for whom shared care GP prescribing arrangements are in place under normal conditions of use in primary care.
Country(-ies) of study	England
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2 List of Abbreviations

Abbreviation	Term
A and E	Accident and Emergency
ADR	Adverse Drug Reaction
ACS	Acute coronary syndrome
AE	Adverse Event
AF	Atrial fibrillation
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	aspartate aminotransferase
BMA	British Medical Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CYP2CP	Cytochrome P450 2C9
CYP P450	Cytochrome P-450
DMP	Data Management Plan
DSRU	Drug Safety Research Unit
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drugs Administration
FDR	False Discovery Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HLT	Higher Level Term
ID	Incidence Density
INR	International normalized ratio
IRAS	Integrated Research Application System
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile Range
LFT	Liver Function Test

Abbreviation	Term
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NICE	National Institute for Health and Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-The-Counter
PCI	Percutaneous coronary insert
PE	Pulmonary embolism
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
PS	Propensity Scores
PSC	Project Steering Committee
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VKORC1	Vitamin K epoxide reductase complex subunit 1
VTE	Venous thromboembolism

3 Responsible Parties

Responsible party	Appointed person(s)
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4 Abstract

Title

An observational post-authorization Modified Prescription-Event Monitoring safety study to monitor the safety and utilization of rivaroxaban (XARELTO®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England

Rationale and Background

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements.(1) On 19 December 2011, the European Commission granted authorization of extension of the license of rivaroxaban to include prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.(2) A further variation of marketing authorisation for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults' was approved on 20 November 2012 (3) More recently, a marketing authorisation variation application has been approved in the EU for rivaroxaban to be 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.(4) A Risk Management Plan (RMP) has been developed for rivaroxaban by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use).(5)

This post-marketing Modified Prescription-Event Monitoring (M-PEM) safety study of rivaroxaban is to be carried out by the Drug Safety Research Unit (DSRU) as part of the RMP required by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice. This study, the aim of which is to proactively capture safety and drug utilisation data in the post-marketing phase of an extension to license approval of rivaroxaban as prescribed to patients by general practitioners in England, is one of three complementary studies. The second is a Specialist Cohort Event Monitoring study (SCEM), designed to monitor

the safety and drug utilisation of rivaroxaban, as initiated by specialist Health Care Professionals (HCPs) for prevention of stroke and systemic embolism in adult patients with non-valvular AF, for the treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults. The third is another SCEM study designed to monitor the safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated by specialist healthcare professionals within the secondary care hospital setting in England and Wales as part of a treatment strategy to reduce overall and cardiovascular mortality in patients with recent ACS.

Research question and objectives

In addition to the routine and other pharmacovigilance activities, this M-PEM study will monitor clinically important identified and potential risks within a cohort of patients treated with rivaroxaban. The primary focus of the study will be to quantify the cumulative incidence (risk) of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed (Table 2)) and all intracranial sites) occurring in the twelve months observation period after treatment initiation and if treatment is continuous, during long-term exposure (at least twelve months continuous use). The secondary focus will be on 1) advancing the understanding of the patient population prescribed rivaroxaban in the primary care setting; 2) describing any prescribing and use of rivaroxaban outside terms of marketing authorisation ('off-label'), for example the approved indications and/or populations with special label precautions; 3) describing changes of health profile of patients, assessment of adherence, number of indication related episodes and duration, plus any alterations of the treatment programme during the twelve month study observation period; and 4) quantifying the risk of a) other major or minor bleeding outcomes not specified in the primary objectives b) all major and minor bleeds within a composite outcome, c) Haemorrhage (major bleeding during treatment (individual quantification per organ site) d) thromboembolism (recurrent and incident) and e) any other events[1] reported in the 12 month observation period overall and, if number of reports are sufficient, in patient subgroups of special interest. The study also includes several exploratory analyses to 1) where possible, to quantify the incidence of other important identified and potential risks (not mentioned in the primary objective), other frequently and rarely reported adverse events; 2) describe clinical features and management of cases of overdose, major bleeding and VTE events indicating failure of anticoagulation in the cohort exposed to rivaroxaban; and 3) characterise differences in prevalence of prognostic factors and

[1] The term 'event', as used in this study, is defined as, "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes."

clinical risk factors between patients with haemorrhage and those without, as reported during the first 12 months after treatment initiation in the cohort exposed to rivaroxaban.

Study design

This study will be a prospective observational, population-based cohort study based on review of patient medical charts.

Population

Patients prescribed rivaroxaban in the primary care setting in England.

Variables

At least three months after the first identified prescription has been issued for each patient (treatment index date), the prescribing doctor will be sent a M-PEM questionnaire to gather data on rivaroxaban treatment prescribing patterns, acute adverse events and baseline patient characteristics such as: the year of birth, sex and body mass index (BMI) of the patient (closest available measurement prior to initiation), confirmation of indication for treatment, start dose of rivaroxaban, date of starting treatment, non-clinical[2] reasons for prescribing, baseline and past medical history, prior and baseline (concurrent) medication use (including CYP3A4 and P-gp inhibitors), date of stopping treatment (and reason for discontinuing therapy if treatment was stopped (including switching to other antithrombotic treatments)) and selected events occurring early after starting treatment with rivaroxaban. A second M-PEM questionnaire will be sent at least twelve months after treatment index date (i.e. at least nine months after three month survey) to gather data on events occurring during longer term treatment with rivaroxaban and events after stopping up to the end of the observation period, including cause of death (where applicable); date of stopping treatment (and reason for discontinuing therapy if treatment was stopped (including switching to other antithrombotic treatments)) and changes in concomitant medication during treatment.

Data sources

Patients will be identified from dispensed National Health Service (NHS) prescription data for rivaroxaban, sent to the DSRU by the NHS Business Services Authority (NHSBSA) in England. Data collection will be in two phases via questionnaires sent to the prescribing doctor.

[2] Non-clinical reasons for prescribing include: factors associated with accumulation of authoritative evidence (formulary committee approval; recommendation from NICE; expert committee guidelines); trigger factors (crisis resulting from or challenge to usual prescribing) and behavioural factors (personal expertise in treating condition; history of clinical success with similar treatments) .

Study size

The study aims to collect exposure and outcome data for a cohort of approximately 10,000 evaluable patients.

Data analysis

Summary descriptive statistics, event incidence risk and rate calculation and time to onset regression modelling will be used.

Milestones

A final report will be produced.

5 Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	19/06/2013	All	Creation	
2	16/08/2013	All	Amendment	Revision of text in accordance with GVP module VIII general guidance
3	05/11/2014	10.3 Variables	Amendment	Addition of eGFR monitoring
4	14/11/2014	12 Management and reporting of adverse events/ adverse reactions	Amendment	DSRU statement on reporting in light of GVP module VI
5	16/01/2015	10.7 Data analysis 10.9.2 Potential for bias	Amendment	Addition of section to handle missing data Addition to limitation section

The original M-PEM study protocol (December 2011) was updated in 2013 to comply with the new post authorisation safety study protocol format issued by the European Medicines Agency (EMA).

6 Milestones

Milestone	Planned date
Start of data collection	December 2011
End of data collection	December 2014 (tbc)
Interim report 1	November 2013
Registration in the EU PAS register	Not registered
Final report of study results	June 2015 (tbc)

7 Rationale and Background

7.1 Post-marketing surveillance

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.(6) This applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing. In the UK, the Yellow Card spontaneous reporting scheme and Prescription-Event Monitoring (PEM) provide complementary systems of post-marketing surveillance on a national scale of newly marketed drugs prescribed by general practitioners (GPs) in the primary care setting.

7.2 Prescription-Event Monitoring

Standard PEM provides surveillance on a national scale. Using a study questionnaire, GPs who have prescribed the new medicine are asked to report all events[3] that have been recorded in the patients' notes during a specific time-period after beginning treatment with the medicine, regardless of whether any events are thought to be associated with any specific drug or treatment. By removing the need for the prescribing doctor to give an opinion about whether an event might have been caused by the medicine, PEM provides an opportunity to generate safety signals not previously associated with the drug under surveillance. The technique of PEM has been described previously.(7)

7.3 Modified Prescription-Event Monitoring

The technique of PEM can be used to examine a variety of issues relating to the use of prescription drugs. In certain situations however, it may be desirable to modify this methodology – such studies are referred to as Modified Prescription-Event Monitoring (M-PEM) studies because they require modifications to the standard PEM methodology Customised data-collection questionnaires are designed for such studies. Examples of the modifications may relate to establishing baseline characteristics of patients in relation to pre-specified risks, identifying physician prescribing and decision making behaviour, and evaluating risks of adverse events over various timeframes, including periods prior to starting or after discontinuation of treatment.(8) Modified PEM studies involve a payment to GPs for the data-collection questionnaires. Requests for 'follow-up' data are made, as in standard PEM studies, using a postal questionnaire. GPs receive

[3] The term 'event', as used in this study, is defined as, "*any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's note.*

an additional payment to cover any administrative costs for completed questionnaires for 'follow-up' information returned. Modified PEM studies are carried out under the same ethical guidelines as standard PEM studies (section 11).

7.4 Study Rationale

The aim of this study is to monitor clinically important identified and potential risks within a cohort of patients treated with rivaroxaban in the real-life primary care setting in England following approval of MA variations of the license in England.

7.5 Rivaroxaban formulation and licensed prescribing indications

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements.(1) On 19 December 2011, the European Commission granted authorization of extension of the license of rivaroxaban to include prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.(2) A further variation of marketing authorisation for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults' was approved on 20 November 2012.(3) More recently, a marketing authorisation variation application has been approved in the EU for rivaroxaban, 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.(4)

Rivaroxaban is a highly selective direct factor Xa inhibitor with high oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated. It is formulated as a film-coated tablet containing 2.5 milligram (mg), 10mg, 15mg or 20mg of active ingredient for oral administration. The absolute bioavailability of rivaroxaban is high (80 % - 100 %) for the 10 mg dose, with peak plasma levels attained between 2-4 hours.(1)

7.5.1 Dosage and duration

Duration depends on individual risk of patient for VTE, which is determined by indication for treatment (Table 1).

Table 1. Dosage and duration of treatment with rivaroxaban according to licensed and proposed indications.(9)

Indication	Initial dose (mg)	Maintenance/maximum dose	Duration	Food intake
Prevention of VTE in adult patients undergoing elective major hip or knee replacement surgery	10 Initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established	10	For patients undergoing major hip surgery, -5 weeks For patients undergoing major knee surgery - 2 weeks	Can be taken with or without food
Treatment of DVT and prevention of recurrent DVT and PE	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of PE and prevention of recurrent DVT and PE	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults (in patients with moderate or severe renal impairment)[4]	15 (twice daily for first 3 weeks)	15 or 20 (daily)	Continued treatment	To be taken with food
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack	20 (daily)	20 (daily)	Continued treatment	To be taken with food
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (in patients with moderate or severe renal	15 (daily)	15 (daily)	Continued treatment	To be taken with food

[4] In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling

impairment)				

7.5.2 Safety Profile and Undesirable Effects

The clinical trial safety profile data for rivaroxaban for prevention of VTE in patients undergoing elective hip or knee replacement is based on the RECORD trials (10) (11-13) For the new indications of treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults, treatment of PE and prevention of recurrent DVT and PE in adults and prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, additional clinical trials have been performed.(14-18) The role of rivaroxaban for the treatment of VTE was investigated in three large randomised trials in the EINSTEIN programme: the EINSTEIN-DVT study was planned to probe the role of rivaroxaban as a standalone drug for the treatment of acute DVT; the EINSTEIN-Extension study was designed to evaluate extended anticoagulation treatment with rivaroxaban in patients who have been treated for acute VTE; and the EINSTEIN-PE study evaluated the role of rivaroxaban for the treatment of acute PE. The ROCKET-AF trial was designed as double-blind, double dummy trial comparing rivaroxaban with warfarin for the prevention of stroke and thromboembolic events in people with non-valvular atrial fibrillation at risk of future thromboembolic events. The clinical trial safety profile data for rivaroxaban for secondary prevention in ACS is based on the ATLAS trials.(19) Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of rivaroxaban. A Risk Management Plan has been developed for rivaroxaban by the MAH. This plan includes tools designed to monitor the important risks (including class effects and off-label use). The current safety specification (important risk, potential risk, missing information) is based on the Xarelto EU RMP version 7.5.(5)

Important identified risks, including class effects, are

- Haemorrhage

Important potential risks, including class effects, are

- Embryo-foetal toxicity

Missing information includes:

- Patients undergoing major orthopaedic surgery **OTHER** than the approved indication "elective hip or knee replacement surgery[5]"

[5] This study is not designed to monitor the safety and use of rivaroxaban in this group of off-label **surgical** patients. However since there is a need to inform on off-label use in non-orthopaedic

- Patients with severe renal impairment (CrCl <30ml/min).
- Patients receiving concomitant systemic treatment with CYP3A4 or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir).
- Remedial pro-coagulant therapy for excessive haemorrhage.
- Pregnant or breast-feeding women.
- Patients with AF and a prosthetic heart valve.
- long term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting.
- Patients < 18 years.

Outcomes of special interest

- Increase in liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], Gamma-Glutamyl Transferase (GGT)] and bilirubin.
- Management of homeostasis in patients with the indications of interest who also undergo surgery (elective or urgent) during the observation period in this study.

The safety profile and efficacy of rivaroxaban in children aged <18 years have not been established. No data are available. Therefore, rivaroxaban is not recommended for use in children below 18 years of age.(1) A Paediatric Investigation Plan (PIP) has been agreed with EMA, the aim of which is to contribute to the insight in the efficacy and safety profile of rivaroxaban in paediatric populations.

Off label prescribing of rivaroxaban (in terms of medical indication, dose etc) is possible so any data relating to off label use will be examined in this study.

8 Research Question and Objectives

8.1 Overall aim:

To study the utilisation and long-term safety of rivaroxaban in new-user patients (rivaroxaban naïve who may or may not be antithrombotic therapy naïve) initiated in primary care and patients initiated in secondary care for whom shared care GP prescribing arrangements are in place under normal conditions of use in primary care.

8.2 Specific objectives:

8.2.1 The primary objective

This is given below. Its purpose is to provide timely information on:

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medical conditions requiring anticoagulation, data from any patients within this latter category will be eligible for inclusion and evaluated as part of the secondary objective (ii)

(i) Estimation of the cumulative incident risk (separately) of the following important identified risk for rivaroxaban users which is:

- Haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (Table 2)).

8.2.2 Secondary Objectives

These are given below. Their purpose is to provide timely information on:

(i) Prescriber and cohort accrual and the type of prescriber responsible for and the setting of initiation of treatment with rivaroxaban.

(ii) Prevalence of non-clinical reasons for prescribing, prognostic health factors and clinical risk factors for haemorrhage as reported in medical charts for patients undergoing anticoagulation with rivaroxaban in the primary care setting and the treatment programme they received to advance the understanding of the patient population prescribed rivaroxaban in actual clinical practice in the primary care setting.

(iii) Changes of health profile of patients, assessment of adherence, plus any alterations of the treatment programme during the 12 month observation period, as recorded in medical charts.

(iv) To quantify the risk of:

(a) all major bleeding specified in primary objective for rivaroxaban (as composite)

(b) (separately) haemorrhage (major bleeding according to Table 2) within critical organ sites other than specified in primary objective for rivaroxaban

(d) all major and clinically relevant non-major bleeds (as a composite outcome)

(e) thromboembolic complications (incident and recurrent)

(f) other[6] events including special outcomes of interest (severe hepatic failure and abnormal LFTs above 3x ULN) as recorded in medical charts during the 12 month observation period and, if number of reports are sufficient, in patient subgroups of special interest, including:

- reported indications
- paediatric (<18 years), elderly (>= 65 years), other contraindicated or special groups (e.g. pregnant and breastfeeding women, patients with concurrent significant renal or hepatic impairment; patients with known VTE and/or haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease) and off-label groups (patients with other non-orthopaedic medical conditions)

[6] Other than major and clinically relevant non major bleeding outcomes, or thromboembolic complications (recurrent or incident)

- concomitant use of medications that are contraindicated or to be used with caution (e.g. CYP3A4 inducers/inhibitors, P-gp inhibitors, anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, hormone and oral contraception therapy and platelet aggregation inhibitors)

8.2.3 Exploratory objectives

The specific objectives that follow are all exploratory. The purposes of these objectives are:

(i) Where possible, to quantify the incidence of other important identified and potential risks (not mentioned in the primary objective), other frequently and rarely reported adverse events as recorded in the medical charts.

(ii) To describe clinical features and management of cases of overdose, major bleeding (according to pre-specified definition (Table 2), VTE events indicating failure of anticoagulation and management of homeostasis during surgery as recorded reporting the medical charts in the first 12 months after treatment initiation in the cohort exposed to rivaroxaban.

(iii) To characterise differences in prevalence of prognostic factors and clinical risk factors between patients with haemorrhage and those without, as reported during the first 12 months after treatment initiation in the cohort exposed to rivaroxaban.

Table 2. Haemorrhage outcomes

A major[†] bleeding event will be defined using ISTH criteria (20) as clinically overt bleeding that is associated with:

- A fall in haemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

A clinically-relevant nonmajor bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention[7], unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of nonmajor clinically relevant bleeding events are:

- Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)
- Gingival bleeding if it occurs spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes
- Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal haemorrhage: at least 1 episode of melena or haematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Haemoptysis, if more than a few speckles in the sputum, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm^2 or larger than 100 cm^2 if provoked
- Multiple source bleeding events

[†] *The three organ sites included in the primary objective are gastrointestinal and, urogenital (which meet the criteria for major bleed) and intracranial. Case definition will be confirmed by an expert committee.*

[7] Such as: Surgical or endoscopic intervention; decompression of a closed space to stop or control the event; protamine sulphate administration

9 Research Methods

9.1 Study Design

This study will use an observational cohort design. Randomisation will not be required. Study start is defined as the date of the first prescription issued as notified by the NHS BSA after the date of market launch in England for the new indication (December 2011). The duration of the M-PEM study will be dependent on the level of prescribing of rivaroxaban by GPs in England. Slow uptake may impact the ability to meet the study objectives; in this instance due consideration should be given to the need to continue data collection and the feasibility of study completion should be open to re-evaluation. This will be an important area of review by the study team and MAH in order to monitor and agree upon any appropriate remedial actions.

Another important consideration is the capture of data on the initial period of usage. We anticipate that a proportion of patients (% as yet unknown) will be initiated within hospital and affiliated secondary care institutions. This study design will capture data on patients in primary care who continue therapy that was started in secondary care, as well as patients newly initiated on rivaroxaban by the GP. Therefore, this design will not capture data on patients who start and stop treatment within the hosptial/secondary care setting. This could introduce error through selection bias (see section 9.9.2) into interpretation of results because the M-PEM study population may not be entirely representative of the total target population of new users of this product. However, as the data are sampled at national level, the cohort is representative of the population registered within the NHS in England in the general practice setting. As described previously, two complementary studies to examine treatment initiation within the secondary care setting are proposed. Separate full final protocols are available. Therefore, at twelve months, cohort accrual will be examined to determine the proportions of patients initiated in primary care and in secondary care (based on response to relevant question on treatment initiation on the questionnaire). This is possible because GPs in England typically receive summary information on in-patient episodes and for out-patient care. In addition, in some cases, decisions by hospital doctors to start treatment with medicines are conveyed to GPs who issue the first prescriptions for the medicines recommended by the hospital based doctors; these are patients for who shared care arrangements with GP are in place for prescribing.

All patients who receive a prescription from a GP for rivaroxaban in the primary care setting will be eligible for inclusion (see section 9.2.1). Patients will be observed from start of treatment with rivaroxaban (index date) and for a minimum of twelve months (or less if patient is censored because of treatment cessation or attrition) in order to

allow for detection of acute outcomes associated with treatment initiation and events with delayed onset that might occur within twelve months after starting rivaroxaban treatment. Data will be captured using a two-phased approach. The first questionnaire will be sent at least three months after the patient's first rivaroxaban prescription and aims to capture information on baseline characteristics and acute adverse events associated with specific risks of interest. The second questionnaire will be sent at least twelve months after the patient's first prescription and aims to capture time-variant data such as changes in health-status, medications and adverse events with delayed onset associated with specific risks of interest, as well as alterations of the treatment programme.

The process of capture of patient data for this study is summarised in Figure 1.

Figure 1. M-PEM study of rivaroxaban

DSRU notifies NHS Business Services Authority (NHS BSA) of **rivaroxaban** study

↓

DSRU receives data from dispensed National Health Service primary care prescriptions issued in England by GPs from the date of market launch

↓

Part 1: M-PEM three month questionnaires sent to GPs (≥ 3 months after NHS FP10 1st prescription issued for patient)

↓

Part 2: M-PEM 12-month observation questionnaires sent to GPs (≥ 12-months after NHS FP10 1st prescription issued for patient)

↓

M-PEM questionnaires returned from Part I and II, scanned, reviewed and data entered onto DSRU database

↓

Selected events of medical interest, deaths (where cause not known) and pregnancies undergo further evaluation.

[Patient confidentiality maintained throughout]

9.1.1 Strengths

- All patients who are dispensed rivaroxaban in primary care are identifiable and will be eligible for inclusion. There are no exclusion criteria.
- The observational non-interventional nature of PEM study design is maintained; prescribing of relevant pharmacological therapy should not be affected because of participation in this study.
- Data is collected on large numbers of rivaroxaban users in conditions of routine clinical practice.
- Special populations can be characterised.

- Time-dependent effects can be examined.

9.2 Setting

9.2.1 Inclusion Criteria

Patients will be identified by means of data extracted from dispensed National Health Service (NHS) primary care prescriptions for rivaroxaban, written by any GPs in England (irrespective of past participation within PEM studies[8]) and supplied in confidence to the DSRU by the NHS BSA for England. M-PEM questionnaires are sent according to the chronological order of prescription issue date to those GPs who prescribed the newly marketed medicine until the target sample size is achieved. The intention as per study aim is to recruit a cohort prescribed rivaroxaban, irrespective of indication. Thus, since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximize external validity.

Patients for whom a study questionnaire containing useful information has been returned, will be included in the study cohort regardless of the dose or frequency of administration of rivaroxaban, and irrespective of whether any medicines are concurrently administered.

9.2.2 Exclusion Criteria

Patients will also be excluded if the GP reports that the patient is no longer registered with the practice and no information is provided (NB. Where information is available up to a specific date that data will be included). In addition, patients will also be excluded for whom the information provided on the M-PEM relates to either another antithrombotic drug, or the index date is an improbable date (i.e. before market launch date), or if the GP reports that the patient did not take or was never prescribed rivaroxaban.

Patients who are identified within the SCEM study may be considered for exclusion from M-PEM evaluable cohort.

9.2.3 Evaluable patients

Evaluable patients for primary objective (i) and secondary objective (i) will not include those where the initial three-month survey questionnaire was returned blank (contain no clinical information) or has not been returned. Evaluable patients for all other objectives will not include those patients for whom both the three-month or twelve-month

[8] Those GPs who have informed the DSRU that they do not wish to participate in PEM studies are excluded from receiving questionnaires

questionnaires were returned blank (contain no clinical information) or had not been returned.

9.3 Variables

Data obtained from the three-month M-PEM questionnaire will include:

- setting and prescriber type.
- non-clinical reasons for prescribing (e.g. formulary decision, patients request etc).
- Physician prescribing preference factors.
- date and dose details of first rivaroxaban prescription.
- details of prior and use at index date of oral and parenteral anticoagulant therapy (thienopyridines, aspirin, glycoprotein Iib/Iia inhibitors, heparins) and details of transition plan if switching.
- history of response to prior anticoagulation treatment [whether INR was stable (and within desired therapeutic range), and/or events associated with poor tolerability].
- indications[9] (based on clinical diagnosis/decision and supported by information recorded using diagnostic codes (e.g. READ) held at each relevant practice, where available).
- Use of concomitant drugs which are not recommended for concomitant use (including azole antimycotics,and HIV protease inhibitors).
- Use of concomitant drugs which should be used with caution (including fluconazole, strong CYP3A4 inducers, P-gp inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents).
- demographic characteristics (age, gender and ethnicity).
- presence of general health factors (BMI status, weight, eGFR - date of most recent measurement).
- relevant medical history for important potential and identified risks of interest (and dates first diagnosis/report thereof prior to index date). **For example:** past history of VTE, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), other recent surgery within three months prior to index date, presence of thrombophilia and other

[9] General practitioner-based electronic medical records are not specifically designed to capture thromboembolic or cardiovascular disorders for research purposes. **READ** codes are a coded thesaurus of clinical terms used by clinicians to encode such data and which thus facilitate the access of information within patient records to enable reporting, auditing, research, automation of repetitive tasks, electronic communication and decision support.

coagulation disorders, malignancy, pregnancy, family and/or personal history of congestive heart failure, hypertension, diabetes mellitus, hypercholesterolaemia, peripheral arterial disease, stroke, COPD etc.).

- events including reports of selected risks of interest (Table 3).
- date and reasons for stopping (if stopped within first three months after starting).
- if stopped because of switch to alternative anticoagulant treatment.
- if stopped because remedial pro-coagulation therapy required.
- date of death (if died) in the first three months after starting treatment.
- reported pregnancies at start or during the first three months after starting treatment and outcome of birth.

Table 3. Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
IDENTIFIED AND POTENTIAL RISKS for targeted data collection on M-PEM questionnaires		
Major bleeding episode (into a critical organ sites)	Targeted outcome questions on critical sites	Selected risk factors collected on M-PEM questionnaire. Further data on severity, management and risk factors to be collected via follow-up.
Clinically relevant minor bleeding episodes	Targeted outcome question to specify details	Selected risk factors collected on M-PEM questionnaire. Not for follow-up
Incident and recurrent thromboembolic complications (DVT, PE, Stroke)	Targeted outcome questions	Selected risk factors collected on M-PEM questionnaire. Further data on symptoms, severity, management and risk factors to be collected via follow-up.
Overdose , accidental trauma and reversal of anticoagulation therapy	Targeted outcome question	Events of overdose (dose > 50mg/day) and accidental trauma are those of clinical medical importance which require acute medical/surgical treatment (with or without) hospitalisation.. Further data to be collected via follow-up
Concomitant use of contraindicated medications and medications to be used with caution	Targeted outcome question on other medications to gather use at baseline	Further data may be collected via follow-up
MISSING INFORMATION for general surveillance		
Use during pregnancy and lactation	General event report	Further data to be collected via follow-up

Data obtained from the twelve-month M-PEM questionnaire will include:

- changes in general health factors (BMI status, weight, eGFR) and date last measured (closest to end of twelve-month observation date).
- changes in medication treatment regimen (date, dose and frequency).
- events including reports of selected risks of interest (Table 3).

- date and reasons for stopping (if stopped since date of three-month survey):
  - if stopped because of switch to alternative anticoagulant treatment
  - if stopped because remedial pro-coagulation therapy required
- date of death (if died) since date of three-month survey.
- reported pregnancies [10] since date of three-month survey and outcome of birth.
- frequency of behaviours regarding anticoagulant treatment adherence.

9.4 Data Sources

9.4.1 M-PEM Questionnaires

Records-based data collection in this study will be conducted in two parts.

9.4.2 Three-month M-PEM questionnaires

For each eligible patient, at least three months post index date, data on relevant past medical history (see section 9.3) and additional exposure data contained within GPs' primary care medical records will be requested from and abstracted onto this three-month questionnaire, by the GP.

9.4.3 Twelve-Month M-PEM questionnaires

For each evaluable patient for whom a valid three-month questionnaire has been received, at least twelve-months observation post index date (approximately nine months after the three-month M-PEM questionnaire was sent), the GP will be prompted to complete a second M-PEM questionnaire which will gather information on clinical events of medical interest and serious adverse event reports [serious defined according to the International Conference on Harmonisation definitions (21)].

9.4.4 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from Section 9.3, Table 3) may undergo further evaluation for aggregate assessment of drug- relatedness to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours (see section 9.7.9). Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may gather additional relevant information where recorded within medical charts.(22)

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey

[10] All reported pregnancies are followed up post estimated delivery date to capture additional information on outcomes relevant to the birth. Information on lactation is obtained through routine event reports.

period. In accordance with Good Pharmacovigilance Practice (GVP) sections VI.C.1.2.1 and VI.C.2.2.2, (23) data will be analysed at aggregate level partially at the time of compiling the interim report (because all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytic study. Because of the epidemiological nature of the design of this cohort study, any *conclusions* on drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 12).

If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

In summary, specific outcomes of interest for further evaluation are:

1. Pregnancies: All reported pregnancies will be specifically followed-up using a supplementary questionnaire to ascertain the outcome of pregnancy.

2. Deaths: All reported deaths will be followed-up to try to establish the cause of death.

3. Events: Selected events of interest as defined in Table 3 may be followed-up for additional information on relevant risk factors, where insufficient information is provided on the questionnaire. The event of switching given as a reason for stopping rivaroxaban (although not defined in Table 3) will undergo further evaluation.

4. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.

5. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) events compiled by the DSRU (Appendix 1) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

9.4.5 Methods to Maximise Questionnaire Response Rate

9.4.5.1 Three month (Baseline) and 12- month M-PEM questionnaires

A proportion of GPs are likely to fail to respond to these questionnaires at this monitoring stage. Single reminder questionnaires are sent by post to those GPs who have not responded within one month of the date the initial questionnaire was sent.

9.4.5.2 Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

9.5 Study Size

The ability to detect any particular adverse event is dependent on the expected incidence rate of the adverse event in those exposed to the drug, the background rate in those not exposed to the drug, and the total number of patients.

9.5.1 Sample size for general safety surveillance of events where background event rate is known

It is possible to estimate a sample size necessary to detect a specified adverse event with known background incidence rate (BR) by effect size (Table 4). Table 4 displays the sample sizes for a given power across a range of background rates and rate ratios or incidence density ratios (IDR). The table may also be used to interpret sample sizes for risk differences or incidence density differences (IDD) by the following formula: IDD = (BR × IDR) – BR.

For this M-PEM study, a sample size of 10000 evaluable patients is desirable to detect an effect size (relative incidence rate) of at least 2.0 with power of 90 % at 5% significance for analysis of major bleeding events of interest within the primary objectives (section 8.2.1) for which the hypothesised background rate is uncommon (>0.1%).(9)

As sample size calculations are based on overall cohorts, further unplanned subgroups or stratification of the data would underpower subsequent analyses. For this study, it is also desirable to have appropriate sample size sufficient to detect 2.0 fold increase in events of interest such as clinically non-major bleeding events and recurrent VTE assuming the hypothesised background rate is common (>1.0%) or more in a sub-set population of interest (e.g as defined by indication).(9) Thus a sub-set sample size of 1423 would be sufficient to detect a 2.0 fold increase in such events with power of 90% at 5% significance.

Table 4. Sample sizes of evaluable patients for detection of a specified adverse event with known background incidence rate by effect size.

	Rate Ratio > 1.5	Rate Ratio > 2.0	Rate Ratio > 3.0	Rate Ratio > 3.5	Rate Ratio > 4.0
Background Rate (%)	**Power 80%**				
0.1	35,778	9924	2920	1999	1475
0.5	7156	1985	584	400	295
1.0	3578	992	292	200	147
2.0	1789	496	146	100	74
3.0	1193	331	97	67	49
4.0	894	248	73	41	37
5.0	716	198	58	40	29
Background Rate (%)	**Power 90%**				
0.1	49,831	14,231	4367	3038	2273
0.5	9966	2846	873	608	455
1.0	4983	1423	437	304	227
2.0	2492	712	218	152	114
3.0	1661	474	146	101	76
4.0	1246	356	109	65	57
5.0	997	285	87	61	45

Notes: alpha = 0.05 (two-sided); Reference: Machin D, Campbell M, Fayers P, Pinol A. 1997. *Sample Size Tables for Clinical Studies*, 2nd edn, Blackwell Science: Oxford, pp. 144. (24)

9.5.2 Sample size for general safety surveillance of events where background event rate is unknown

For purposes of general safety surveillance (for events arising from exploratory objective ii) for the population of interest, it is possible to estimate a sample size necessary to detect a minimum of three cases[11] based on an assumed rate in that exposed sub-group and assuming the background rate is zero.(26) For this study, a sample size of 10000 evaluable patients is desirable and should allow for the detection of at least three cases of an adverse event, if the event occurs at a rate of at least one in 2000 patients with 85% power (where the background rate is unknown); (26) a sample size of 5000 evaluable patients would allow for the detection of at least three cases of an adverse event with 85% power, if the event occurs at a rate of at least one in 1000, whilst a sample size of 1000 evaluable patients should allow for the detection of at least three cases with a rate of at least one in 200 at 85% power.

[11] In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution and the 95% CI calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often that 3/X. (25)

9.5.3 Cohort accrual considerations

At the first interim (datalock at the beginning of Month 19 of study observation[12]), cohort accrual by indication and the frequency rates for selected outcomes of interest can be reviewed and the adequacy of the sample size reassessed to determine the requirement for the final cohort size. Thus, although the speed of data collection during the study will be driven by the level of prescribing of rivaroxaban in England, study duration and cohort size will ultimately be determined by the quantity and content of the data gathered. Due consideration should be given to the need to continue data collection as necessary to meet study objectives. Data collected during later years can be compared with earlier periods to identify any trends in drug utilisation that may be emerging.

9.6 Data Management

GP and patient identifiable information will be stored within the DSRU database. All original documents, individual correspondence from health care professionals will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see section 9.6.3).

9.6.1 Review of data

All returned questionnaires with clinical data will be reviewed by a DSRU research fellow and coded onto the study database. Medically important adverse events that have been selected for follow-up will be coded as a priority. There will be regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

9.6.2 Coding of data

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from targeted closed format questions on the questionnaire (which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology) and coded onto the DSRU database. Other events reported on the questionnaires as free text will be coded onto this database using the DSRU Event Dictionary Doctor Summary Term synonym list that is mapped to MedDRA, in order to enable consistent reporting to be provided using MedDRA terminology.

[12] From month of first three month survey questionnaire send

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific PEM database region and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion would be reached by medically qualified staff.

9.6.3 Confidentiality procedures

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personnel receive training regarding security awareness.

All original documents, individual correspondence from health care professionals, will be stored for 15 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database after two years from receipt by NHSRxS, as per current policy. Until this time, only appointed staff would have access to such data.

9.7 Data Analysis

9.7.1 To estimate of the cumulative incident risk (separately) of haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (Table 2))

The following relates to Section 8.2.1 primary objective (i) and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (Table 2)).

The incidence of these events will be explored by estimating the hazard rates of these events over time. Such methods account for truncation of exposure time and censoring; for these analyses the exposure time would be censored at the time of the first event. Smoothed hazard plots will be used to describe how the baseline risk of an event changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the

drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of the selected event in patients prescribed rivaroxaban will be constant during the twelve-month period following the start of treatment will be tested by fitting a parametric time to event model (e.g Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. At least five reports of an event are deemed necessary for modelling purposes.* A sensitivity analysis will be performed to include in the numerator events reported within 30 days of stopping, and extend the denominator by 30 days.

**When the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p greater than one the hazard is increasing, if p less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one*.

Graphs of cumulative counts of events of interest, by month over the study period, will be examined for possible change in reporting over calendar time.

9.7.2 Cohort accrual, the type of clinician responsible for, the setting of initiation of treatment, physician prescribing preference factors and non-clinical reasons for prescribing

The following relates to Section 8.2.2 Secondary objective (i). Data on prescriber and valid cohort response rates will be presented, as will data on prescriber type, setting, physician prescribing preference factors and non-clinical reasons for prescribing. These data will be used to inform on cohort accrual and study timelines to target sample size.

9.7.3 To describe the health profile of patients at index date prescribed treatment with rivaroxaban in the primary care setting and the treatment programme they received to advance the understanding of the rivaroxaban patient population in actual clinical practice

The following relates to Section 8.2.2 secondary objective (ii). Valid cohort demography (age, gender and ethnicity) will be presented, as reported at baseline. Other baseline general health factors [BMI, weight] and indication-related characteristics [primary (and secondary if provided) diagnosis/decision, recent INR/APTT if switching from prior anticoagulant] and treatment initiation programme (rivaroxaban starting dose and frequency, if first initiated by specialist – duration between initiation date and first GP NHS FP10 prescription date) as reported on the M-PEM questionnaire will be described.

A synopsis of prior and baseline relevant morbidities and medication use will also be provided. Patient subgroups defined by indication or other subgroups of special interest [Table 5 - off-label arising from contraindications and those for which: precautions for

use are recommended and limited information is available] will be characterised in order to inform on missing information regarding use of rivaroxaban. Where possible, these groups will be compared in terms of demographic factors and other study variables. Further stratification by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

The proportion of patients within each special population sub-group prescribed rivaroxaban who had *one or more* relevant characteristics/conditions/co-prescribed medications at baseline will be summarised within each indicator group by simple aggregation of counts (see Table 5).

Table 5. Special population Indicators of Use for Rivaroxaban

5a) Indicators of Contraindicated Use *(Patients can have up to 5 indicators)*
Treatment for medical indications other than licensed indications
Clinically significant active bleeding
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Use in pregnancy and lactation
Hypersensitivity to the active substance or to any of the excipients
5b) Indicators of Use with Special Warnings or Precautions *(Patients can have up to 11 indicators)*
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy
Severe renal impairment (patients with creatinine clearance < 30 ml/min)
Moderate renal impairment (patients with creatinine clearance 30-49 ml/min)
Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Active ulcerative gastrointestinal disease
Recent gastrointestinal ulcerations
Vascular retinopathy
Recent intracranial or intracerebral haemorrhage
Intraspinal or intracerebral vascular abnormalities
Recent brain, spinal or ophthalmological surgery.
5c). Indicators of Use in Patients with Limited Information *(Patients can have up to 1 indicators)*
Patients with AF and a prosthetic heart valve
Children aged $\leq$ 15 years
5d) Indicators of Use with Potential Drug-Drug Interactions *(Patients can have up to 4 indicators)*
Concomitant systemic treatment with azole-antimycotics, e.g ketoconazole or HIV protease inhibitors
Concomitant treatment with CYP3A4 inhibitors/inducers or P-gp inhibitors
Concomitant treatment with other anticoagulants
Concomitant use with NSAIDs and platelet aggregation inhibitors

9.7.4 Changes of health profile of patients, assessment of adherence; number of indication related episodes and duration, plus any alterations of the treatment programme during the twelve months observation period

The following relates to Section 8.2.2 secondary objective (iii). Status of general health (BMI, weight) and indication-related characteristics (alteration of diagnosis) will be summarised, plus pattern of rivaroxaban treatment adherence at the end of the twelve month observation period will be summarised. The frequency and reasons for hospitalisation including hospital referrals will also be summarised, where reported. Alterations in treatment programme (change in dose, other drugs) will be described, as will any reason(s) for stopping rivaroxaban (including switching). Characteristics of censored patients (i.e. those lost to follow-up during the study observation period for reason other than stopping) will be compared with those who remain in the study.

Changes in these general health factors, indication-related characteristics and treatment details will be examined by comparing values at baseline and at twelve months post index date. Exploratory analysis may include data mining and descriptive measures for describing alterations in treatment programme.

The number of pregnancies, trimester of first exposure and details of births, terminations and miscarriages will be presented. The number of deaths in the total cohort for each month of exposure will be calculated. Underlying causes of death (as recorded in patient notes by specialist or GP) will also be described by system-organ class.

9.7.5 To quantify the incidence risk and rate of events reported in the 12 month observation period and in patient subgroups of special interest

The following relates to Section 8.2.2 secondary objective (iv) and exploratory objective (i) regarding a) other major or non-major clinically relevant bleeding outcomes not specified in the primary objectives , b) thromboembolism (recurrent and incident) and c) any other events reported in the twelve-month observation period.

For major bleeding events not specified in the primary outcome, each of the individual components of the major bleeding criteria (a fall in haemoglobin of 2 g/dL or more, or a transfusion of two or more units of packed red blood cells or whole blood, or a fatal outcome - as per Table 2) will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event.

For clinically relevant non-major bleeding events, each of the individual associated components (as per Table 2 such as requiring medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life) will be summarised. Where an individual has one or more criterion for a clinically relevant non-major bleeding event, this will also be summarised – in such individuals the first event report will be regarded as the incident event.

PEM methodology provides a numerator (the number of reports of an event) and a denominator (the number of patient-months at risk), both collected within a known time frame. This allows for the calculation of risk (percent of total valid cohort exposed) and incidence densities (ID; person-time incidence rates) for each event. Such analyses will be performed using 'Higher-level' event terms from the MedDRA dictionary. The risk profile of the overall cohort and sub-group of interest (based on characteristics defined at baseline, including whether rivaroxaban naïve or past user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Crude Incidence Densities (ID) [13]can be calculated by month in order quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to take rivaroxaban for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-months. This assumes pattern of use is continuous. The numerator will be the first reports of events reporting as occurring after the index date and during treatment.[14] For this study, IDs will be calculated for each event as for each month as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period t} \times 1000}{\text{Number of patient-months of treatment for period t}}$$

Thus, $ID_t = \frac{N_t \times 1000}{}$

[13] It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

[14] Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

D_t

where: N_t = Number of first reports of an event during treatment for period t,

and D_t = Number of patient-days of treatment for period t / 30

IDs will also be calculated for all twelve-months during treatment combined (ID_A) and the first month after stopping (ID_{S1}) if patient stopped (and where patients are recorded as remaining on treatment for at least four weeks) after index date.

9.7.6 To describe clinical features and management of cases of overdose, major bleeding and VTE events indicating failure of anticoagulation reported in the first twelve months after treatment initiation in the cohort exposed to rivaroxaban

The following relates to Section 8.2.3 exploratory objective (ii). A qualitative assessment of the summary characteristics of patients reported with these outcomes. This will include evaluation of treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the M-PEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

9.7.7 To characterise differences in prevalence of prognostic factors and clinical risk factors between patients with haemorrhage and those without, as reported during the first 12 months after treatment initiation in the cohort exposed to rivaroxaban

This is relates to Section 8.2.3 exploratory objective (iii) , the aim of which is to explore the association between selected prognostic and clinical characteristics as potential risk factors for newly reported cases of haemorrhage in users of rivaroxaban compared to those users reported to have not experienced such events. This analysis will use logistic regression to model the impact of important determinants (prognostics characteristics, selected relevant risk factors on the probability of the primary outcomes of interest (haemorrhage) and calculate adjusted Odds ratios and 95% confidence intervals. Two physician anticoagulant prescribing preference factors will be explored as a suitable conditioning (instrumental variable for inclusions within the model.

9.7.8 Multiple comparison adjustments

The methods of signal surveillance require a large number of multiple comparisons on adverse events, which involve inferring statistical significance on multiple *p*-values. To control for an excess of false positive signals, suitable multiple comparison adjustments

will be made with the false discovery rate (FDR) approach.(27) The Simes method (28;29)in addition to the double FDR method (27) will be implemented to maintain the false discovery rate at the acceptable 10% level for all statistical tests. Such approaches would allow for a balance between false positive and false negative signals.

9.7.9 Aggregate Assessment of Drug- Relatedness of Selected Events

As described previously (section 9.4.4) selected events of interest (Table 4) that require further characterisation and evaluation will be followed-up via a questionnaire sent to the patient's GP seeking further information. The information received at follow-up for events of medical significance or those which require further clarification will facilitate further evaluation at the aggregate level, including assessment of drug-relatedness, by experienced research staff at the DSRU (two qualified members of staff, independently, with a third adjudicator if necessary). This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e., three-month questionnaire, twelve-month questionnaire, and follow-up questionnaire if applicable) has been received. In the process of aggregate assessment of event data, the application of elements of the Austin Bradford Hill criteria, when the necessary information is available and the use of the method is considered appropriate, will be used.(30) This assessment takes into consideration of the points (see Box 1). (31)

Box 1. Points for consideration in evaluation of reported events

- *The distribution of time to onset (temporal relationship);*
- *The principle clinical and pathological characteristics of the group of events;*
- *The pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *Similar reports in medical literature*
- *patient's clinical characteristics, including:*

- previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.

-concomitant medications or medications taken prior to and during treatment;

- *Management and remedial action;*

The relatedness of selected events to rivaroxaban will be assessed as the following four categories: 1) probable[15], 2) possible[16], 3) unlikely[17], and 4) not assessable[18].(31) This

[15] Events are assessed as 'probable' if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

assessment will take account of time to onset of event, whether the event was the reason for stopping therapy, concurrent medication, concurrent disorders, positive or negative dechallenge (resolution or not of symptoms after withdrawal of rivaroxaban, with or without specific treatment of such symptoms), rechallenge if applicable (recurrence or absence of symptoms after re-exposure to the medicine), previous history of similar problems, or another specified cause.(31)

9.7.10 Missingness

Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the reported data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results. It is not possible to fully predict the pattern of missingness for each study variable, however several approaches will be initially undertaken to mitigate the potential for missingness in the process of data collection:

1. Collection of data within questionnaires will be through use of closed questions with binary response (Y/N) where possible. Responders who are uncertain will be encouraged to review available information to provide suitable response.
2. Returned questionnaires will be examined upon receipt for data completeness. The responder may be contacted to obtain the missing or correct information and data revised as appropriate on source document when possible.
3. Reminders will be sent for those questionnaires where the document has not been received as anticipated in accordance with return dates.

Specific methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Data Management Plan (DMP) which will be constructed to assist database development and data analysis. In brief, the missingness pattern of primary covariates and proportions thereof in the study subjects will be presented to explore plausibility of missing at random (MAR) assumption to justify

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[16] Events are assessed as 'possible' if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

[17] Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

[18] Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

subsequent regression analysis. Multiple imputation is planned. However, we will compare the results of this to a complete case analysis. If the two are substantially different we will evaluate what the reasons may be. Thus, imputation will be performed using STATA SE 12 ICE imputation for study variables (such as associated with exposure e.g dose or duration, and covariates e.g patient characteristics and risk factors) with less than 20% missing data and a sensitivity analysis conducted to determine magnitude and direction of bias arising from missing data from complete case analysis as relevant to Section 8.2 primary and secondary objectives.

9.8 Quality Control

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased PEM study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured through a number of methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training.
- Vigilance of operators at the various stages of processing.
- On screen validation during data entry.
- Adoption of and adherence to study-specific data coding conventions.
- Coding review meetings.
- Code list and algorithms.
- Double entry (random sample of 10% of M-PEM questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff.
- Coding of M-PEM questionnaires are randomly reviewed by a quality assurance assessor.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff.
- Relevant maintenance of reference tables, e.g., Event Dictionary.
- Pilot testing of study documentation.

9.9 Limitations of the Research Methods

9.9.1 Limitations

- Possible delay in new user cohort accrual if adoption by primary care physicians is low.
- PEM prescription data will only identify those initiated in primary care. Treatment initiation date will be required from hospital discharge summary to obtain

estimate of true index date. However, this will addressed in the complementary Specialist Cohort Event Monitoring Study (SCEM).

- Only GP prescribers are identifiable from Organisation Data Service (ODS; which relate to General Medical Practitioner Codes and GP Practice Codes) data – hospital prescribers are not identifiable in PEM despite FP10 HP prescription data supplied by NHS BSA. A hospital event monitoring study is proposed to develop a systematic process for monitoring the safety of rivaroxaban prescribed to patients in the secondary care setting, to address possible selection bias arising through restriction of data collection in primary care.
- There is no comparator cohort, however where appropriate, within cohort comparisons will be considered. A contextual comparator group of new warfarin users will be included in the SCEM study.
- Design may preclude obtaining information for some newly registered with UK primary care services from abroad and have limited information on past medical history.

9.9.2 Potential for bias

As for other observational epidemiological studies, we recognise several potential sources of bias:

- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to antithrombotic agents. This needs to be examined since such channelling may result in apparent association of increased risk of such events in this population. It may be introduced through prescribing of treatment based on certain characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.
- Confounding by severity is possible and needs to be accounted for.
- Patients started and stopped in hospital will not be identified. Exclusion of this subset will introduce selection bias in that patients who may have more severe disease will not be included. See SCEM protocol for DSRU proposal for study to monitor the safety and use of rivaroxaban in such a cohort.
- Immeasurable time bias in terms of inaccurate measurement of exposure is likely as a result of unidentified hospitalisation.
- Patient attrition and loss to follow-up if significant, may introduce selection bias
- Non-response bias as a result of GPs being unwilling to complete a complex questionnaire with multiple outcomes is possible, however, this will be addressed by a) payment to cover administrative costs of completing a more complex

questionnaire (response rate for M-PEM studies is approximately 64%, which is similar to average GP response rate to postal surveys in general (32) and b) sending two questionnaires (at three months and twelve months after the first prescription), either of these forms is less complex than sending one form.

- Under-reporting, including that of serious or fatal events, is possible in PEM, as for any other observational study. However, a ten fold difference in reporting of serious events between PEM and the Yellow card spontaneous reporting system has been identified, in favour of PEM.(33)
- Given the M-PEM questionnaires prompts prescribers to report on selected and often serious outcomes of interest through use of specific questionnaires, differential over-recording (and reporting) of serious to non-serious events is possible.
- Misclassification bias of outcomes may occur which is of particular importance for rare outcomes, however, it will be minimised by follow-up of medically important events. Patients with events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness.
- Misclassification of indication is possible. Of particular relevance to this study is the potential bias that may be introduced through variations in diagnosis and case definition between practitioners.
- Time bias may also become an issue if the study collection period, and thus the observation period, is extended because of low prescribing rates.
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. In PEM, exposure is based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions, e.g. CPRD. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. While it is not possible to be sure the patient used the medication, it is almost certain that the patient received it. Repeat prescriptions would indicate that a patient continued to obtain the medication, whilst GP awareness of adherence would inform on pattern of dosing.
- Calculating ID differences (plus 95%CI) is one of a number of quantitative evaluations of hundreds of events that can be used in PEM for signal generation purposes. It is used as a means of alerting early potential signals as priorities for further evaluation. Medical judgment however is also part of this evaluation and prioritization process. As part of the initial inspection of event data, it is acknowledged that the generalised approach to segregation of time periods (month 1 vs. months 2-6 combined) for calculating ID differences may not appropriate for all events with respect to their most relevant time periods of excess. In addition, when event counts are low in the periods being compared

and the risk periods are of different lengths then there is a risk of false positives (Type I error).(34) However, since ID differences are tested at the 5% level, the probability of concluding that a relative difference is greater than the null (i.e. a signal) when it is not, is low (2.5%). PEM methodology (which is hypothesis generating) enables further exploration of events for which the ID difference is significant, using other quantitative and qualitative methods before any conclusions on signals can be made.

- The potential exists for misclassification of mild renal failure since severe forms of renal failure will be more readily identified. However, to limit this, specific information about renal function (e.g. eGFR and serum creatinine levels) will be collected during the course of the observation period to provide details of renal function.

9.10 Other Aspects

9.10.1 Study sponsorship

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in association with the University of Portsmouth and is sponsor of the study. For this study, the DSRU (the academic sponsor) receives support from Bayer.

10 Protection of Human Subjects

This study will be conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organisation (2002).(35) The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians.(36) PEM is also included in the BMA report detailing methods in which healthcare professionals can help improve reporting of adverse drug reactions.(37)

In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009).(38) Reference to Section 251 is made in the General Medical Council booklets, 'Confidentiality' and 'Confidentiality: disclosing information for education and training purposes' whereby clinicians may disclose identifiable information without consent (if it is required by law), if it is

approved under section 251 of the NHS Act 2006 or if it can be justified in the public interest. (39;40)

11 Management and Reporting of Adverse Events/ Adverse Reactions

This observational, non-interventional cohort study is based on secondary use of data; therefore the reporting of individual adverse reactions is not required. Reports of adverse events/reactions should only be summarized in the observational study report, where applicable. As a consequence, the DSRU does not have any direct reporting requirements to the competent regulatory authorities. The DSRU shall, on an ongoing basis, notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof. The DSRU will comply with the requirements of GVP Module VI in the appropriate way that it applies to our study.

Since the clinicians are prescribing a licensed product, they will be reminded in the study documentation that it is their responsibility to report any suspected adverse reactions (including serious[19] adverse drug reactions) to the company and/or to the MHRA (using Yellow Cards) as they would normally do in their practice in support of routine pharmacovigilance. In cases where the DSRU receives, by mistake, such reports it will forward them to the MHRA and/or the MAH as appropriate.

12 Plans for Disseminating and Communicating Study Results

A cohort accrual progress report will be produced in time for inclusion in the scheduled Periodic Safety Update Reports for the product (i.e., every six months for the first two years after launch and then annually thereafter) or regular updates of the RMP for as long as the study continues.

Examination of aggregate event data will be limited to one interim report on a study cohort of 2500 valid patients or on the valid cohort achieved at approximately 18

[19] **Definition of Serious Adverse Event**
"Serious Adverse Event means an adverse event which is fatal or life-threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

months, whichever is the sooner and a detailed final report based on a study cohort of 10000 valid patients achieved at 36 months unless a decision is made to end the study early.

13 References

(1) Bayer Pharma AG. XARELTO (Rivaroxaban) 10mg tablets : Summary of Product Characteristics. 2012.

(2) Bayer Pharma AG. Bayer's Xarelto® Approved in the EU for the Prevention of Stroke in Patients with AF and in the Treatment of DVT. www bayer com 2011 December 19 [cited 2012 Jan 2];Available from: URL: http://www.bayer.com/en/news-detail.aspx?newsid=15486

(3) Bayer Pharma AG. Bayer's Xarelto® (Rivaroxaban) Approved for the Treatment of Pulmonary Embolism (PE) and the Prevention of Recurrent Deep Vein Thrombosis (DVT) and PE in the EU. www bayer com 2012Available from: URL: http://www.xarelto.com/html/press/pdf/2012-0533E.pdf

(4) Bayer Pharma AG. Bayer's Xarelto® (Rivaroxaban) Recommended for Approval in the EU for the Prevention of Atherothrombotic Events after an ACS. www bayer com 2013Available from: URL: http://press.healthcare.bayer.com/en/press/news-details-page.php/14953/2013-0172

(5) Bayer Pharma AG. EU - Risk management Plan (RMP) for Rivaroxaban. EU RMP v 7.5. 2012.

(6) Rawlins MD, Jefferys DB. United Kingdom Product Licence applications involving new active substances, 1987-1989: their fate after appeals. Br J Clin Pharmacol 1993 Jun;35(6):599-602.

(7) Shakir SAW. Prescription-Event Monitoring. In: Mann RD, Andrews EB, editors. Pharmacovigilance. 2 ed. Chichester,UK: John Wiley & Sons Ltd.; 2007. p. 307-16.

(8) Layton D, Hazell L, Shakir SA. Modified Prescription-Event Monitoring Studies: A Tool for Pharmacovigilance and Risk Management. Drug Saf 2011 Oct 12.

(9) Bayer Schering Pharma AG. EU - Risk management Plan (RMP) for Rivaroxaban. BAY59-7939 v 6.1. 2011 Jun 20.

(10) Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty. NEJM 2008;358:2765-75.

(11) Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. The Lancet 2008;372:31-9.

(12) Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty. NEJM 2008;358:2776-86.

(13) Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. The Lancet 2009;373:1673-80.

(14) Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011 Oct;32(19):2387-94.

(15) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011 Sep 8;365(10):883-91.

(16) Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010 Dec 23;363(26):2499-510.

(17) Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012 Apr 5;366(14):1287-97.

(18) Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). Expert Rev Cardiovasc Ther 2011 Jul;9(7):841-4.

(19) Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet 2009 Jul 4;374(9683):29-38.

(20) Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.

(21) ICH Harmonised Tripartite Guideline. Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting E2D. 2003.

(22) Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997 Dec;17(6):374-89.

(23) European Medicines Agency. Guideline on good pharmacovigilance practices. Module VI - management and reporting of adverse reactions to medicinal products. EMA/873138/2011
Available at URL:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf
Date accessed:02/07/2012. 2012 Jun 22.

(24) Machin D, Campbell M, Fayers P, et al. Sample Size Tables for Clinical Studies. Table 7.2. Oxford,UK: Blackwell Science Ltd; 1997.

(25) Strom B. Sample size considerations for pharmacoepidemiology studies. In: Strom B, editor. Pharmacoepidemiology. 2 ed. Chichester, UK: John Wiley & Sons; 1994.

(26) Machin D, Campbell M, Fayers P, et al. Sample Size Tables for Clinical Studies. Table 7.1. Oxford,UK: Blackwell Science Ltd; 1997.

(27) Mehrotra DV, Heyse JF. Use of the false discovery rate for evaluating clinical safety data. Stat Methods Med Res 2004 Jun;13(3):227-38.

(28) Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73:751-4.

(29) Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B 1995;57:289-300.

(30) Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the austin bradford-hill criteria. Drug Saf 2002;25(6):467-71.

(31) Shakir S. Causality and correlation in pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' Detection of New Adverse Drug Reactions. 5 ed. Chichester: John Wiley & Sons Ltd.; 2004. p. 329-43.

(32) Barclay S, Todd C, Finlay I, Grande G, Wyatt P. Not another questionnaire! Maximizing the response rate, predicting non-response and assessing non-response bias in postal questionnaire studies of GPs. Fam Pract 2002 Feb;19(1):105-11.

(33) Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: observational study. BMJ 1998 Jul 11;317(7151):119-20.

(34) Li X, Chan ISF, Gould AL. Impact of length difference in risk and comparison windows: a cautionary note. Statistics in Biopharmaceutical Research. In press 2011.

(35) CIOMS-WHO. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, Switzerland; 2002.

(36) Royal College of Physicians of London. Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects. 3. 1996. Royal College of Physicians of London.
Ref Type: Pamphlet

(37) British Medical Association Board of Science, British Medical Association Science & Education. Reporting adverse drug reactions. A guide for healthcare professionals. Web address:http://www.bma.org.uk/ap.nsf/Content/AdverseDrugReactions Date accessed: 31/05/2006. London, UK; 2006.

(38) Health Research Authority. Advisory Group advice and approval decisions. Prescription–event monitoring, CAG ref: ECC 5-07(b)/2009. HRA 2013 [cited

2013 Dec 23];Available from: URL: http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/cag-advice-and-approval-decisions/

(39) General Medical Council. Confidentiality. Web address: http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf Date accessed: 08/07/2011. 2009.

(40) General Medical Council. Confidentiality: disclosing information for education and training purposes. http://www.gmc-uk.org/Confidentiality_disclosing_info_education_2009.pdf_27493403.pdf Date accessed: 11/07/2011. 2009.

14 Annex 1 List of Stand-alone documents

Number	Document reference number	Date	Title
1	Stand-alone document 1	17/04/2015	DSRU RAIDAR list

15 Annex 2 ENCePP Checklist for study protocol

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
An observational post-authorization Modified Prescription-Event Monitoring safety study to monitor the safety and utilization of rivaroxaban (XARELTO®) for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England

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]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	47
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☐	☒	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

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.

ENCePP registration in process

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)	☒	☐	☐	19
2.1.2 The objective(s) of the study?	☒	☐	☐	19
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	23
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:

There are no formal hypotheses to be tested in this study

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)	☒	☐	☐	23
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19
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)	☒	☐	☐	19

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	23
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	23
4.2.2 Age and sex?	☒	☐	☐	23
4.2.3 Country of origin?	☒	☐	☐	23
4.2.4 Disease/indication?	☒	☐	☐	23
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	23

Comments:

There is no need to define the study population according to seasonality or co-morbidities in this study

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	☒	☐	☐	23

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	23
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	23
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

New user cohort- exposure consists of all patients prescribed rivaroxaban, regardless of the dose prescribed.

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?	☒	☐	☐	23
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)	☒	☐	☐	26

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)	☒	☐	☐	23
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	23

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.)	☒	☐	☐	26
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.)	☒	☐	☐	26
8.1.3 Covariates?	☒	☐	☐	26
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	23
8.2.2 Endpoints? (e.g. date of occurrence, multiple event,				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
severity measures related to event)	☒	☐	☐	23
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	32
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	32
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	26
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	24,43

Comments:

Events (disease/endpoints) are reported as recorded in patient medical charts, then coded into MedDRA by the DSRU. Exposure to study drug and medications is based on prescription records, however for analysis purposes concommitant medications will be presented by ATC Classification system. Prescription data and questionnaire data are linked via unique patient study identifier.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	30

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?	☒	☐	☐	33
10.3 Are descriptive analyses included?	☒	☐	☐	34
10.4 Are stratified analyses included?	☒	☐	☐	34
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	39
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	39

Comments:

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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?	☒	☐	☐	41
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	32
11.3 Are methods of quality assurance described?	☒	☐	☐	42
11.4 Does the protocol describe possible quality issues	☒	☐	☐	42

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
related to the data source(s)?				
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Expert external review by specialist consultant and statistician will be undertaken

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	43
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)	☒	☐	☐	43
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	32
12.3 Does the protocol address other limitations?	☒	☐	☐	42

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?	☐	☐	☒	45
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	33

Comments:

The DSRU has section 251 approval for conducting M-PEM studies without need for patient consent, as referenced in the protocol.

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?	☒	☐	☐	12

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)?	☒	☐	☐	47
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	47

Comments:

Name of the main author of the protocol: Deborah Layton

Date: 24/4/2015

Signature: 

16 Annex 3 Additional information

Not applicable