Drug Safety Research Unit (DSRU)

Rivaroxaban in Acute Coronary Syndrome

Protocol Amendment
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PASS information

Title	An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales
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Research question and objectives	Aim: To monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) by specialist HCPs in the secondary care hospital setting in England and Wales. Objectives: 1. To quantify the cumulative incidence (risk and rate) of haemorrhage (major bleeding within intracranial, gastrointestinal and urogenital organ sites) occurring in the 12 week observation period 2. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics 3. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period 4. Quantifying the risk of other major or minor bleeding outcomes not specified in the primary objectives reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting

	in England and Wales.
Country(-ies) of study	England and Wales
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2 List of Abbreviations

Abbreviation	Term
AC	Advisory committee
ACS	Acute coronary syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BP	Blood Pressure
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CYP P450	Cytochrome P-450
DSRU	Drug Safety Research Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drugs Administration
GGT	Gamma-Glutamyl Transferase
GP	General Practitioner
HCP	Healthcare Professional
HLT	Higher Level Term
ID	Incidence Density
IQR	Interquartile Range
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application
NHS	National Health Service
NHSBSA	National Health Service Business Services Authority
OTC	Over-The-Counter
PCI	Percutaneous coronary intervention
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SPC	Summary of Product Characteristics
TIMI	Thrombolysis In Myocardial Infarction
UK	United Kingdom
US	United States

3 Responsible Parties

Responsible party	Appointed person(s)
Principal investigator	Professor Saad Shakir, Drug Safety Research Unit
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4 Abstract

Title

An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales.

Rationale and background

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers in the EU.

Research question and objectives

Aim: To monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated to patients for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) by specialist HCPs in the secondary care hospital setting in England and Wales.

Objectives:

1. To quantify the cumulative incidence (risk and rate) of haemorrhage (major bleeding within intracranial, gastrointestinal and urogenital organ sites) occurring in the 12 week observation period
2. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics
3. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period
4. Quantifying the risk of other major or minor bleeding outcomes not specified in the primary objectives reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales.

Study design

This study will be a prospective observational, population-based cohort study of rivaroxaban with a contextual comparator (reference cohort). The rivaroxaban cohort consists of new rivaroxaban users (no anticoagulant prescription within 6 months prior to index date) with any combination of oral antiplatelet therapy for the prevention of atherothrombotic events following ACS. The contextual cohort consists of patients receiving the current standard treatment of care for the prevention of atherothrombotic events following an ACS (at least dual antiplatelet therapy, but not monotherapy) utilising the technique of specialist cohort event monitoring (SCEM), based on review of patient medical charts. The contextual comparator will be recruited concurrently to the rivaroxaban cohort in order to characterise the adoption of rivaroxaban into clinical practice and the prevalence of reasons for prescribing and those clinical characteristics which are known risk factors for the primary outcomes of interest.

Population

Patients in the secondary care hospital setting in England and Wales.

Variables

Demographic data on prescribers, a summary of non-clinical reasons for prescribing, demography (age and sex), indication, selected treatment details, medical history and medication use prior to or present on index date; changes on general health and medications during treatment, clinical events of medical interest.

Data sources

Medical chart based data collection from review of patient medical charts (secondary use of medical records information) in England and Wales.

Study size

A sample size of 1193 patients in each cohort (total 2386) is desirable for this study.

Data analysis

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

Milestones

One interim report 18 months after study start and one final report at 36 months.

5 Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	05/03/2013	All	Creation	-
2	31/03/2014	All	Amendment	Amended to incorporate comments from Bayer and additional updates
3	14/11/2014	12 Management and reporting of adverse events/ adverse reactions	Amendment	DSRU statement on reporting in light of GVP module VI
4	16/01/2015	10.7 Data analysis	Amendment	Addition of section to handle missing data Addition to limitation section
5	16/4/2015	PASS Information Section 5- abstract Various sections renumbering Addition of Annex 1 and 2	Amendment	Request from PRAC following review
6	24/03/2017	9.1 Study Design 9.2 Setting	Amendment	To broaden the inclusion criteria and minimize exclusions for patients prescribed rivaroxaban for ACS.
7	25/08/2017	4 Abstract 9.1 Study Design 9.2 Setting	Amendment	In response to the questions from PRAC

6 Milestones

Milestone	Planned date
Start of data collection	18th September 2015

End of data collection	18th September 2018
Interim report 1	1st November 2017
Final report of study results	August 2019

7 Rationale and Background

7.1 Rivaroxaban

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 Pulmonary Embolism (PE) and prevention of recurrent DVT and PE following an acute DVT in adults.(2) Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is also indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers in the EU, where approval was obtained in May 2013.(3) The marketing application for secondary prevention in ACS patients was based on data from the pivotal ATLAS ACS 2 TIMI 51 study (4) which showed that 2.5 mg of the drug twice daily significantly reduced the primary composite end point of cardiovascular death, MI, or stroke after ACS compared with standard oral antiplatelet therapy.

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) A postmarketing safety study of rivaroxaban (XARELTO®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice, with a focus on ACS.

This Specialist Cohort Event Monitoring (SCEM) study, which is designed to monitor the safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated by specialist healthcare professionals (hereafter Specialist HCPs)

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, is one of three complementary studies conducted by the DSRU. One is another SCEM study, designed to monitor the safety and drug utilisation of rivaroxaban, as initiated by specialist 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, based in primary care, is a Modified Prescription-Event Monitoring (M-PEM) Study, the aim of which is to proactively capture safety and drug utilisation data in the post-marketing phase of license approval of rivaroxaban as prescribed to patients by general practitioners in England for all relevant indications.

7.2 Acute Coronary Syndrome

The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) convened a consensus conference in 1999 in order to re-examine jointly the definition of myocardial infarction (published in the year 2000 in the European Heart Journal and Journal of the American College of Cardiology).(6) Given the considerable advances in the diagnosis and management of myocardial infarction since the original document was published, the leadership of the ESC, the ACC and the American Heart Association (AHA) convened, together with the World Heart Federation (WHF), a Global Task Force to update the 2000 consensus document.(7)

The acute coronary syndrome model espoused by the American College of Cardiology places unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) at increasingly severe points along a disease continuum.(6;8) At presentation, the working diagnosis of non-STE-ACS (NSTE-ACS), based on the measurement of troponins, is further classified into non-ST elevation MI, (NSTEMI) or unstable angina. The therapeutic management is guided by the final diagnosis.(9)

Registry data consistently show that NSTE-ACS is more frequent than STE-ACS.(10) The annual incidence is ~ 3 per 1000 inhabitants, but varies between countries.(11) Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7% vs. 3-5% respectively), but at six months the mortality rates are very similar in both conditions (12 and 13%, respectively).(10;12;13)

Rivaroxaban is the only novel oral anticoagulant to have received a licence for this indication in the EU.

7.3 ATLAS ACS 2 TIMI 51

ATLAS ACS 2 TIMI 51 (Anti Xa Therapy to Lower cardiovascular events in addition to standard therapy in subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51) study was published in the NEJM, in January 2012.(4)

The study recruited over 15000 patients diagnosed with a recent acute coronary syndrome. Patients were randomised to three different treatment groups receiving either placebo, 2.5mg Rivaroxaban or 5mg Rivaroxaban (both given twice daily). The mean duration of study treatment was 13 months, however patients were treated with rivaroxaban for up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The patients' medical condition was stabilized before enrollment into the trial, with the initial management strategies (e.g. revascularization) completed before entry. All patients received standard pharmacotherapy - including low dose aspirin; they received a thienopyridine (either clopidogrel or ticlopidine) according to the national or local guidelines. Randomization was stratified on the basis of planned use of a thienopyridine. Patients were seen at four weeks, at 12 weeks, and thereafter every 12 weeks. The primary safety end point was TIMI (Thrombolysis in Myocardial Infarction) major bleeding not related to coronary artery bypass grafting (CABG).

In the analysis of the two doses of rivaroxaban, each of the doses reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates in patients receiving the 2.5-mg dose of 9.1% and 10.7%, respectively (hazard ratio, 0.84; 95% CI, 0.72 to 0.97; P = 0.02) and rates in patients receiving the 5-mg dose of 8.8% and 10.7%, respectively (hazard ratio, 0.85; 95% CI, 0.73 to 0.98; P = 0.03).(4) Rivaroxaban significantly increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, and these events were lower in patients receiving the 2.5 mg dose than in those receiving the 5 mg dose.(4)

8 Research Question and Objectives

8.1 Overall aim:

The aim of this SCEM study is to proactively monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed to patients for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) as initiated by specialist HCPs in the secondary care hospital setting in England and Wales.

8.2 Objectives:

Primary objective

- to quantify the cumulative incidence (risk and rate) of major bleeding according to the TIMI classification of non-CABG Related Bleeding (Table 1) occurring in the 12 week observation period, overall and stratified by the following bleeding sites:
    - Intracranial,
    - Gastrointestinal
    - Urogenital

Secondary objectives

1. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics
2. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period
3. Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12 week observation period overall (Tables 1 and 2) and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales.

Both the primary and secondary objectives relate to the rivaroxaban cohort and the contextual comparator (reference) cohort.

Exploratory objectives

The study will also include (for rivaroxaban cohort only) several exploratory analyses to

1) where possible, to quantify the incidence of other important identified, potential and special risks not mentioned in the primary objective and any other events reported during treatment with rivaroxaban; and

2) describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) (Tables 1 and 2) during observation of the cohort exposed to rivaroxaban.

Table 1. Haemorrhage outcomes (TIMI definitions for use in the primary secondary and exploratory objectives)

A non CABG related major[†] bleeding event will be defined using TIMI criteria as:
• Any symptomatic intracranial haemorrhage
• Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL
• Fatal bleeding (bleeding that directly results in death within 7 days)
A non CABG related minor bleeding event will be defined using TIMI criteria as:
• any clinically overt sign of haemorrhage that was associated with a fall in haemoglobin concentration of 3 to <5 g/dL
A CABG related major bleeding event will be defined using TIMI criteria as any of the following bleeding events that were CABG related:
• Fatal bleeding (bleeding that directly results in death
• Perioperative intracranial bleeding
• Reoperation following closure of the sternotomy incision to control bleeding
• Transfusion of greater than or equal to 5 units of whole blood or PRBCs within a 48 hour period
• chest tube output > 2 L within a 24 hour period

[†] The three organ sites included in the primary objective are gastrointestinal and urogenital, in addition to intracranial.

Table 2. Haemorrhage outcomes (Bleeding Academic Research Consortium [BARC] definitions for use in the secondary and exploratory objectives only)

Type 0
• No bleeding

Type 1

- Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2

- Any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Table 2. Haemorrhage outcomes (Bleeding Academic Research Consortium [BARC] definitions for use in the secondary and exploratory objectives only) (continued)

Type 3
Type 3a
• Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding
Type 3b
• Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) • Bleeding requiring intravenous vasoactive agents
Type 3c
• Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Type 4: CABG-related bleeding
• Perioperative intracranial bleeding within 48 h • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† • Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
• Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
• Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).*
†Cell saver products are not counted.

9 Research Methods

9.1 Study Design

This study will be a observational, population-based cohort study with a contextual comparator (reference cohort) utilising the technique of cohort event monitoring (with retrospective patient chart review) to study the short-term (up to 12 weeks) safety and use of rivaroxaban in combination with standard oral antiplatelet therapy in patients following an ACS event, as initiated by specialist HCPs in the secondary care hospital setting. Secondary use of medical records information will be used in this study as specialist HCPs will be asked to abstract information from patient medical charts onto a questionnaire.

Twelve weeks observation is regarded as a period of time sufficient for data from all relevant patient populations (which informs on any post initiation health events related to short-term exposure that they might have experienced) to be recorded in medical charts.

In addition to the desire to study the use of rivaroxaban in combination with standard oral antiplatelet therapy in a population that is more heterogeneous than those observed in clinical trials, it is also desirable to put these observations into context. This will be achieved through comparison with current standard care treatments for the prevention of atherothrombotic events following an ACS in order to examine treatment decisions and differences. Therefore, a contextual cohort of evaluable patients treated with current standard treatment of care (dependent on clinical manifestation, early management and subsequent surgical intervention) will be recruited concurrently in order to characterise the adoption of rivaroxaban into clinical practice and the prevalence of (non-clinical)[1] reasons for prescribing and those clinical characteristics which are known risk factors for the primary outcomes of interest.(14) To avoid confusion, for the contextual cohort, patients who receive other factor Xa inhibitors or direct thrombin inhibitors will be excluded from the study.

According to the forthcoming NICE appraisal scope document for the use of rivaroxaban in the treatment of ACS[2] (15) the following possible contextual comparators have been

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

[2] http://www.nice.org.uk/media/6F2/BD/AcuteCoronarySyndromeRivaroxabanDraftScope.pdf

identified based on different clinical needs of subgroups (the contextual comparator will be a single group consisting of all possible standard of care combinations combined) :

- Clopidogrel in combination with aspirin
- Ticagrelor in combination with aspirin
- Prasugrel in combination with aspirin
- Additional dual antiplatelet therapies (not specified above)

After the pharmacotherapeutic treatment decision has been made by the clinician, such that the most appropriate treatment based on clinical need is prescribed, a patient will be invited to participate in the study and consent obtained for access to information from secondary care medical charts and general practice primary care medical charts via the GP. Participants will be invited to take part in the study by a member of the research or clinical team. This will usually be a research nurse, or practitioner, or clinical researcher or treating clinician (junior doctor or consultant).

To allow inclusion of patients with a previous history of ACS or other co-morbidities requiring antiplatelet treatment, a modified version of the new user design will be used in this study. The new user design will be used for the anticoagulant treatment and is defined as no use of oral anticoagulants including rivaroxaban within the 6 months prior to index date in both cohorts. In the rivaroxaban cohort, naïve users are defined as those who never used any oral anticoagulants in the past and they will be distinguished from non-naïve users in the analysis. The new user design will not be applied to antiplatelet treatments; ongoing antiplatelet treatment will be allowed in both cohorts and presented by naivety status.

Study start is defined as the date that the first patient is recruited into the study (18th September 2015), and continue for a maximum of 36 months, or until the target sample size (1193 tbc) for both cohorts has been achieved (whichever is the soonest). The final cohort sizes, period of observation and the duration of the SCEM study will be dependent on the level of prescribing of rivaroxaban in combination with standard oral antiplatelet therapy by specialist HCPs in England and Wales. Data collected during later calendar time periods can be compared with earlier periods to identify any trends that may emerge. Slow uptake may impact on the ability to meet the study objectives; in this instance, further discussions with the regulatory authorities regarding study feasibility will be needed.

Patients will be observed from the date antiplatelet therapy was prescribed as part of the acute management of the ACS in both the rivaroxaban group and the contextual

cohort for 13 weeks in order to allow for detection of outcomes associated with treatment initiation (this will allow for a delay between antiplatelet therapy administration as part of the acute treatment for the ACS, and the subsequent start of rivaroxaban to ensure 12 complete weeks of observation time for analysis). The index date for analysis for both groups will be defined dependent on the prescribing patterns observed in real life use. Since patient care is likely to be shared between secondary and primary care for most patients during the observation period, the patient's GP will be contacted[1] at least 13 weeks after antiplatelet therapy start date to complete an abridged questionnaire to collect any information on outcomes of interest that they are aware of during the observation period to minimise under-reporting on selected outcomes. For the main statistical analysis, events will be censored at 12 weeks post index date, should they be reported after this time period. However, events of interest will be included and detailed in study reports even if they occurred after the 12 week time period. Where additional outcomes are identified that have not be reported by the initiating prescriber, these will be followed-up with the GP to ascertain further information.

9.1.1 Strengths

- The observational and inclusive design allows for the surveillance of a diverse patient population under the care of specialist HCPs, particularly those with different characteristics in terms of underlying disease, co-morbidities and concomitant medications that would not have been included in clinical trials. Thus bias introduced through selection based on disease severity or type will be minimised. The approach also allows for surveillance of rivaroxaban when used off-label within the context of ACS.
- The prescribing of relevant pharmacological therapy should not be affected because of participation in this study, as the decision to prescribe has already been made prior to patient inclusion therefore the observational non-interventional nature of the study design is maintained.
- Data is collected on large numbers of cohorts given the relevant treatment combinations under study in conditions of routine clinical practice.
- Special populations can be characterised.

[1] Overlap of data collection between SCEM and M-PEM should minimise any under-reporting of events of interest associated with the primary objective. However due consideration should be given to a) possible non-response of GPs for the long-term M-PEM study that might arise from the GP's knowledge that the patient is participating in the SCEM and b) that some patients are managed by specialist GPs purely on an outpatient basis and thus may never be officially admitted to hospital. The emphasis must be made that the two studies are complementary and participation in both is highly desirable.

- Time-dependent effects can be examined. This method is longitudinal and thus will enable more reliable examination of exposures in relation to outcomes over time.
- By obtaining patient consent, additional information from medical charts from other clinical specialities may be examined for selected outcomes.
- Extension to monitor long-term safety is possible.
- The DSRU uses established networks of specialists in the UK to conduct such studies.

9.2 Setting

9.2.1 Selection of specialists

Specialists and members of their clinical team from within the secondary care hospital setting will be systematically identified across the country, facilitated where possible by existing clinical research networks, and will be invited to participate in the study prior to study start (exact date to be determined). These specialist HCPs will be informed that they will be participating in a cohort study which will monitor the use of rivaroxaban in any combination with standard oral antiplatelet therapy, in accordance with requirements within the Risk Management Plan. In addition they will be informed that a contextual cohort of patients taking standard antiplatelet combination therapy for secondary prevention following ACS will also be monitored.

9.2.2 Selection of patients

The accessible study population will be that portion of the target population of interest to whom participating HCPs have access. The identification of the study population, will be through (non-probability) systematic sampling whereby all consecutively identified[1] eligible new rivaroxaban user patients (within the context of ACS) treated by any specialist HCP (after the pharmacotherapeutic treatment decision has been made) and who provide consent (see section 10.3) will be enrolled until the desired sample size is reached. A corresponding procedure will be used for the contextual cohort. This method will be used because a probability sampling framework is not feasible and because participation within the study is not required as a condition of receiving treatment. This approach is intended to reduce conscious or unconscious selection bias on the part of the prescriber as to whom to enrol in the study, especially with regard to prognostic factors that may be related to prognosis.

New users of rivaroxaban will be comprised of rivaroxaban patients, who may or may not be naïve to anticoagulant treatment, with no use of oral anticoagulants including rivaroxaban prior to 6 months of index date and who are newly initiated by specialist HCPs after the ACS event. In the UK, when stabilised many patients may then have medicines management transferred to the GP in primary care. Thus, the GP may take on the primary role of monitoring treatment, providing prescriptions and altering the dose when necessary, with the option of referral to secondary care if and when required. Alternatively, the patient may be primarily managed within the secondary care hospital setting alone.

[1] As relevant to the date that the specialist HCP registers to participate in the study

By enrolling new rivaroxaban users (an inception or incidence cohort), this study avoids the introduction of a number of biases associated with existing users (including incidence/prevalence bias, survivorship bias, and follow-up bias). Furthermore, data will be available for the contextual comparator group which will have been collected prospectively during the same calendar period, for similar indications using the same data collection methods, and all subject to the same protocol.

A cross sectional random sample of investigative sites will be surveyed to explore the representativeness of the study population. Using medicines management audit information the demographic characteristics of patients treated for ACS will be examined and compared to those enrolled within this study.

Cohort recruitment will be examined regularly to monitor the number of evaluable patients included, so as to ensure that the desired ratio of 1:1 for the two exposure groups is achieved in the final overall study cohort for analysis.

9.2.3 Patient Inclusion Criteria

Since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity. The inclusion criteria are:

- Age 18 years or above
- Patients newly prescribed rivaroxaban in any combination with standard oral antiplatelet therapy for the indication of secondary prevention in patients after ACS
- Patients prescribed dual antiplatelet therapy (contextual cohort) for the indication of secondary prevention after ACS
- Patients have provided signed, informed consent

9.2.4 Patient Exclusion Criteria

Patient exclusion criteria are:

- Patients prescribed with oral anticoagulants including rivaroxaban within 6 months prior to the index date for any indication
- Patients commenced rivaroxaban between date of market launch (28th October 2014) for the indication of secondary prevention after ACS and study start (18th September 2015)

9.2.5 Evaluable cohort

Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the 12 week survey questionnaire (from both specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will

only be included for analysis of secondary and exploratory objectives, where appropriate.

Consented patients will not be considered evaluable if the specialist HCP reports that the patient did not take either combination therapies. If there is evidence to suggest duplication of patients, either through inadvertent duplication between different prescribers within the same clinical setting, or if a patient was switched from one combination therapy to the other, then the records identified will be considered for inclusion on a case by case basis by the advisory committee.

Patients will be automatically withdrawn if the patient or specialist HCP provides informed written or verbal notification that they no longer wish to participate at any stage of the study.

9.3 Variables

9.3.1 Eligible patient baseline information

For all eligible patients invited to participate, the following anonymised information will be collected on a baseline questionnaire from the specialist HCP using information contained within medical charts:

- Demographic characteristics (age, gender)
- Setting of first prescription- (e.g. inpatient hospital ward, outpatient clinic)
- Reasons for prescribing (clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines)
- Which anticoagulant/antiplatelet regimen was prescribed and start date
- Clinical condition requiring anticoagulant/antiplatelet therapy (indication) and details of the clinical condition (e.g. STEMI, NSTEMI)
- Any prior anticoagulant/antiplatelet treatment
- Risk factors for bleeding at baseline (e.g. creatinine, white cell count, anaemia, presentation, antithrombotic medications)

9.3.2 Patient 12 week end of observation questionnaire

For evaluable patients providing consent and for whom a completed baseline questionnaire has been received by the DSRU, at least 13 weeks after starting antiplatelet therapy, a second questionnaire will be systematically generated to collect clinical information from the specialist HCP relevant to start of observation and any clinical events of medical interest as recorded in the medical charts during the first 13 weeks (to ensure a full 12 week observation period post index date for each patient).

Data obtained from the 12-week end of observation questionnaire will include:

- Additional information on anticoagulation treatment regimen:
  - Details of prior use of oral and parenteral anticoagulant and antiplatelet therapy (e.g. thienopyridines, aspirin, glycoprotein IIb/IIa inhibitors, heparins) in the past 12 months if known
  - Treatment regimen during the 12 weeks observation period
  - If study treatment regimen has changed: date and reason for change, details of transition plan to alternative; if required, details of reversal of anticoagulation therapy and management of bleeding complication
- Recent (< 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - to be used with caution (including fluconazole, strong CYP3A4 inducers, strong 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)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report)
- Specific information on renal function status and creatinine clearance at index date and any changes during 12 week observation period
- Specific information on hepatic disorders present at index date and any recent abnormal liver function tests
- Event reports including selected risks of interest (Table 3)
- Cause and date of death (if died) in the first 12 weeks after starting treatment;
- Behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse)
- Demographic characteristics of specialist HCP; (age, sex, ethnicity, medical profession, year of first registration as HCP and awarding institution, specialism and year of first registration as specialist and awarding institution, year of start of employment at current institution)
- Institution type (teaching, general, private) and region of location
- Participation response/non-response rates (of eligible specialist HCPs within relevant existing research networks where available)

Table 3. Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
IDENTIFIED, POTENTIAL AND SPECIAL RISKS AND OUTCOMES for targeted data collection on SCEM questionnaires		
Non CABG major bleeding episode	Targeted outcome questions on major bleeds	Selected risk factors collected on SCEM questionnaire. Further data on severity, management and risk

		factors to be collected via follow-up.
Non CABG minor bleeding episodes	Targeted outcome question on minor bleeds	Selected risk factors collected on SCEM questionnaire. Not for 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 may be collected via follow-up
Management of homeostasis	Targeted outcome question	Data on management of homeostasis in patients reported with events of surgery (elective or urgent) during the observation period will be collected via follow-up
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT)	Targeted outcome question	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will 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 duration and changes	Further data may be collected via follow-up
IMPORTANT MISSING INFORMATION for general surveillance		
Use during pregnancy and lactation	General event report	Further data to be collected via follow-up

9.3.3 Abridged 12 week end of observation questionnaire for GP

For evaluable patients providing consent and for whom a completed baseline questionnaire has been received by the DSRU, at least 13 weeks after starting antiplatelet therapy, their GP will be contacted and invited to complete an abridged "end of observation" SCEM questionnaire. This will gather information on clinical events of medical interest reported since the date of discharge from secondary care up to the end of the 12 week observation period, and recorded within patients medical charts. This may not be required for all patients and will be dependent on the care pathway, as some patients may not be seen again by the specialist. The purpose of sending an abridged questionnaire to the GP is to ensure complete information on the primary outcomes of interest is obtained where possible. Data obtained from this abridged 12 week SCEM questionnaire will include:

- Anticoagulant/antiplatelet treatment regimen which the patient had received
- Event reports of selected risks of interest (Table 3)
- Cause and date of death (if died)
- Date and reasons for treatment regimen change (if changed) including switching
- Any newly prescribed concomitant treatments

9.3.4 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from 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. 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.(16)

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 survey period. In accordance with Good Pharmacovigilance Practice (GVP) sections VI.C.1.2.1 and VI.C.2.2.2,(17) 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 analytical 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 12.1.1 on Communications).

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.

Specific events of interest for further evaluation:

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

2. 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 changing treatment regimen (although not defined in Table 3) will undergo further evaluation, though may not be followed up.

3. 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.

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

9.3.5 Methods to Maximise Questionnaire Response Rate

Patient 12 week end of observation questionnaire

A proportion of Specialist HCPs or GPs are likely to fail to submit these questionnaires. Methods to maximise response rates will include prompts from study facilitators by phone, email and personal contact and reminder questionnaires targeted at those who have not responded within one month of the date the initial questionnaire was sent.

Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to specialist HCPs or 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. Specialist HCPs and GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

9.4 Data Sources

Medical chart based data collection in this study will be conducted in various phases; relevant documentation (such as information leaflets, questionnaire, consent forms, etc) will be available both as hard copies and electronically for download by the participating specialist HCPs.

9.4.1 Recruitment

This first phase will have two parts.

<u>Part 1: Recruitment of eligible specialist HCPs.</u>

The DSRU will allocate a unique study reference number to each participating specialist HCP for study audit and data management processes.

<u>Part 2: Recruitment of eligible patients initiated with the study drug combination under clinical care of participating specialist HCPs.</u>

For all eligible consented patients invited to participate, the specialist HCP or a member of their clinical team, will be asked to record anonymously (using the study reference number provided on patient study documentation) a summary of non-clinical reasons for prescribing, demography (age and sex), indication and selected treatment details onto a simple questionnaire and submit these data to the DSRU coordinating centre either through a secure online website, or via surface mail. Date of recruitment into the study

will also be recorded by the specialist HCP, if known, or, retrospectively once the consent form is obtained, by the DSRU research staff. The unique study reference number allocated to each patient will be used for study audit and data management processes.

9.4.2 Exposure and outcome data

This second phase will also have two parts.

Part 1: Covariate data

Thirteen weeks post antiplatelet therapy start date, the specialist HCP will be prompted to complete a second questionnaire which will gather information on medical history and medication use prior to or present on start date; changes on general health and medications during treatment and clinical events of medical interest. For some patients, the patient's GP will also be contacted to complete an abridged end of survey questionnaire. This will depend on the care pathway and whether the specialist HCP will have any further contact with the patient after discharge to primary care.

Part 2. Follow-up.

Events of interest will be collectively evaluated to inform on clinical features that may be important when considering drug-relatedness; this requires follow-up using event-specific questionnaires sent to the specialist HCP (see 9.3.4) or GP depending on reporter. 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 period.

9.5 Study Size

The ability to detect an 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.

Where studies, such as clinical trials, have already estimated the impact of the exposure on the outcome of interest, the objective should be to estimate the magnitude of the effect as precisely as possible (21). As such, in this study it is more appropriate to choose a sample size that will yield a confidence interval of a predefined width for those identified risks defined within the primary outcome which are of greatest clinical and medical importance i.e. major bleeding outcomes. Table 4 displays the samples sizes (95% confidence intervals) across a range of expected incidences and levels of precision.

From rivaroxaban clinical trial data, the cumulative incidence risk of first occurrence of adjudicated major bleeding events (intracranial, GI and urogenital) in patients taking rivaroxaban for secondary prevention after ACS over the first 12 weeks of treatment was approximately 0.5% (0.1%, 0.3% and 0.1%). Thus in this population of patients with ACS treated with rivaroxaban, in order to estimate the expected (true) cumulative incidence of primary outcomes of major bleeding events of 0.5% within +/- 0.4%, we would ideally need a sample size of 1193 patients (Table 4). An equivalent number of patients within the contextual comparator cohort is desirable.

Table 4. Sample sizes of evaluable patients required to estimate the expected (true) cumulative incidence of a specified adverse event with 95% confidence intervals of different precisions (0.2% to 5%).

Incidence from RCT (%)	Precision 0.2%	Precision 0.3%	Precision 0.4%	Precision 0.5%	Precision 0.6%	Precision 1%	Precision 2%	Precision 3%	Precision 5%
0.10	958	426	240	153	107	38	10	4	2
0.20	1913	851	479	307	213	77	19	9	3
0.30	2864	1275	718	459	319	115	29	13	5
0.40	3812	1698	956	612	425	153	38	17	6
0.50	4755	2119	1193	764	531	191	48	21	8
0.70	6631	2958	1666	1067	741	267	67	30	11
0.80	7564	3376	1902	1218	846	305	76	34	12
1.00	9418	4208	2371	1519	1055	380	95	42	15
1.25	11716	5241	2955	1893	1315	474	119	53	19
1.50	13991	6267	3535	2265	1574	567	142	63	23
2.00	18475	8296	4684	3003	2087	752	188	84	30
3.00	27187	12268	6938	4452	3096	1117	279	124	45
4.00	35566	16126	9135	5866	4081	1473	369	164	59
5.00	43627	19871	11276	7246	5043	1821	456	203	73

9.6 Data Management

9.6.1 Data Processing

Specialist HCP/ GP/ patient identifiable information will be stored within a unique database. All original documents and individual correspondence from HCPs will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

9.6.1.1 Review of data

All returned questionnaires with clinical data will be coded onto the study database. Medically important adverse events selected for follow-up will be coded as a priority. There will be a 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.

9.6.1.2 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 bespoke study 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.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific SCEM database 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 will be reached by medically qualified staff.

9.6.1.3 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 personal receive training regarding security awareness.

All original documents, individual correspondence from specialist HCPs, 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 at an appropriate time point (provisionally this is at datalock or earlier if patients have provided informed

notification that they wish to withdraw from the study, but the DSRU will request an extension to this to comply with CHMP requirements). Until this time, only appointed staff would have access to such data.

9.6.2 Project Advisory Committee

A Project Advisory Committee (AC) will be set up to be comprised of the study investigators and other experts. The role of the AC will be to oversee the smooth running of the project and provide scientific, statistical and technical advice when needed and will meet at regular intervals (3 to 12 monthly depending on the stage of the study, either in person or by teleconference).

The AC is broadly analogous to a Safety Monitoring Committee or Review Board, but the purpose may be slightly different in that the AC advises on the effective progress of the study. The first AC meeting will orientate the project team members and establish the logistics for specialist and patient recruitment and confirm patient inclusion criteria. Subsequent AC meetings will clarify the understanding of the ongoing project requirements, monitor progress through assessment of data within the interim reports [specialist/cohort accrual rates, preliminary analyses of individual variable responses on questionnaires], consider any additional proposed inclusion criteria, and act as a forum to review and discuss any queries.

9.7 Data Analysis

The data analysis plan and study objectives will be constructively aligned to meet study aim.

9.7.1 To quantify the cumulative incidence (risk and rate) of major bleeding according to the TIMI classification of non-CABG Related Bleeding (Table 1) occurring in the 12 week observation period, overall and stratified by intracranial, gastrointestinal and urogenital bleeding sites.

The following relates to Section 8.2 primary objective and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a TIMI major non CABG related bleed) and all intracranial sites (as defined in Table 1). This time to event analysis will be performed separately for the rivaroxaban exposed cohort and the contextual cohort, as defined according to exposure at index (date antiplatelet therapy was prescribed as part of the acute management of the ACS).[1]

[1] In the event of a change in treatment resulting in a switch in treatment group, person-time contributed will be censored at the time of switching, thus analysis will not be 'intention to treat' as this is an observational study.

For each cohort, for whom acute management of ACS applies[1], the numerator for this analysis will comprise of adjudicated incident major bleeding events (overall and stratified by intracranial, gastrointestinal and urogenital bleeding sites) defined according to primary objective that were reported during the 12 week observation period post index date. These adjudicated events will have been reviewed by an expert panel using all available information from SCEM questionnaires, follow-up and any additional documentation. Patients for whom events were misreported will be excluded from the analysis (events will be excluded, but denominator data will still be included); patients for whom events were misclassified will be reclassified as appropriate. In addition, for each cohort, for the three organ sites specified in the primary outcome, counts of each of the individual components of the TIMI major non CABG related bleeding criteria will be summarised. Where an individual has one or more criterion for an individual organ site of interest, counts will also be summarised – in such individuals the first report will be regarded as the incident event. Since SCEM data are right censored, the cumulative incidence (risk and rate) of the primary outcomes reported during treatment within the 12 week observation period will be calculated using survival analysis methodology.

For each individual case, relevant person-time will be estimated according to duration of observation up to event date. For each individual non-case, relevant person-time will estimated by either exit date – index date; or censor[2] date – index date; or stop date (+ 2 days [3]) – index date. For each cohort separately, a semi-parametric time-dependent Cox Proportional Hazards regression model will be used to estimate the crude cumulative incidence over the 12 week observation period.

Non-parametric Kaplan-Meier plots will be presented to describe time-to event as well as smoothed estimates of the empirical hazard function to describe how the crude baseline risk of the 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 will be constant during the 12 week period following the start of treatment will be tested

[1] This excludes patients prescribed rivaroxaban 2.5mg for non-ACS related indications

[2] Censor date = date of loss to follow-up

[3] 2 days allocated to person-time to account for half-life of drug

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.[1]

Several sensitivity analyses will be performed to assess the robustness of findings. In one, the possible impact of misclassification of exposure because of possible immortal time on hazard estimates will be explored. In the primary analysis, patients within either cohort may have the same entry event prior to chosen exposure to treatment regimen, however the proportion of unexposed survival time is unknown, particularly for the rivaroxaban cohort where rivaroxaban is regarded as an add-on therapy. The inclusion of a time-varying covariate to define exposure status (0 before time of first rivaroxaban or standard care prescription and 1 after until end of observation) will enable examination of the impact of the transition from existing treatment regimen given as part of initial standard care to additional anticoagulation therapy on the results. In addition, since the primary analysis will be run only to include all reported cases of incident major bleeding irrespective of adjudication to explore the impact of exclusion of incomplete cases on the estimated hazard.

Where possible, data may be stratified according to relevant strong risk factors (e.g. gender, age ($\leq$60, 60-74, $\geq$75 years), indication and past history of haemorrhage) considered significant from a univariate analysis performed to explore associations of potential risk factors on case status, with calculation of stratum-specific incidence rates.

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 Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics

The following relates to Section 8.2 secondary objective 1.

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

9.7.2.1 Descriptive exploratory analysis

Valid cohort demography (patient self-reported: age, gender, ethnicity, socioeconomic index) will be presented separately for both rivaroxaban and the contextual cohort, as reported at index date using all available information from questionnaires (completed by patient and specialist HCP). Other patient self-reported general health factors [BMI, weight, height, smoking and alcohol use] and indication-related characteristics [primary (and secondary if provided) diagnosis/decision, date and duration since first ever recorded; reported bleeding risk factors]; antiplatelet treatment initiation programme by specialist HCP (index date, dose and frequency) and prescribing reasons. A synopsis of pre-index and concurrent relevant morbidities and medication use will also be provided.

For rivaroxaban cohort only, patient subgroups of special interest (Table 5 – 'off-label' use defined as arising from contraindications and those for which: a) precautions for use are recommended; b) appropriate clinical monitoring is recommended; c) limited information is available; and d) selected concomitant drug use) will be summarised in order to inform on real-life use of rivaroxaban. The proportion of patients within each special population sub-group prescribed rivaroxaban who had *one or more* relevant characteristics/conditions/co-prescribed medications at index date will also be summarised within each indicator group by simple aggregation of counts (Table 5).

Further stratification within-cohort by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

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 indicator)*
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

9.7.2.2 Understanding treatment decisions between trusts

A multilevel framework approach with its simultaneous examination of characteristics of individuals at one level and the setting in which they are located at another level offers a contextual framework for understanding the way in which setting can affect patient health. Clustering can also arise from sampling strategy; this SCEM study involves HCPs within hospital settings as well as individual patients which generates a hierarchical clustered structure. Individual patients treated by the same HCP within a hospital can be expected to be more similar than if sampling were truly random. Because of hierarchical structure of the data, with patients (first level) nested within HCP specialist clinics (second level) which are in turn nested within trusts (third level) the probability of prescribing rivaroxaban will be analysed using multilevel logistic regression analysis of pooled study data. This type of analysis reveals the role of different levels for understanding drug prescription and utilisation. Thus it will enable the study of a) the influence of the patient, HCP and trust characteristics on anticoagulation use simultaneously and b) the variance in prescribing.

The multivariate analysis will inform on the influence of those characteristics identified for each level as significant from a univariate analysis of association between those characteristics and treatment (rivaroxaban or not). A base model will describe the crude association between treatment decision, HCP and trust. This will give the variance estimate for levels 2 and 3 without correcting for differences that might exists in patients within each cluster. In the first model, the variance estimates for levels 2 and 3 will be obtained, accounting for significant predictors (identified from univariate analysis). This will inform on which patient characteristics are associated with treatment with rivaroxaban. The association between selected fixed level 1 patient characteristics and prescribing anticoagulation medication will be expressed using odds ratios and 95% confidence intervals from the regression coefficients and their standard error (SE) in the fixed-effect part of the multi-level analysis. In the random-effects part of the multi-level analysis, the variance (SE) at HCP and trust level will be obtained as will the variance that is unexplained by these patient characteristics. A second model will allow level 2 HCP factors to be explored, whilst a third model will allow level 3 (trust) factors to be explored. Thus this analysis will identify source of variation in prescribing and identify whether there are significant differences in treatment decisions between trusts after taking into account individual differences.

9.7.3 Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period

The following relates to Section 8.2 secondary objective 2. Status of indication-related characteristics (alteration of diagnosis and bleeding risk score if available) will be summarised, plus pattern of antiplatelet treatment adherence at the end of the 12 week observation period (as estimated from Medication Possession Ratio[1]) will be summarised. The frequency and reasons for attendance to clinics for review and management of ACS and/or acute hospitalisations (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 changing treatment regimen (including switching) and transition plans to other antiplatelets.

Changes in these indication-related characteristics and treatment details will be examined by comparing values at index and at 12 weeks 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 (as recorded in medical charts) in the total cohort for each month of exposure will be calculated. Causes of death will also be described by system-organ class.

Sensitivity analyses will examine any under-reporting using data provided from the patients GP.

[1] For this study, MPR will be defined as: $\frac{\text{No. days supply held during treatment}}{\text{No. days supply expected during treatment}} \times 100$

Where no. days held will be calculated from information derived from 12 week questionnaire on number of prescriptions and average treatment length of prescriptions (usually given in 7, 14,28,56 day repeats); no. days supply expected will assume chronic use from start to end of study observation or treatment stop date (if stopped)

9.7.4 Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12 week observation period overall (Tables 1 and 2) and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales. Also, where possible, to quantify the incidence of other important identified, potential and special risks not mentioned in the primary objective and any other events reported during treatment with rivaroxaban (rivaroxaban cohort only)

The following relates to Section 8.2 secondary objective 3 and exploratory objective 1) and 2) regarding a) other major and minor bleeding outcomes not specified in the primary objectives in both cohorts and b) any other events reported in the 12 week observation period for rivaroxaban cohort only.

For major bleeding events not specified in the primary outcome, each of the individual components of the major bleeding 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 minor bleeding events, each of the individual associated components (as per Table 1) will be summarised. Where an individual has one or more criterion for a minor bleeding event, this will also be summarised – in such individuals the first event report will be regarded as the incident event.

Analysis of event data for purposes of signal detection includes exploring overall risk and rate for the observation period and time to onset profiles. The methodology provides a numerator (the number of reports of an event) and a denominator (person-time at risk), both collected within a known time frame. This allows for the calculation of crude risks (percent of total valid cohort exposed) and rates (Incidence Densities-ID; person-time incidence rates) for each event separately. Each event may be reported in response to a closed question (for example information on each individual major and/or clinically relevant non-major bleeding risk component), or as free text in response to open questions on the data collection forms. Such analyses will be performed using 'Higher-level' event terms from the MedDRA dictionary where possible. The risk profile of the overall cohorts and sub-group of interest (based on index date characteristics, including whether anticoagulant naïve, rivaroxaban naive or past (other anticoagulant user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Calculating and ranking crude ID rates is one of a number of standard quantitative evaluations used in event monitoring methodology for signal generation purposes as part of initial inspection of all event data for general safety surveillance. 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. Crude Incidence Densities (ID)[1] can be calculated by week in order to 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-weeks. This assumes the pattern of use is continuous. The numerator will be the first reports of events reported as occurring after the index date and during treatment.[2] For this study, IDs will be calculated for each event for each week as follows:

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

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

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 / 7

IDs will also be calculated for each event for all 12 weeks during treatment combined (ID_A), and the first week after stopping (ID_{SW1}) if patient stopped (and where patients are recorded as remaining on treatment for at least 1 week) after index date.

Sensitivity analyses will examine any under-reporting by including events of interest recorded in primary care medical charts and confirmed on follow-up for those patients discharged to primary care, during the 12 week observation period.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g. previous history of ACS or haemorrhage, previous/concurrent use of selected medications, off-label indication

[1] 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

[2] 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.

groups, rivaroxaban naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is possible to explore the time taken for an event of interest using parametric time to event models (e.g. Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts $\geq$ 5. If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within seven days of stopping, and extend the denominator by seven days.

9.7.5 To describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) (Tables 1 and 2) during observation of the cohort exposed to rivaroxaban.

The following relates to Section 8.2 exploratory objective 2) for the rivaroxaban cohort only. A qualitative assessment of these cases will include evaluation of patient demographic characteristics, 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 SCEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

Selected events of interest (Table 3) that require further characterisation and evaluation may be followed-up via a questionnaire sent to the responsible specialist HCP or 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. Where it is appropriate to do so, drug relatedness assessments may be performed on selected events. The aim of the collective drug-relatedness assessment for groups of events during the analysis of the interim and final reports, is to put events in context regarding temporality co-morbidity, pre-existing disease and concomitant medications. This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e. baseline questionnaire, 12 week end of observation 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 (see Box 1).(18)

Box 1. Points for consideration in collective 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;*

Where undertaken, the collective drug-relatedness of selected groups of events of interest will be categorised in terms of proportions of reports assessed within the following four categories: 1) probable[1], 2) possible[2], 3) unlikely[3] and 4) not assessable[4].(19)

9.7.6 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] 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).

[2] 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.

[3] 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.

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

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 will 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.
4. Each patients' GP will be contacted to obtain information on key study variables – this supplementary information will contribute to identification of relevant cases, where information may be missing from questionnaires completed by specialists

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 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 exposure variables 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 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 questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of 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
- Pilot testing of study documentation

9.9 Limitations of the Research Methods

- Possible delay in new user cohort accrual if adoption by secondary care hospital trusts and specialists is low.
- Since this is an observational epidemiological study, we recognise several potential sources of bias. The most important is selection bias and the possibility that the cohorts will not be representative of the population for who anticoagulation is clinically desirable for ACS. Because of the nature of patient recruitment, bias in recruitment may be introduced by some participating specialists through awareness of some form of remuneration (regardless of how and when payment is made). The same number of patients treated with other treatment combinations for ACS will be collected to explore factors which may contribute to selection bias. We have deviated from the new user design for antiplatelet treatment. This was done to allow inclusion of patients who might already be antiplatelet users for primary or secondary prevention of ACS. Although this deviation may have implications for the bleeding risk because these patients may have a higher baseline risk at start of rivaroxaban use, this allows inclusion of rivaroxaban patients that would otherwise be excluded based on a new user design.
- Knowledge of which patients will be participating may affect the non-interventional nature of observational research, however this will probably be minimised by the fact that they are members of broad research networks within the UK healthcare system. It is also possible that specialists who participate in the study will be a self-selected group, but we do not believe that this selection bias will affect the types or number of events experienced and reported by a patient after treatment has been initiated.
- 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.
- Under- and mis- reporting of outcomes is possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes of interest associated with current treatment. The two-phase data capture approach could facilitate compliance with data reporting as well as spreading workload for specialist HCPs. By obtaining information from all patients GPs and access to primary medical charts, under ascertainment of outcomes can be minimised. In contrast, over-recording of health related events in the period following the administration of the baseline questionnaire are possible due to increased specialist HCP attention to special populations of interest (patients with concomitant complications) as detailed in the questionnaire, however since information is being abstracted from medical charts such bias is unlikely. However, this is likely to be similar in the contextual cohort.
- Regarding the definition of bleeding, in this study case definitions are based on acceptable agreed clinical standards and aim to address specific regulatory questions in the context of the risk management plan for the product.
- Immortal time bias is possible arising from misclassification of exposure to the study drug.
- With this patient population, patient attrition and loss to follow-up may introduce selection bias, however, the relatively short period of observation should mitigate this possibility at least to some extent.
- Misclassification bias will be minimised by well defined outcome and follow-up of medically important events. Patients with selected events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when safety signals are investigated (i.e. confounding by indication).
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. Whilst it is not possible to be sure the patient used the medication, it is almost certain that the patient received it since starting treatment is required for study participation. This is unlikely to be significant in this patient population, and for the 12 week period of observation.
- 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

Not applicable

10 Protection of Human Subjects

10.1 Good pharmacovigilance practices

Studies conducted by the DSRU are undertaken according to national and international guidelines for ethical conduct ofresearch involving human subjects (20-23). Following the principles of good pharmacovigilance practice (17;24;25), a full protocol is written for each study to monitor and research the safety of medicines.

10.2 Confidentiality

Patient information security is assured through strict measures as laid out in the DSRU Information Governance Policy.

10.3 Patient consent

For this cohort study, ethics approval via IRAS (integrated research application system) in the UK will be required. Participating specialist HCPs will be asked to provide patients with documentation (with a unique study reference code). Patient study documentation will include a patient information sheet about the study which will describe that their primary and secondary care medical charts will be accessed during the time-frame of active study data collection by the HCP and/or DSRU research staff in order to extract exposure and outcome data relevant to the 12 week observation period[1]. It will also provide contact details of the DSRU study team if they have any questions.

Specialist HCPs will provide patients with a consent form so that patients can consider and give consent for their participation within this project. The consent form will stress confidentiality, that no specific details of their treatment will be released to external parties, that the patient may withdraw consent at any time by contacting either the specialist HCP or the DSRU study research team directly, and that the patient will not be asked to attend clinics more than usual or undergo any additional treatment or questioning. The consent form will also request information to be provided on patient ethnicity, current marital status, current employment status, smoking and alcohol use. This is optional and will be used to inform on representativeness of study cohort. Three

[1] The exception will be if a female patient becomes pregnant, the outcome of the birth will be requested.

signed copies are required. Those patients who wish to inform the DSRU immediately of their decision will give the signed consent form to the specialist HCP. They in turn will send the original to the DSRU, retain one copy for their records and issue a copy to the patient.

For those patients who wish to have a further opportunity to reflect on their participation, the specialist HCP will ask the patient to complete a 'consent to contact' form, which will enable DSRU study research staff to contact the patient through their preferred route of contact (surface post, email, or telephone) after a period of at least two days to obtain consent. This will be the only point at which DSRU research staff will contact the eligible patients directly. If the patient agrees to participate, they will sign the consent form , retain a copy and send the original and one further copy via surface mail to the DSRU study coordinating centre, or, if preferred, to the specialist HCP (who will then submit the original form to the DSRU). Receipt of the signed consent to contact form or the fully completed consent form (if patient provides immediate consent) by the DSRU study team should be within four weeks after index date, if possible.

In addition, within the same time frame, the specialist HCP will be asked to summarise selected data from the medical charts (non-clinical reasons for prescribing, demographic and treatment details) using a simple questionnaire (anonymised using the patient's allocated study reference number) and send these data to the DSRU coordinating centre either through a secure electronic website, or via surface mail.

11 Management and Reporting of Adverse Events/ Adverse Reactions

For SCEM, study data are derived through secondary use of medical records information as abstracted onto study specific questionnaires by specialist HCPs in England and Wales. For observational studies based on secondary data collection, individual adverse reaction reporting 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 Marketing Authorisation Holder (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.

Aggregate event data is collated during the course of this study. Since the clinicians are prescribing a licensed product, it is their responsibility to report any suspected adverse reactions (including serious adverse drug reactions) to the company and/or to the MHRA using Yellow Cards as they would normally do in their practice. Reports received by the DSRU in error are forwarded to the MHRA and/or the MAH as appropriate.

12 Plans for Disseminating and Communicating Study Results

12.1 Communications

Progress reports (relevant to specialist and patient cohort accrual) will be produced in time for inclusion in the scheduled regular updates of the RMP for and Periodic Safety Update Reports for the product as long as the study continues. Examination of aggregate event data will be limited to one interim report on the valid cohort achieved at approximately 18 months post date of first patient recruited; and a detailed final report based on a study cohort of per protocol evaluable patients or on the valid cohort achieved at approximately 36 months post date of first patient recruited, whichever is the sooner (unless an extension to study period is required).

12.1.1 Reporting

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 shall deliver interim and final reports in accordance with the Protocol and with content sufficient for the MAH to meet its regulatory obligations. The DSRU will comply with the requirements of GVP Module VI in the appropriate way that it applies to our study.

12.1.2 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 the sponsor of the study. For this study, the DSRU (the academic sponsor) will receive support from Bayer.

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Annex 1 List of Stand-alone documents

Number	Document reference number	Date	Title
1	1	16/4/2015	DSRU RAIDAR list

Annex 2. ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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 Safety Specialist Cohort Event Monitoring Study (SCEM) to monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales.

Study reference number:
SCEM ACS (SN 17542)

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

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.

Dates to be confirmed following outcome of ethics application; study to be registered post approval

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)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14
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)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	28
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)	☒	☐	☐	31

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	21
4.2.2 Age and sex?	☒	☐	☐	21
4.2.3 Country of origin?	☒	☐	☐	21
4.2.4 Disease/indication?	☒	☐	☐	21
4.2.5 Co-morbidity?	☒	☐	☐	21
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)	☒	☐	☐	22

Comments:

Seasonality is not applicable 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	☒	☐	☐	28

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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
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:

Exposure is based on specialist prescription of rivaroxaban, as reported by the specialist from the patients medical charts

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?	☒	☐	☐	31
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)	☒	☐	☐	

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

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	27
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.)	☒	☐	☐	27
8.1.3 Covariates?	☒	☐	☐	28
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)	☒	☐	☐	27
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)	☒	☐	☐	27
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	27,28

Comments:

Events (diseases/outcomes) are reported as recorded in patient medical charts, then coded into MedDRA by the DSRU. Exposure on study drug and medications is based on prescription records. for analysis purposes, medications will be presented according to ATC classification system, not a classification system. Specailist, patient and questionnaires will be linked using unique study reference number in this study.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

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?	☒	☐	☐	31
10.3 Are descriptive analyses included?	☒	☐	☐	31
10.4 Are stratified analyses included?	☒	☐	☐	31
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	33,36
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	36

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	41
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	30,31
11.3 Are methods of quality assurance described?	☒	☐	☐	42
11.4 Does the protocol describe possible quality issues	☒	☐	☐	43

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?	☒	☐	☐	31

Comments:

project Advisory Committee

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)	☒	☐	☐	43
12.3 Does the protocol address other limitations?	☒	☐	☐	43

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?	☒	☐	☐	30

Comments:

Ethics application has been submitted but outcome is not available yet

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?	☒	☐	☐	11

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: _____  _____

Annex 3. Additional information

Not applicable