PASS Information

Title	Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages
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Marketing authorisation holder(s)	Bayer Pharma AG, 13342 Berlin, Germany Please note that, effective 1st January 2017, Bayer Pharma AG transfers its assets to Bayer AG, an affiliated company within the Bayer Group. Thereby, Bayer AG assumes all rights and obligations of Bayer Pharma AG, including the role as initiator and funder of this study. No study procedures will change.
Joint PASS	No
Research question and objectives	The primary objective of this cross-sectional epidemiologic study is to measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient alert card. Specifically, the following objectives will be addressed: ▪ Investigate whether physicians and their patients have received the educational materials. ▪ Assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide and assess how physicians use the materials in their daily practice. ▪ Assess knowledge and understanding of patients regarding the key safety information contained in the patient alert card and determine if the patients use and carry the patient alert card with them. Evaluations were planned for administration at approximately 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) post drug launch. The wave 1 assessment was conducted among both patients and physicians. Based on the results of wave 1 and in agreement with the EMA, the wave 2 and wave 3 assessments will be conducted only among physicians.
Country(-ies) of study	France, Germany, Italy, Spain, and the United Kingdom
Author	[redacted]

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	[redacted]

Approval Page - Bayer

Project Title: Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

Protocol ID Number: 16167

Effective Date: 5 December 2016

Authors

[redacted]

Version and Date: Version 4.0, 5 December 2016

The following people have reviewed the protocol and give their approval:

[redacted]

Approval Page – RTI Health Solutions

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[redacted]

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List of Abbreviations

ADR	adverse drug reaction
AF	atrial fibrillation
CI	confidence interval
DVT	deep vein thrombosis
EC	ethics committee
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres of Pharmacoepidemiology and Pharmacovigilance
HCP	health care professional
HR	hazard ratio
INR	international normalised ratio
IRB	institutional review board
ITT	intention to treat
PE	pulmonary embolism
PVCH	Bayer pharmacovigilance country head
RTI-HS	RTI Health Solutions
SPAF	stroke prevention in atrial fibrillation
TTR	time in target INR range of 2.0–3.0
UAT	user acceptance testing
UK	United Kingdom
US	United States

2 Responsible Parties

RTI-HS, an independent, non-profit research organisation, developed this protocol and is responsible for the design, conduct, analysis, and reporting of the study.

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Bayer is the sponsor of the study. Bayer is responsible for fulfilling any responsibilities for reporting results to regulatory agencies.

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Kantar Health is responsible for physician recruitment for the physician and patient assessments, monitoring sites for patient recruitment, data collection, cognitive pretesting, and ethics submissions.

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The below country-level investigators were involved in the wave 1 assessment.

Country-Level Investigators	Country	Institutional Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3 Abstract

Title: Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

Version 4.0, 5 December 2016

[redacted]

Rationale and background: At the request of the European Medicines Agency (EMA), a prescriber guide and patient alert card (PAC) were developed and distributed to increase awareness and understanding about risks associated with rivaroxaban. The current study is being conducted to evaluate the understanding and use of these materials. Evaluations were planned for administration at approximately 18 months (wave 1), 3 years (wave 2), and 7 years (wave 3) post drug launch. The wave 1 assessment was conducted among both patients and physicians. Based on the results of wave 1 and in agreement with the EMA, the wave 2 and wave 3 assessments will be conducted among physicians only. Reference to the patient assessment throughout this amended protocol refers to wave 1 activities only.

Research question and objectives: The primary objectives are to measure whether physicians and patients received and used the prescriber guide and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages.

Study design: The study is an observational, cross-sectional study among physicians and patients with recent rivaroxaban experience. Eligible physicians and patients are invited to complete a brief questionnaire regarding their knowledge of key safety in the rivaroxaban educational materials.

Population: Countries include France, Germany, Italy, Spain, and the United Kingdom. Due to drug approval delays in Italy at the time of the wave 1 assessment, this assessment did not include Italy. Given that the drug is now approved in Italy, subsequent assessments will include all five countries as originally planned. Physicians are eligible to participate if they had prescribed rivaroxaban in the past 6 months for one of the indications of interest. Patients are eligible if they had taken rivaroxaban within the last 3 months for one of the indications of interest.

Variables: The physician questionnaire will assess physician knowledge of the key safety messages outlined in the prescriber guide and evaluate their receipt and use of the prescriber guide as well as counselling of patients and distribution of the patient alert card. In addition, physicians will be asked to characterise their practice in terms of years in practice, size of practice, and history of treating patients with the diagnoses of interest. The patient questionnaire will assess patient knowledge of the key safety messages outlined in the PAC and evaluate receipt and use of the PAC. It will also include demographics and other patient information to help characterise patterns of knowledge and behaviour through stratification of results.

Data sources: Data are obtained through questionnaire responses.

Study size[1]: Each wave of the study will target 300 participating physicians per country for a total of approximately 1,500 physicians per wave and 100 patients per country for a total 500 patients in wave 1 to allow reasonable precision around estimates of participant knowledge and understanding of the educational materials.

Data analysis: Analyses will include detailed review of responses to individual questions as well as potential summary measures across logical groupings of response items. Physician results will be stratified by country and other logical variables. Patient results will be stratified by country and other logical variables, potentially including a measure of the knowledge level of their physician. A detailed analysis plan describing methods of analysis and presentation and including table shells will be developed before data analysis is initiated. In addition to a description of the analysis of the questionnaire data, the analysis plan will describe any planned comparisons of participants and non-participants.

Milestones:

- EMA approval of protocol: 09 December 2011
- Registration in the EU PAS register: 06 December 2013
- Wave 1 lead ethics committee approvals: 05 November 2013 to 27 August 2014
- Wave 1 data collection for physician assessment: 15 September 2014 to 20 November 2014
- Wave 1 data collection for patient assessment: 11 November 2014 to 30 April 2015
- Wave 1 summary report: 16 October 2015
- Wave 2 data collection for physician assessment: Planned for Q1 2017-Q2 2017
- Wave 2 summary report: Planned for Q4 2017

[1] [1]Due to drug approval delays in Italy, the wave 1 assessment did not include Italy. Therefore, the total sample size for the wave 1 assessment was approximately 1,200 physicians and 400 patients.

4 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or update	Reason
1	26 April 2013	Section 2 (Background), Section 4.1.4 (Physician Sample Size), Section 4.2.4 (Patient Sample Size), Section 6 (Strengths and Limitations)	Amendment	The protocol was amended to remove Italy from the wave 1 assessment due to drug approval delays in Italy.
2	22 April 2016	Section 2 (Background), Section 3 (Specific Aims), Section 4 (Study Design), Section 5 (Analysis and Interpretation), Section 6 (Strengths and Limitations)	Amendment	The protocol was amended to reflect the completion of the patient and physician assessments in wave 1 and the planned repeat of the physician assessment only in waves 2 and 3.
3	5 December 2016	Sections 3 (Responsible Parties), 4 (Abstract), 6 (Milestones), and 9 (Study Design)	Amendment	The protocol was converted to the latest EMA GVP protocol template. Sections 3, 4, 6, and 9.2 were added per EMA GVP protocol template. Minor changes were made throughout Section 9 to further clarify that text related to the patient assessment refers to the wave 1 assessment.

5 Milestones

Milestone	Estimated Date	Actual Date
EMA approval of protocol version 1.0		09 December 2011
Registration in the EU PAS register		06 December 2013
Wave 1 lead ethics committee approvals		05 November 2013 to 27 August 2014
Wave 1 data collection for physician assessment		15 September 2014 to 20 November 2014
Wave 1 data collection for patient assessment		11 November 2014 to 30 April 2015
Wave 1 summary report		16 October 2015
Wave 2 data collection for physician assessment	Q1 2017-Q2 2017	
Wave 2 summary report	Q4 2017	
Study progress reports (to be submitted with Periodic Safety Update Reports)	Every 6 months throughout the study	

6 Rationale and Background

Xarelto® (rivaroxaban) is a highly selective direct Factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II), and no effects on platelets have been demonstrated. It does not require routine coagulation monitoring and has no food interactions and only a few drug interactions compared to standard of care (Xarelto Summary of Product Characteristics—EU, 2016).

Rivaroxaban is approved in the European Union for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. In addition, Xarelto, 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 with elevated cardiac biomarkers. (Xarelto Summary of Product Characteristics—EU, 2016.)

Atrial fibrillation is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for cardiogenic thromboembolic events. The prevalence of atrial fibrillation (AF) increases with age, being less than 1% among people under 60 years of age, with estimates of more than 6% among those over 80 years of age (Feinberg et al., 1995). AF is estimated to affect over 6 million patients in Europe and approximately 2.3 million in the United States (US), and the number of patients with AF continues to grow in the ageing population (Kannel and Benjamin, 2008). AF is associated with a four- to five-fold increased risk of ischemic stroke (Wolf et al., 1991) and accounts for up to 15% of all strokes and 30% of strokes in patients over the age of 80 (Wolf et al., 1987). In addition, there is evidence that AF-associated stroke is more disabling than non–AF-associated stroke (Jorgensen et al., 1996).

Acute venous thromboembolism (i.e., DVT or PE) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1,000 persons in the general population and is the third most common cause of vascular death, after myocardial infarction and stroke. The current standard treatment for DVT is overlapping parenteral anticoagulation (i.e., low-molecular-weight heparin) and a vitamin K antagonist (i.e., warfarin). Parenteral anticoagulation needs to be continued for 5 to 7 days, at least until an international normalised ratio (INR) of 2.0 has been obtained, followed by a minimum of 3 months of treatment with the vitamin K antagonist. Treatment with vitamin K antagonists requires frequent monitoring of the INR, and multiple interactions of vitamin K antagonists with foods and other drugs have been reported. The duration of treatment is determined by individual risk factors of the patient.

Two clinical programmes were undertaken to evaluate the efficacy and safety of rivaroxaban in the expanded indications

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive

heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, and prior stroke or transient ischaemic attack.

- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults.

1. The ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for the Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was conducted to evaluate the efficacy and safety of rivaroxaban compared with the vitamin K antagonist warfarin in the prevention of thromboembolic events in patients with non-valvular AF. In the pivotal double-blind study, 14,264 patients were assigned to either Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30-49 mL/min) or warfarin titrated to a target INR of 2.5 (therapeutic range, 2.0 to 3.0). The median time on treatment was 19 months, and overall treatment duration was up to 41 months. Overall, 34.9% of patients were treated with acetylsalicylic acid, and 11.4% were treated with a class III antiarrhythmic, including amiodarone.

   Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non–central nervous system systemic embolism (Kannel and Benjamin, 2008; Wolf et al., 1991). In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.66–0.96; $P < 0.001$ for non-inferiority). Among all randomised patients analysed according to intention to treat (ITT), primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR, 0.88; 95% CI, 0.74–1.03; $P < 0.001$ for non-inferiority; $P = 0.117$ for superiority). Among patients in the warfarin group, INR values were within the therapeutic range (2.0–3.0) a mean of 55% of the time (median, 58%; interquartile range, 43–71). The effect of rivaroxaban did not differ across the level of centre TTR (time in target INR range of 2.0–3.0) in the equally sized quartiles ($P = 0.74$ for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49–1.12). The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups.

2. The EINSTEIN clinical trial programme was designed to evaluate the use of rivaroxaban for the acute treatment and secondary prevention of DVT (EINSTEIN-DVT) and PE (EINSTEIN-PE) and in long-term secondary prevention of recurrent DVT and PE (EINSTEIN-EXT). A unique aspect of the EINSTEIN-DVT and PE studies is the use of rivaroxaban as a single agent (single drug approach) in contrast to the use of intravenous anticoagulants and vitamin K antagonists.

   The EINSTEIN-DVT study demonstrated that rivaroxaban is at least as effective as the current standard therapy, with similar safety, in the treatment and secondary prevention of DVT. EINSTEIN-EXT demonstrated that continued treatment with rivaroxaban 6 or 12 months after initial treatment is superior to placebo in preventing recurrences and has an acceptable risk of bleeding.

As a part of this safety risk management plan revision, a physician educational pack has been developed that includes the summary of product characteristics, prescriber guide (Appendix C), and patient alert card (Appendix D), with the aim to increase awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban.

The prescriber guide covers the following topics:

- Switching from or to rivaroxaban treatment
- Necessity of taking the 15-mg and 20-mg tablets with food
- Management of overdose situations
- Use of coagulation tests and their interpretation
- Dosing recommendations
- Perioperative management
- Populations at higher risk of bleeding
- Necessity of providing all patients with a patient alert card and counselling about the details of the patient alert card

The patient alert card contains the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a health care provider
- Importance of treatment compliance
- Necessity of taking the 15-mg and 20-mg tablets with food
- Necessity of carrying the patient alert card with them at all times
- Necessity of informing health care professionals (HCPs) that they are taking rivaroxaban if they need to have any surgery or invasive procedure

The patient alert card was initially provided to patients by their treating physicians. It is now included in the product packaging so patients receive the card every time they fill a prescription for rivaroxaban.

RTI Health Solutions (RTI-HS) is collaborating with Bayer to develop and implement this study to evaluate physician and patient awareness and understanding of the key messages in the prescriber guide and patient alert card. This protocol describes the planned evaluation of these elements of the risk management plan. Evaluations were planned for administration at 18 months (wave 1), 3 years (wave 2), and 7 years post-launch (wave 3). The status of these assessments is presented regularly in periodic safety update reports. The five countries included in the study are the United Kingdom (UK), Germany, France, Italy, and Spain.

The wave 1 assessment was conducted in the UK, Germany, France, and Spain. Due to drug approval delays in Italy at the time of the 18-month (wave 1) assessment, the study did not include Italy. The wave 1 assessment was completed in October 2015, and the final report was submitted to the European Medicines Agency (EMA) in November 2015. In light of the wave 1 survey results as well as changes in the distribution method for patient alert cards (i.e., cards are now distributed via the product information in the medication packs), EMA endorsed a request by Bayer to omit the patient survey from subsequent assessments. Accordingly, no patient survey will be conducted in the 3-year (wave 2) and 7-year (wave 3) assessments. Reference to the patient assessment throughout this protocol refers to wave 1 activities only. The wave 2 and 3 assessments will evaluate physicians' knowledge of the key messages in the prescriber guide only. Given that rivaroxaban is now approved in Italy, waves 2 and 3 will be conducted in the UK, Germany, France, Italy, and Spain as originally planned.

7 Research Question and Objectives

The primary objective of this cross-sectional epidemiologic study is to measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient alert card.

Specifically, the following objectives will be addressed:

- Investigate whether physicians and their patients have received the educational materials.
- Assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide and assess how physicians use the materials in their daily practice.
- Assess knowledge and understanding of patients regarding the key safety information contained in the patient alert card and determine if the patients use and carry the patient alert card with them.

The wave 2 and wave 3 assessments will only be conducted among physicians.

8 Research Methods

8.1 Study Design

8.1.1 Physician Assessment Overview

A geographically dispersed and diverse set of physicians prescribing rivaroxaban in the UK, Germany, France, Italy, and Spain will be selected to reflect the distribution of physician specialities who prescribe rivaroxaban. Physicians will be asked to complete an online questionnaire evaluating their knowledge of key safety information as well as their receipt and use of the educational materials for rivaroxaban. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

The wave 1 physician assessment was conducted in the UK, Germany, France, and Spain and completed in October 2015. Subsequent waves 2 and 3 of the physician assessment will include Italy.

8.1.2 Patient Assessment Overview

Patients taking rivaroxaban will be identified through a diverse selection of medical practices representing specialities that prescribe rivaroxaban across the target countries. The medical practices selected for participation in the patient assessment will not be included in the physician assessment described above; however, they will be asked to complete the physician questionnaire to allow exploratory evaluation of the possible impact of the study on physician knowledge and to evaluate patient responses by level of knowledge of their physician. Patients will be invited to participate by their physicians and will complete a paper questionnaire. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

The wave 1 patient assessment was conducted conducted in the UK, Germany, France, and Spain and completed in October 2015. Subsequent waves of the study will not include a patient assessment.

8.2 Setting

This cross-sectional study includes five western European countries (the UK, Germany, France, Spain, and Italy). Five countries are included to provide some diversity in practice patterns and to observe physician and patient knowledge in different settings. In addition, it was anticipated that the drug utilisation in these countries would be such that there would be a sufficient number of eligible physicians and patients with rivaroxaban experience to participate in the study.

The wave 1 assessment was conducted in the UK, Germany, France, and Spain. Due to drug approval delays in Italy at the time of the 18-month (wave 1) assessment, the study did not include Italy. Subsequent waves will include all five countries.

8.2.1 Physician Assessment

8.2.1.1 Physician Population and Eligibility

This cross-sectional study will be conducted in each of the five countries (the UK, Germany, France, Italy, and Spain) with distribution among a variety of physician specialities including, for example, general practitioners, cardiologists (office and hospital), haematologists, hospital stroke physicians, emergency care physicians, phlebologists, neurologists, angiologists, and other specialists in internal medicine (office and hospital). Representation by each physician group will reflect, to the extent possible, prescribing patterns in each country.

Physicians will be eligible to participate in this study provided they have prescribed rivaroxaban to at least one patient in the past 6 months for one of the following indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF).
- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults.

8.2.1.2 Physician Selection and Recruitment

The physician sampling frame will be constructed from a physician panel and/or prescriber list. The final frame will be determined with the objective of achieving a generally representative sample of physicians prescribing rivaroxaban. Geographic location, speciality, practice size, practice type, etc. will be taken into consideration. If the distribution of physicians in the sampling frame appears consistent with the distribution believed in the targeted population, physicians will be randomly selected from the sample frame. However, if the distributions do not appear consistent with the targeted population, the sampling frame will be stratified by speciality and/or geography, and specific numbers of physicians within each stratum will be selected in order to recruit a sample that matches the distribution in the target population. In this case, the physician recruitment within each stratum will be done randomly. The final sampling strategy will be designed to minimise bias and to allow for the study results to be generalised to the entire population of rivaroxaban prescribers to the extent feasible.

8.2.2 Patient Assessment

This section describes the patient assessment as previously conducted in wave 1.

8.2.2.1 Patient Population and Eligibility

Patients will be identified through selection of a diverse set of medical practices across the five targeted countries. To be eligible for the study, the patients must meet all of the following criteria:

- Patient has taken rivaroxaban within the last 3 months for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) or treatment of DVT and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
- Patient is aged 18 years or older.
- Patient is able to understand and complete the consent form and patient questionnaire.
- Patient can read and understand the native language of the country in which the study is being conducted.
- Patient has not participated in a clinical trial for a treatment to prevent blood clots in the past 12 months.

8.2.2.2 Patient Selection and Recruitment

The study will target 100 patients per country to complete the assessment. This estimate is based upon the anticipated number of eligible patients for participation. This target study size is dependent upon the actual number of patients filling a prescription within the established time frame and on response rates for the study. At least 10 physician practices in each country will be selected from a list of eligible physicians in order to identify and recruit a sufficient number of eligible patients (up to 10 patients per physician). Several factors will be evaluated to ensure a diverse representation of sites, including geographic location, physician speciality, and patient mix. To participate in the study, sites must (1) see a sufficient number of eligible patients; (2) be able to provide a semiprivate space for patient recruitment, the consent process, and completion of the patient-reported questionnaire; and (3) have a staff member available to coordinate research activities.

Physicians who are selected to participate in the patient assessment will be excluded from participating in the physician assessment.

Participating physicians will also be asked to collect a limited amount of de-identified information on all patients receiving rivaroxaban so that characteristics of participants can be compared with non-participants.

Patients will be eligible if they have taken rivaroxaban within the last 3 months for either SPAF or DVT treatment and secondary prevention. The patient sampling methodology will be designed with the goal of maximising the probability that each patient treated with rivaroxaban will have an equal opportunity to be selected. In some sites, it is likely that all treated patients will be selected. The sampling approach for those sites with larger numbers of patients will be customised for the site (based on patient volume) and will be devised to achieve an efficient method of obtaining a representative patient sample in centres with varying patient administration systems. The sites will be asked to recruit the patients for the study when the patient is at the physician practice for a previously scheduled visit, or by telephone.

8.3 Variables

8.3.1 Physician Questionnaire Development

Standard survey methodologic principles have been used to develop the physician questionnaire, which will assess physicians' knowledge of the following concepts as outlined in the prescriber guide and educational materials:

- Switching from or to rivaroxaban treatment
- Necessity of taking the 15-mg and 20-mg tablets with food
- Use of coagulation tests and their interpretation
- Dosing recommendations
- Perioperative management
- Populations at higher risk of bleeding
- Necessity of providing all patients with a patient alert card and counselling about the details of the patient alert card (included in wave 1 questionnaire only)

Physicians will be asked about their receipt and use of the prescriber guide (Appendix C) as well as counselling of patients and distribution of the patient alert card. In addition, physicians will be asked to characterise their practice in terms of years in practice, size of practice, and history of treating patients with the diagnoses of interest. Other characteristics will be collected to facilitate stratified analyses to explore factors associated with knowledge and behaviour. The physician questionnaire is designed to take 10-15 minutes to complete. The physician questionnaire was cognitively tested with physicians in each of the target countries prior to wave 1. Section 9.4 provides a detailed description of the cognitive pretesting process. Modifications have been made to the questionnaire based on the pretesting results and additional feedback from the sponsor. Some modifications to the questionnaire are anticipated based on country-specific requirements.

8.3.2 Patient Questionnaire Development

This section describes the patient questionnaire included in wave 1.

The patient questionnaire has also been developed following standard survey methodologic principles and has been cognitively tested with patients in each of the target countries. Modifications have been made to the questionnaire based on the results of testing and additional feedback from the sponsor. Some modifications to the questionnaire are anticipated based on country-specific requirements. The questionnaire will assess patient knowledge of the following concepts:

- Receipt and use of the patient alert card

- Knowledge of the key safety messages outlined in the patient alert card:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider
  - Importance of treatment compliance
  - Necessity of taking the 15-mg and 20-mg tablets with food
  - Necessity of carrying the patient alert card at all times
  - Necessity of informing HCPs that they are taking rivaroxaban if they need to have surgery or invasive procedures

The questionnaire includes demographics and other patient information to help characterise patterns of knowledge and behaviour through stratification of results. The questionnaire has been designed to take approximately 20 minutes to complete.

8.4 Data Sources

In order to thoroughly evaluate the physician and patient questionnaires in preparation for fielding the wave 1 assessment, RTI Health Solutions (RTI-HS) conducted cognitive pretesting with physicians and patients in each country.

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (Groves et al., 2009). Specifically, trained interviewers asked pretest participants to complete the questionnaires while thinking aloud or describing their thought processes as they answer the questionnaire items. Pretest interviewers used an interview guide that included probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaires. The pretest interviews helped to identify problems with questionnaire items, wording, response choices, etc., and ensured that participants understand the questions. The pretest interview data were used to optimise the language used in the questionnaires prior to fielding the patient and physician wave 1 assessments. Likewise, the cognitive testing helped to identify cultural or translational issues with the draft questionnaires so that they could be modified to meet the individual needs of each country while maintaining comparability across the study. The pretest interviews also provided an opportunity to test procedures and introductory materials in an effort to increase participation and thoughtful consideration of the questionnaires by participants during collection of the study data.

Cognitive pretesting of the physician questionnaire was conducted with 25 physicians across the five countries who prescribe rivaroxaban for SPAF or DVT treatment and secondary prevention. Additionally, cognitive pretesting of the patient questionnaire was conducted with 25 patients across the five countries who were being treated for SPAF or DVT/PE. Changes to both questionnaires were made based on the results of the cognitive testing and additional feedback from the sponsor. In addition, the patient questionnaire included re-administration of selected questions to evaluate patients' understanding of key safety information following exposure to the patient alert card.

8.5 Study Size

8.5.1 Physician Sample Size

The study will target 300 participating physicians per country, for a total of approximately 1,500 physicians overall[1], to allow reasonable precision around estimates of physicians' knowledge and understanding of the prescriber guide. Due to the limited number of eligible physicians on the panel or list, it is anticipated that waves 2 and 3 will include a mix of new participants and physicians who have participated in a previous assessment. If we assume that the total sample of participating physicians can be treated as a simple random sample and that the percent of correct responses to a true/false question is 85%, then for a sample of size 300, the two-sided 95% confidence interval will be 80.4% to 88.8%. Table 1 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages.

Table 1. Exact 95% Confidence Limits for Various Combinations of Sample Size and Correct Response Percentage

Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	80	70.8	87.3
100	85	76.5	91.4
300	80	75.0	84.4
300	85	80.4	88.8
500	80	76.2	83.4
500	85	81.6	88.0
1,500	80	77.9	82.0
1,500	85	83.1	86.8

8.5.2 Patient Sample Size

This section describes the patient sample size for wave 1.

The study targeted 100 patients per country, for a total 400 patients overall[2], to allow reasonable precision around estimates of patients' knowledge and understanding of the patient alert card at the study level. Since we planned to recruit up to 10 patients per physician practice, the responses from patients within the same practice could be correlated. Assuming no intraclass correlation and the percentage of correct responses to a true/false question is 50.0%, then for a sample of size 500, the two-sided 95% confidence interval would be 45.6% to 54.4%; whereas the corresponding confidence interval will be 41.2% to 58.8% if there is an intraclass correlation of 0.33. Table 1

[1] Due to drug approval delays in Italy, the wave 1 assessment did not include Italy. Therefore, the total sample size for the wave 1 assessment was 1,200 physicians.

[2] Due to drug approval delays in Italy, the wave 1 assessment did not include Italy. Therefore, the total sample size for the wave 1 assessment was 400 patients.

shows 95% confidence limits assuming various combinations of sample size, correct response percentages, and intra-class correlation coefficients.

Table 2. Confidence Limits (95%) for Various Combinations of Sample Size, Correct Response Percentage, and Intraclass Correlation Coefficient

Patient Sample Size	Intraclass Correlation Coefficient[a]	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	0.00	50	40.2	59.8
100	0.11	50	36.1	63.9
100	0.33	50	30.4	69.6
100	0.00	80	72.2	87.8
100	0.11	80	68.9	91.1
100	0.33	80	64.3	95.7
200	0.00	50	43.1	56.9
200	0.11	50	40.2	59.8
200	0.33	50	36.1	63.9
200	0.00	80	74.5	85.5
200	0.11	80	72.2	87.8
200	0.33	80	68.9	91.1
500	0.00	50	45.6	54.4
500	0.11	50	43.8	56.2
500	0.33	50	41.2	58.8
500	0.00	80	76.5	83.5
500	0.11	80	75.0	85.0
500	0.33	80	73.0	87.0

Note: Table calculations assume that, on average, 10 patients come from each practice (cluster).

[a] With an average cluster size of 10 patients, correlation coefficients of 0.11 and 0.33 correspond with a design effect of 2 and 4, respectively.

8.6 Data Collection and Data Management

8.6.1 Data Collection

8.6.1.1 Physician Data Collection

A Web-based electronic data capture (EDC) system will be used in this study. An invitation will be sent to the selected sample of physicians, inviting them to participate and providing a link to the Web-based questionnaire. During the data collection period, invitations will be made via e-mail or issued by phone to each sampled physician up to two times. Each invited physician will be asked to log in to the study Web site by entering a unique identification number and password assigned to each participant and provided in the invitation to participate. The questionnaire will begin with informed

consent. After participants consent, they will be prompted to complete the questionnaire. A screening question will be included at the beginning of the questionnaire to confirm that the physician has prescribed rivaroxaban at least once within the past 6 months for at least one of the two new indications.

The questionnaire will be self-administered (closed-ended questions with predefined answers) and can be completed at the participants' convenience. Although participants will be encouraged to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time, pick up where they left off, should that be necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimises the likelihood of the respondent searching for answers via the Web or other sources.

Participants will also not be allowed to access the questionnaire once it has been completed. Based on potential country-specific requirements, the recruitment process and physician questionnaire may be different between countries. Country-specific differences will be described and appended to the final study protocol.

8.6.1.2 Patient Data Collection

This section describes the patient assessment as previously conducted in wave 1.

The patient questionnaire will be self-administered (closed-ended questions with predefined answers) on hard copy forms at the site. While there are a number of advantages to using an electronic format for questionnaire administration, we anticipate a paper format will be preferred in this case based on the study population (e.g., older patients). Written informed consent will be obtained from each patient prior to completion of this questionnaire.

Patients will be asked to complete the questionnaire in the physician's office in a private setting. Sites will provide patients with appropriate privacy so there is no influence by the physician (or patient perception thereof) in this process. Patients will be asked to complete the questionnaire without referring to the patient alert card. Once they have completed the questionnaire, the patient will be asked to review the patient alert card and then re-answer selected questions related to key safety information to gather data on patient knowledge immediately after exposure to the card. Patients will then place their completed forms in an envelope and give the sealed envelope to a study coordinator or designee. While participating physicians will be informed of the purpose of the study, they will be counselled not to alter routine practice and patient education so as not to influence the study results. Physicians will be advised that the ultimate goal of the study is to evaluate the educational materials.

8.6.2 Data Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. Physician data will be entered directly into a Web-based EDC system. Patients will fill out data on paper forms, which will be sent to a data processing centre for double data entry that will be used to minimise data entry errors. Edit and logic checks will be conducted and queries resolved

to ensure high-quality data. However, due to the self-reported nature of the data some such resolutions may not be possible.

RTI-HS data managers will conduct user acceptance testing (UAT) and will sign the UAT report before the EDC system is used in the field. Staff will be trained on data collection forms and the EDC system before the study is fielded. RTI-HS data managers will approve the data management plan, all annotated data collection forms, the EDC and double–data entry system data dictionaries, the data cleaning specifications document, and the testing summary reports before authorizing the data systems to go "live." RTI-HS data managers will ensure that the EDC and paper data systems are tested and valid, and will require that testing documentation, database documentation, and change control documentation will be created and maintained.

Once the systems are is in the field, data management activities will include review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging data sets if required.

8.6.2.1 Record Retention

A copy of all the study materials (informed consent forms, patient questionnaires) will be retained according to Bayer's standard operating procedures and in keeping with local regulatory requirements.

Any paper data files collected in the European Union will be maintained within the European Union. Only data based on case identification numbers will be transferred to the US for the purpose of analysis and generation of the final report. Data analysis and storage of de-identified data sets will be in the US

8.7 Data Analysis

Analyses will include detailed review of responses to individual questions as well as potential summary measure across logical grouping of response items. Physician results will be stratified by country, speciality, participation in the previous waves, and other logical variables. Patient results will be stratified by country and other logical variables, potentially including a measure of the knowledge level of their physician. A detailed analysis plan describing methods of analysis and presentation, as well as table shells, will be developed prior to starting analysis of data. In addition to a description of the analysis of the questionnaire data, the analysis plan will describe any planned comparisons of participants and non-participants; this will depend upon data available on non-participants.

The analysis plan will also describe the following:

- Analysis of subgroups
- Methods for handling missing data
- Level of statistical precision

All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS, Cary, North Carolina). Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

Descriptive tables summarising demographics, results, and other available characteristics will be generated for the physicians and patients by country. For continuous-type data, the mean, standard deviation, median, and range will be presented. For categorical data, frequencies and percents will be reported. The specific tables to be included will be finalised in the analysis plan.

Whenever possible, we will provide comparisons of participants to non-participants, and/or compare characteristics of the participants to what is known about the overall physician and patient populations. In addition, exploratory analyses were conducted in wave 1 comparing responses between the physicians who participated in only the physician questionnaire component of the study to those who also recruited patients into the patient component to explore the potential that the study itself created greater awareness of the safety information. Multivariable analyses may be conducted to evaluate predictors of high/low knowledge levels.

8.8 Quality Control

This project will be conducted in accordance with the guidances in Section13 and the internal standard operating procedures of participating institutions. The RTI Health Solutions (RTI-HS) Office of Quality Assurance, an independent unit that reports to the Vice President of RTI-HS, will oversee quality assurance for this study.

8.9 Strengths and Limitations of the Research Methods

A key strength of the study is the diversity of the sites, physicians, and patient populations to be included in both assessments. Based on available information, geographic location, and physician practice type (clinic, hospital, internists, haematologists, etc.), sites and patients recruited for participation will constitute a generally representative sample of rivaroxaban prescribers and users.

The physician assessment will be conducted after physicians have received the prescriber guide and have had a chance to utilise that guide in their practice. This portion of the study will evaluate how physicians are using the materials in their daily practice with patients.

The patient questionnaire will be conducted after patients have received rivaroxaban. Therefore, the study will evaluate recall about the process of receiving and reading the patient alert card, awareness of the key information contained in the patient alert card, and whether the patient carries the patient alert card during treatment.

Among the strengths of the patient assessment will be the collection of information on participants and on non-participants. Sites will keep a simple log with information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. Site logs will be produced weekly during the data collection period. These data will allow calculation of the participation rate. Patients who are approached by the study coordinator and then refuse to participate will be asked the reason for refusal. Reasons for non-participation will be described in the report. In addition, we will compare characteristics of the participants with those of the total rivaroxaban patients to evaluate any differences that should be considered in the analysis.

Other strengths of the patient assessment include the probability of high response rates given that the study is being introduced to patients by a trusted HCP, and the ability to stratify knowledge results based on duration of use, patient use and receipt of the patient alert card, and provider knowledge.

The study will target a total of 1,500 physicians[1] (approximately 300 per country) and 500 patients[2] (approximately 100 patients per country) to complete the assessment. The majority of the analysis will focus on aggregated data. Although the report may display country-specific findings, there may be limitations with drawing country-specific conclusions, particularly for the patient assessment given the relatively small samples sizes within each country.

As with all voluntary studies, some limitations are inherent. Although the study is designed to ensure the selection of a diverse and generally representative sample of prescribers and patients to participate in this study, there exists no exhaustive list of all rivaroxaban prescribers and patients from which to draw a sample; hence, it is impossible to select a random sample of all prescribers/patients. Therefore, the study participants may not necessarily represent all users of rivaroxaban. In addition, as is true with most surveys, it is possible that respondents who complete the questionnaire will differ from non-respondents in characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials). The direction and magnitude of such potential respondent bias is not known. In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., Internet access). However, it is anticipated that the majority of physicians will be Internet enabled.

Another potential limitation of the patient assessment is that the study could influence sites to provide more education to patients than they normally would provide. To minimise this risk, sites will be trained to provide only limited information about the study prior to the patients' participation in the study, and patients will be asked to complete the questionnaire at the site prior to receiving any additional counseling about treatment. In addition, it is not possible to restrict patients from changing their responses on the paper questionnaire based on information learned as they complete the questionnaire. However, the questionnaire will emphasize that the patients should respond based on what they know and explain that the ultimate goal of the study is to make sure that patients are well informed about their medications.

The physician assessment will be repeated in wave 2 and wave 3, allowing for comparison across assessments as prescribing patterns evolve. The patient assessment will not be conducted in subsequent waves, so these comparisons will not be possible.

8.10 Other Aspects

Not applicable.

[1] Due to drug approval delays in Italy, the wave 1 assessment did not include Italy. Therefore, the total sample size for the wave 1 assessment was 1,200 physicians.

[2] Due to drug approval delays in Italy, the wave 1 assessment did not include Italy. Therefore, the total sample size for the wave 1 assessment was 400 patients.

9 Protection of Human Subjects

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including, where applicable, the 2008 version of the Declaration of Helsinki. The institutional review board (IRB) at RTI International (of which RTI-HS is a division) will review the study or deem it exempt from review. IRB/ethics committee (EC) approvals will be obtained in accordance with applicable national and local regulations in each country.

9.1 Informed Consent

Participant informed consent will be obtained for each patient or physician who agrees to complete a questionnaire. Patient informed consent will be obtained in writing in all participating countries. Physicians will be asked to provide electronic acknowledgement of consent prior to completing the Web-based questionnaire.

The questionnaires will not collect any identifying information about the patient or physician, and they will be tracked using a unique study identifying number. For paper questionnaires, the physician will record the patient's study number on the questionnaire before it is given to the patient. Physicians will be required to provide limited data on each participating patient (e.g., diagnosis, surgeries, and treatment duration).

9.2 Participant Confidentiality

The research team will not have access to any participant-identifying information. No personal identifying information will be removed from the centres. Only de-identified data will be made available to the research staff and Bayer. Thus, any reports that are generated will *not* contain any participant identifiers. Data will be provided to Bayer in aggregate only and will not be linked to individual patients or HCPs.

For the patient assessment, sites will maintain an enrolment log with only the names of patients who completed the study and HCPs involved in the study. Site logs will be maintained at the site and will never be shared with the research team, third parties, or Bayer. Additionally, the patient questionnaire will *not* be linked to any patient log or any other patient-identifying information. Additionally, age in lieu of a birth date will be used to further protect confidentiality.

9.3 Compensation

Physician sites participating in the patient assessment will be paid nominal incentives to compensate them for the time spent recruiting patients and providing limited data from patient records, per country-specific regulations. The amount and payment methods will be reviewed and approved by the IRB/EC to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

Patients and physicians participating in the assessments will be paid nominal incentives to compensate them for their time in completing the study questionnaires in those countries where it is acceptable to do so. As with the site compensation, the amount and payment methods will be reviewed and approved by the IRB/EC to ensure that payments

are commensurate with the time needed to complete the forms, not coercive, and made according to local regulations in each country.

10 Management and Reporting of Adverse Events/Adverse Reactions

This study is not designed to collect information on individual adverse drug events, which are better collected using other study designs.

However, spontaneous adverse drug reactions (ADRs) may be identified through the following pathways:

- Communicated during the qualitative cognitive pretesting interviews
- Documented through open-ended responses (if applicable) in the Web questionnaire completed by the HCP
- Documented through open-ended questions (if applicable) or handwritten notes on the questionnaire completed by the patient

For the cognitive pretest interviews, the interviewers completed safety training, which included instructions to complete an ADR case report form and submit it to the Bayer pharmacovigilance country head (PVCH) if a spontaneous ADR was reported.

For each assessment, questionnaire data will be reviewed for possible ADRs. Upon identification of an ADR, this information will be forwarded to the Bayer PVCH within 1 business day by e-mail, fax, or other mechanism developed with Bayer. Bayer will assess the information for possible adverse events and product complaints and forward it for processing to the company safety database and/or to the Product Complaints group as applicable through Bayer's usual reporting processes and standard operating procedures. The local contact to the PVCH will follow up with the patient's physician directly, if Bayer determines that follow-up is needed and if the reporting patient has given consent for his/her physician to be contacted by Bayer. All initial and follow-up information will be de-identified and reported to Bayer.

If a patient spontaneously reports an ADR to a physician during their participation in the study at the site, physicians will be expected to report suspected ADRs to the applicable manufacturer/licensee and/or regulatory authority in accordance with local procedures.

Adverse events are not anticipated as part of the wave 2 and 3 assessments because there are no open-ended questions in the physician survey.

11 Plans for Disseminating and Communicating Study Results

The protocol, study status updates, and report(s) will be included in regulatory communications in line with the risk minimisation plan, periodic safety update reports, and other regulatory milestones and requirements.

In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the International Society for Pharmacoepidemiology (2015) and the International Committee of Medical Journal Editors (2010).

12 Other Good Research Practice

This study is being conducted as a regulatory commitment. As an observational study, the risks for patients linked to their participation in the study are limited to a breach of confidentiality with regard to personal identifiers or health information. Before a patient can participate in the study, he or she must give informed consent. Independent EC approval will be according to the guidance of the each country's research ethics requirements.

The study will be conducted under the following guidelines:

- The International Society for Pharmacoepidemiology 2015 *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (http://www.pharmacoepi.org/resources/guidelines_08027.cfm)
- The study will be designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2016).
- The study will be reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checkl*ist (*http://www.strobe-statement.org/index.php?id=available-checklists).
- This study will comply with the European Medicines Agency (EMA)'s *Guideline on Good Pharmacovigilance Practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products* (EMA, 2014).
- The study will comply with the definition of a non-interventional (observational) study provided i*n the EMA's Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2016).

13 References

European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. European Medicines Agency; 4 August 204. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/08/WC500211714.pdf Accessed 2 Nov 2016

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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:

Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

Study reference number:

EUPAS3911

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

1.1.4 – The study will include an interim report after waves 1 and 2 and a final report after wave 3.

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

[2] Date from which the analytical data set is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5 – The study is descriptive. There are no a priori hypotheses.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.3 and 3.4 – The study is descriptive. No association or occurrence will be measured.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1 and 9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1 and 9.2.2
4.2.2 Age and sex?	☒	☐	☐	9.2.1 and 9.2.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin?	☒	☐	☐	9.2.1 and 9.2.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.1 and 9.2.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1.2 and 9.2.2.2

Comments:

4.2.2 – There are no specific inclusion/exclusion criteria for sex; all will be included. Only patients aged 18 years or older will be included; there are no age limits on physician participation.

4.2.5 – The study is cross-sectional.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for Xarelto. It is not a study of exposure to a medication and clinical outcomes.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for rivaroxaban. It is not a study of exposure to a medication and clinical outcomes.

Outcomes in this study include self-reported responses to questions on knowledge and behaviour. The study materials were evaluated in each group (physicians and patients) in each country through cognitive pretesting.

There is no validation of self-reported information.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☒	☐	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for rivaroxaban. It is not a study of exposure to a medication and clinical outcomes.

The study will capture information on participant characteristics that may be related to the study outcomes (prevalence of accurate knowledge), such as age, experience with the product, and having received and read the educational information.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

The study is descriptive. No effects will be measured.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.6.1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.3 – There will be no need for coding of responses in these studies. Analyses will evaluate the responses to the questionnaire items.

9.4 – This study does not involve linkages between data sources.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

This is a study of physician and patient knowledge of safety and safe use information for rivaroxaban. It is not a study of exposure to a medication and clinical outcomes. Analyses described in the protocol are primarily descriptive, summarizing the responses to individual questionnaire items. A statistical analysis plan will be

developed with details of analysis stratification, any weighting of results, and possible multivariable analyses of predictors of high/low knowledge levels.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.3 - Investigators performing the study will review and interpret the data prior to sharing the initial draft report with the sponsor.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

This is a study of physician and patient knowledge of safety and safe use information for rivaroxaban. Confounding will not be assessed.

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

Comments:

13.2 - Institutional Review Board/Ethics Committee approvals will be obtained in accordance with applicable national and local regulations in each country prior to data collection.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3. Additional Information

None.